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Heart failure

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ABSTRACT

INTRODUCTION: Heart failure occurs in 3% to 4% of adults aged over 65 years, usually as a consequence of coronary artery disease or hypertension, and causes breathlessness, effort intolerance, fluid retention, and increased mortality. The 5-year mortality in people with systolic heart failure ranges from 25% to 75%, often owing to sudden death following ventricular arrhythmia. Risks of cardiovascular events are increased in people with left ventricular systolic dysfunction (LVSD) or heart failure. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of multidisciplinary interventions for heart failure? What are the effects of exercise in people with heart failure? What are the effects of drug treatments for heart failure? What are the effects of devices for treatment of heart failure? What are the effects of coronary revascularisation for treatment of heart failure? What are the effects of drug treatments in people at high risk of heart failure? What are the effects of treatments for diastolic heart failure? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2010 (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 80 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 effectiveness and safety of the following interventions: aldosterone receptor antagonists, amiodarone, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, anticoagulation, antiplatelet agents, beta-blockers, calcium channel blockers, cardiac resynchronisation therapy, coronary revascularisation, digoxin (in people already receiving diuretics and angiotensin-converting enzyme inhibitors), exercise, hydralazine plus isosorbide dinitrate, implantable cardiac defibrillators, multidisciplinary interventions, non-amiodarone antiarrhythmic drugs, and positive inotropes (other than digoxin).

QUESTIONS

INTERVENTIONS

Key points

- Heart failure occurs in 3% to 4% of adults aged over 65 years, usually as a consequence of coronary artery disease or hypertension, and causes breathlessness, effort intolerance, fluid retention, and increased mortality.

  The 5-year mortality in people with systolic heart failure ranges from 25% to 75%, often owing to sudden death following ventricular arrhythmia. Risks of cardiovascular events are increased in people with left ventricular systolic dysfunction (LVSD) or heart failure.

- Multidisciplinary interventions may reduce admissions to hospital and mortality in people with heart failure compared with usual care. Exercise may reduce admissions to hospital due to heart failure compared with usual care. However, long-term benefits of these interventions remain unclear.

- ACE inhibitors, angiotensin II receptor blockers, and beta-blockers reduce mortality and hospital admissions from heart failure compared with placebo, with greater absolute benefits seen in people with more severe heart failure.

  Combined treatment with angiotensin II receptor blockers and ACE inhibitors may lead to a greater reduction in hospital admission for heart failure compared with ACE inhibitor treatment alone.

- Aldosterone receptor antagonists (spironolactone, eplerenone, and canrenoate) may reduce all-cause mortality in people with heart failure, but increase the risk of hyperkalaemia.

- Digoxin slows the progression of heart failure compared with placebo, but may not reduce mortality.

- Hydralazine plus isosorbide dinitrate may improve survival and quality-of-life scores compared with placebo in people with chronic congestive heart failure.

- We don't know whether amiodarone, anticoagulants, or antiplatelets are effective at reducing mortality or hospital re-admission rates.

- CAUTION: Positive inotropic agents (other than digoxin), calcium channel blockers, and antiarrhythmic drugs (other than amiodarone and beta-blockers) may all increase mortality and should be used with caution, if at all, in people with systolic heart failure.

- Implantable cardiac defibrillators and cardiac resynchronisation therapy can reduce mortality in people with heart failure who are at high risk of ventricular arrhythmias. However, studies evaluating cardiac resynchronisation therapy were performed in centres with considerable experience, which may have overestimated the benefits.

- We don't know how coronary revascularisation and drug treatment compare for reducing mortality in people with heart failure and left ventricular dysfunction because all the trials assessing this comparison were conducted before ACE inhibitors, aspirin, beta-blockers, and statins were in routine use, thus limiting their applicability to current clinical practice.

- ACE inhibitors delay the onset of symptomatic heart failure, reduce cardiovascular events, and improve long-term survival in people with asymptomatic LVSD compared with placebo.

  Angiotensin II receptor blockers and ACE inhibitors seem equally effective at reducing all-cause mortality and cardiovascular mortality in people at high risk of heart failure.

  The combination of angiotensin II receptor blockers and ACE inhibitors seems no more effective than ACE inhibitors alone and causes more adverse effects.

- ACE inhibitors or angiotensin II receptor blockers seem no more effective at reducing mortality or rate of hospital admissions for cardiovascular events in people with diastolic heart failure compared with placebo.

  We don't know whether treatments other than angiotensin II receptor blockers are beneficial in reducing mortality in people with diastolic heart failure as we found only one trial.

DEFINITION Heart failure occurs when abnormal cardiac function causes failure of the heart to pump blood at a rate sufficient for metabolic requirements under normal filling pressure. It is characterised clinically by breathlessness, effort intolerance, fluid retention, and poor survival. Fluid retention and the congestion related to this can often be relieved with diuretic therapy. However, diuretic therapy should generally not be used alone and, if required, should be combined with the pharmacological treatments outlined in this review. Heart failure can be caused by systolic or diastolic dysfunction, and is associated with neurohormonal changes. [1] Left ventricular systolic dysfunction (LVSD) is

defined as a left ventricular ejection fraction (LVEF) <0.40. It may be symptomatic or asymptomatic. Defining and diagnosing diastolic heart failure can be difficult. Proposed criteria include: (1) clinical evidence of heart failure; (2) normal or mildly abnormal left ventricular systolic function; (3) evidence of abnormal left ventricular relaxation, filling, diastolic distensibility, or diastolic stiffness; and (4) evidence of elevated N-terminal-probrain natriuretic peptide. [2] However, assessment of some of these criteria is not standardised.

INCIDENCE/ PREVALENCE

Both incidence and prevalence of heart failure increase with age. Studies of heart failure in the US and UK found annual incidence in people 45 years or over to be between 29 and 32 cases/1000 people/year, and, in those over 85 years of age, incidence was considerably higher, at 45 to 90 cases/1000 people/year. [3] [4] The study carried out in the US reported a decline in incidence of heart failure (all age groups) over a 10-year period, with incidence falling from 32.2 cases/1000 people/year in 1994 to 29.1 cases/1000 people/year in 2003. [4] However, analysis of those aged 65 years or over indicated an increase in prevalence of heart failure (from 89.9 cases/1000 people in 1994 to 121 cases/1000 people in 2003). Prevalence of heart failure was higher in men (130 cases/1000 men) compared with women (115 cases/1000 women). [4] In older people (65 years or over), incidence of heart failure after a myocardial infarction (MI) is on the rise, with one study finding an increase of 25.1% in in-hospital heart failure from 1994 through to 2000 (from 31.4% to 39.3%, P = 0.001). [5] Furthermore, the study noted that 76% of people who survived MI had developed heart failure at 5 years' follow-up. Prevalence of asymptomatic LVSD is 3% in the general population, and the mean age of people with asymptomatic LVSD is lower than that of symptomatic individuals. [6] Both heart failure and asymptomatic LVSD are more common in men. [6] Prevalence of diastolic heart failure in the community is unknown. Prevalence of heart failure with preserved systolic function in people in hospital with clinical heart failure varies from 13% to 74%. [7] [8] Less than 15% of people with heart failure under 65 years of age have normal systolic function, whereas prevalence is about 40% in people over 65 years of age. [7]

AETIOLOGY/ RISK FACTORS

Coronary artery disease is the most common cause of heart failure. [9] Other common causes include hypertension and idiopathic dilated congestive cardiomyopathy. After adjustment for hypertension, the presence of left ventricular hypertrophy remains a risk factor for the development of heart failure. Other risk factors include cigarette smoking, hyperlipidaemia, and diabetes mellitus. [6] The common causes of left ventricular diastolic dysfunction are coronary artery disease and systemic hypertension. Other causes are hypertrophic cardiomyopathy, restrictive or infiltrative cardiomyopathies, and valvular heart disease. [8]

PROGNOSIS

The prognosis of heart failure is poor, with 5-year mortality ranging from 26% to 75%. [9] Up to 16% of people are re-admitted with heart failure within 6 months of first admission. In the US, heart failure is the leading cause of hospital admission among people over 65 years of age. [9] In people with heart failure, a new MI increases the risk of death (RR 7.8, 95% CI 6.9 to 8.8). About one third of all deaths in people with heart failure are preceded by a major ischaemic event. [10] Sudden death, mainly caused by ventricular arrhythmia, is responsible for 25% to 50% of all deaths, and is the most common cause of death in people with heart failure. Women with heart failure have a 15% to 20% lower risk of total and cardiovascular mortality compared with men with heart failure (risk after adjustment for demographic and social economic characteristics, comorbidities, cardiovascular treatments, and LVEF). [11] The presence of asymptomatic LVSD increases an individual's risk of having a cardiovascular event. One large prevention trial found that the risk of heart failure, admission for heart failure, and death increased linearly as ejection fraction fell (for each 5% reduction in ejection fraction: RR for mortality 1.20, 95% CI 1.13 to 1.29; RR for hospital admission 1.28, 95% CI 1.18 to 1.38; RR for heart failure 1.20, 95% CI 1.13 to 1.26). [12] The annual mortality for people with diastolic heart failure varies in observational studies (1–18%). [7] Reasons for this variation include age, presence of coronary artery disease, and variation in the partition value used to define abnormal ventricular systolic function. The annual mortality for left ventricular diastolic dysfunction is lower than that found in people with systolic dysfunction. [12]

AIMS OF INTERVENTION

To relieve symptoms; to improve quality of life; and to reduce morbidity and mortality with minimum adverse effects.

OUTCOMES

Effects of treatments in people with heart failure: **mortality**; **functional capacity** (assessed by the New York Heart Association functional classification or more objectively by using standardised exercise testing or the 6-minute walk test); [13] **hospital admission rates**; **quality of life** (assessed with questionnaires); [14] **adverse effects of treatment**. *Effects of treatments in people at high risk of heart failure*: **mortality**; **cardiovascular events (including non-fatal MI and the composite outcomes of cardiovascular mortality, MI, stroke, or hospital admission)**; **hospital admission rates**; **adverse effects of treatment**. Proxy measures of clinical outcome (e.g., LVEF) are used

only when clinical outcomes are unavailable. Where a study reported only the composite outcome of death or hospital admission, we have reported this under hospital admission.

METHODS

Clinical Evidence search and appraisal August 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2010, Embase 1980 to August 2010, and The Cochrane Database of Systematic Reviews, August 2010 (online; 1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). 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 contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >100 individuals of whom >80% were followed up. Generally, RCTs with <500 people have been excluded because of the number of large RCTs available. If, for any comparison, large RCTs or systematic reviews were found, then smaller RCTs have been excluded, even if they include >500 people. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 93). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of multidisciplinary interventions for heart failure?**

OPTION **MULTIDISCIPLINARY INTERVENTIONS**

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Multidisciplinary interventions may reduce admissions to hospital and mortality in people with heart failure compared with usual care, although long-term benefits remain unclear.

Benefits and harms

Multidisciplinary interventions versus usual care:

We found 7 systematic reviews (search date 2004, 33 RCTs, 7387 people; [15] search date 2005, 36 RCTs, 8341 people; [16] search date 2004, 30 RCTs, 7532 people; [17] search date 2006, 26 RCTs, 4671 people; [18] search date 2007, 12 RCTs, 2060 people; [19] search date 2008, 20 RCTs, 6258 people, 12 cohorts, 2354 people; [20] and search date 2008, 25 RCTs, 8323 people [21]) and two subsequent RCTs. [22] [23] The reviews identified some of the same RCTs, however, they included different combinations of RCTs in their meta-analyses, and analysed different aspects of multidisciplinary programmes, and so we report data from all reviews.

Mortality

Compared with usual care Multidisciplinary programmes are more effective at reducing all-cause mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[15] Systematic review	5308 people 28 RCTs in this analysis	**Rate of all-cause mortality** 389/2587 (15%) with disease management programme 492/2721 (18%) with usual care	OR 0.80 95% CI 0.69 to 0.93 P = 0.003	●○○	disease management programme

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The different disease management programmes seemed equally effective; therefore, the choice of a specific programme could depend on the local health service characteristics and the available resources	RCTs of multidisciplinary treatment were generally small, involving highly selected patient populations (see further information on studies for more details)		
[16] Systematic review	Number of people in analysis not reported 30 RCTs in this analysis	**Rate of all-cause mortality** with disease management programme with usual care Absolute results not reported The review included RCTs lasting 3 months or more	ARR –3% 95% CI –5% to –1% P <0.01 Benefit of the intervention was dependent on age, severity of disease, guideline-based treatment at baseline, and disease management programme modalities	○○○	disease management programme
[17] Systematic review	7532 people 27 RCTs in this analysis Most RCTs identified by the review included people who were hospitalised or had been recently hospitalised with a diagnosis of heart failure (26 RCTs)	**Rate of all-cause mortality** 613/3867 (16%) with multidisciplinary programme 661/3580 (18%) with control (not further defined) See further information on studies for review definition of a multidisciplinary intervention	RR 0.79 95% CI 0.69 to 0.92 P = 0.002 There was significant heterogeneity among RCTs (P = 0.04); the review identified 2 RCTs that were outliers as potential sources of heterogeneity	●○○	multidisciplinary programme
[17] Systematic review	7213 people 26 RCTs in this analysis Sensitivity analysis Most RCTs identified by the review included people who were hospitalised or had been recently hospitalised with a diagnosis of heart failure (26 RCTs)	**Rate of all-cause mortality** with multidisciplinary programme with control (not further defined) Absolute results not reported See further information on studies for review definition of a multidisciplinary intervention	RR 0.83 95% CI 0.73 to 0.95 P = 0.002 Sensitivity analysis excluding 1 outlier removed heterogeneity with only a small reduction in results for effectiveness	●○○	multidisciplinary programme
[17] Systematic review	553 people 3 RCTs in this analysis Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme Most RCTs identified by the review included people who were hospitalised or had been recently hospitalised with a diagnosis of heart failure (26 RCTs)	**Rate of all-cause mortality** 35/316 (11%) with televideo or remote monitoring-based programme 51/237 (22%) with control (not further defined) See further information on studies for review definition of a multidisciplinary intervention	RR 0.49 95% CI 0.33 to 0.73 P = 0.0004	●●○	televideo or remote monitoring-based programme

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] Systematic review	3384 people 11 RCTs in this analysis Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme Most RCTs identified by the review included people who were hospitalised or had been recently hospitalised with a diagnosis of heart failure (26 RCTs)	**Rate of all-cause mortality** 220/1679 (13%) with programmes incorporating contact by telephone or mail 279/1705 (16%) with control (not further defined) See further information on studies for review definition of a multidisciplinary intervention	RR 0.70 95% CI 0.53 to 0.94 P = 0.02	●○○	programmes incorporating contact by telephone or mail
[17] Systematic review	1811 people 11 RCTs in this analysis Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme Most RCTs identified by the review included people who were hospitalised or had been recently hospitalised with a diagnosis of heart failure (26 RCTs)	**Rate of all-cause mortality** 149/890 (17%) with programmes consisting of home visits 183/921 (20%) with control (not further defined) See further information on studies for review definition of a multidisciplinary intervention	RR 0.87 95% CI 0.72 to 1.06 P = 0.17	⟷	Not significant
[17] Systematic review	1784 people 3 RCTs in this analysis Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme Most RCTs identified by the review included people who were hospitalised or had been recently hospitalised with a diagnosis of heart failure (26 RCTs)	**Rate of all-cause mortality** 209/982 (21.3%) with programmes delivered in hospital, clinic, or general practice 170/802 (21.2%) with control (not further defined) See further information on studies for review definition of a multidisciplinary intervention	RR 1.00 95% CI 0.84 to 1.20 P = 0.98	⟷	Not significant
[18] Systematic review	3918 people 22 RCTs in this analysis	**Rate of all-cause mortality** with multidisciplinary programmes with control (predominantly usual care) Absolute results not reported	OR 0.69 95% CI 0.56 to 0.85	●○○	multidisciplinary programme

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[18] Systematic review	Number of RCTs and people included in subgroup analysis not reported Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme	**Rate of all-cause mortality** with programmes involving face-to-face contact with control (predominantly usual care) Absolute results not reported Programmes involving face-to-face contact give the healthcare provider an opportunity to observe the patient	OR 0.63 95% CI 0.44 to 0.91	●○○	programmes involving face-to-face contact
[18] Systematic review	Number of RCTs and people included in subgroup analysis not reported Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme	**Rate of all-cause mortality** with programmes involving face-to-face contact plus telephone contact with control (predominantly usual care) Absolute results not reported Programmes involving face-to-face contact give the healthcare provider an opportunity to observe the patient	OR 0.68 95% CI 0.44 to 1.06	⟷	Not significant
[18] Systematic review	Number of RCTs and people included in subgroup analysis not reported Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme	**Rate of all-cause mortality** with programmes involving telephone (non face-to-face) management with control (predominantly usual care) Absolute results not reported	OR 0.82 95% CI 0.48 to 1.40	⟷	Not significant
[19] Systematic review	2060 people 12 RCTs in this analysis	**Rate of all-cause mortality** 117/1001 (12%) with pharmacist care 136/1059 (13%) with no pharmacist care The review focused on the role of pharmacist care (both pharmacist-directed and pharmacist-assisted care) in the management of heart failure	OR 0.84 95% CI 0.61 to 1.15	⟷	Not significant
[20] Systematic review	6133 people 19 RCTs in this analysis	**All-cause mortality** 390/3320 (12%) with remote patient monitoring 397/2813 (14%) with usual care	RR 0.83 95% CI 0.73 to 0.95 P = 0.006	●○○	remote patient monitoring
[21] Systematic review	5563 people 15 RCTs in this analysis	**All-cause mortality** 332/2948 (11%) with structured telephone support 332/2615 (13%) with usual care	RR 0.88 95% CI 0.76 to 1.01 P = 0.08	⟷	Not significant
[21] Systematic review	2710 people 11 RCTs in this analysis	**All-cause mortality** 147/1410 (10%) with telemonitoring 200/1300 (15%) with usual care	RR 0.66 95% CI 0.54 to 0.81 P = 0.00005	●○○	telemonitoring

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT **3-armed trial**	1049 people hospitalised because of heart failure, New York Heart Association (NYHA) functional class II to IV The third arm assessed the effects of a basic support intervention (follow-up with specialised nurse and cardiologist)	**Rate of all-cause mortality , 18 months** 83/344 (24%) with intensive disease management programme 99/339 (29%) with usual care Primary outcome was a composite of all-cause mortality or all-cause hospital admission The intensive disease management programme involved specialised nursing care together with consultation with a cardiologist (353 people) Usual care involved follow-up with cardiologist alone (348 people)	Significance not assessed The RCT was not powered to assess mortality alone The results from this large RCT do not correlate with the results of the 6 systematic reviews reported (see further information on studies for details)		
[23] RCT	1518 people having outpatient care for stable chronic heart failure with mainly NYHA class II or III symptoms	**All-cause mortality , up to 1 year after completion of the trial** 189/760 (25%) with previous telephone monitoring by specialised nurses 197/758 (26%) with previous usual care The intervention of telephone monitoring by specialised nurses had ended 1 year earlier; both groups were getting routine follow-up	RR 0.94 95% CI 0.77 to 1.16 P = 0.59	⟷	Not significant
[23] RCT	1518 people having outpatient care for stable chronic heart failure with mainly NYHA class II or III symptoms	**All-cause mortality , up to 3 years after completion of the trial** 326/760 (43%) with previous telephone monitoring by specialised nurses 308/758 (41%) with previous usual care The intervention of telephone follow-up had ended 3 years earlier; both groups were getting routine follow-up	RR 1.02 95% CI 0.87 to 1.20 P = 0.73	⟷	Not significant

Admission to hospital

Compared with usual care Multidisciplinary programmes are more effective at reducing all-cause hospital admissions, and hospital admissions for heart failure (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause hospital re-admission					
[15] Systematic review	7387 people 32 RCTs in this analysis	**Proportion of people admitted to hospital for any cause** with disease management programme with usual care Absolute results not reported The different disease management programmes seemed equally effective; therefore, the choice of a specific programme could depend on the local health	OR 0.76 95% CI 0.69 to 0.94 P <0.00001 RCTs of multidisciplinary treatment were generally small, involving highly selected patient populations (see further information on studies for more details)	●○○	disease management programme

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		service characteristics and the available resources			
[17] Systematic review	6569 people 21 RCTs in this analysis	**Proportion of people admitted to hospital for any cause** 1332/3331 (40%) with multidisciplinary programme 1442/3238 (45%) with control (not further defined) See further information on studies for review definition of a multidisciplinary intervention	RR 0.87 95% CI 0.79 to 0.95 P = 0.002 There was significant heterogeneity among RCTs (P = 0.04)	●○○	multidisciplinary programme
[19] Systematic review	2026 people 11 RCTs in this analysis	**Proportion of people admitted to hospital for any cause** 363/984 (37%) with pharmacist care 449/1042 (43%) with no pharmacist care The review focused on the role of pharmacist care (both pharmacist-directed and pharmacist-assisted care) in the management of heart failure	OR 0.71 95% CI 0.54 to 0.94	●○○	pharmacist care
[20] Systematic review	4122 people 11 RCTs in this analysis	**All-cause hospital admissions** 918/2137 (43%) with remote patient monitoring 901/1985 (45%) with usual care	RR 0.93 95% CI 0.87 to 0.99 P = 0.03	●○○	remote patient monitoring
[21] Systematic review	4295 people 11 RCTs in this analysis	**All-cause hospital admissions** 822/2140 (38%) with structured telephone support 888/2155 (41%) with usual care	RR 0.92 95% CI 0.85 to 0.99 P = 0.024	●○○	structured telephone support
[21] Systematic review	2343 people 8 RCTs in this analysis	**All-cause hospital admissions** 582/1232 (47%) with telemonitoring 579/1111 (52%) with usual care	RR 0.91 95% CI 0.84 to 0.99 P = 0.022	●○○	telemonitoring
Heart failure-specific hospital re-admission					
[15] Systematic review	3817 people 20 RCTs in this analysis	**Proportion of people admitted to hospital for heart failure-specific causes** with disease management programme with usual care Absolute results not reported The different disease management programmes seemed equally effective; therefore, the choice of a specific programme could depend on the local health service characteristics and the available resources	OR 0.58 95% CI 0.50 to 0.67 P <0.00001 RCTs of multidisciplinary treatment were generally small, involving highly selected patient populations (see further information on studies for more details)	●○○	disease management programme
[17] Systematic review	Number of people in analysis not clear 16 RCTs in this analysis	**Proportion of people admitted to hospital for heart failure-specific causes** with multidisciplinary programme with control (not further defined) Absolute results not reported	RR 0.70 95% CI 0.61 to 0.81 P <0.0001 There was significant heterogeneity among RCTs (P = 0.04)	●○○	multidisciplinary programme

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Most RCTs identified by the review included people who were hospitalised or had been recently hospitalised with a diagnosis of heart failure (26 RCTs)	See further information on studies for review definition of a multidisciplinary intervention			
[18] Systematic review	3844 people 21 RCTs in this analysis	**Proportion of people admitted to hospital for heart failure-specific causes** with multidisciplinary programmes with control (predominantly usual care) Absolute results not reported	OR 0.41 95% CI 0.30 to 0.56	●●○	multidisciplinary programme
[18] Systematic review	Number of RCTs and people included in subgroup analysis not reported Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme	**Proportion of people admitted to hospital for heart failure** with programmes involving face-to-face contact with control (predominantly usual care) Absolute results not reported Programmes involving face-to-face contact give the healthcare provider an opportunity to observe the patient	OR 0.42 95% CI 0.22 to 0.81	●●○	programmes involving face-to-face contact
[18] Systematic review	Number of RCTs and people included in subgroup analysis not reported Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme	**Proportion of people admitted to hospital for heart failure** with programmes involving face-to-face contact plus telephone contact with control (predominantly usual care) Absolute results not reported Programmes involving face-to-face contact give the healthcare provider an opportunity to observe the patient	OR 0.37 95% CI 0.21 to 0.64	●●○	programmes involving face-to-face contact plus telephone contact
[18] Systematic review	Number of RCTs and people included in subgroup analysis not reported Subgroup analysis Subgroup analyses based on type of intervention offered in the multidisciplinary programme	**Proportion of people admitted to hospital for heart failure** with programmes involving telephone (non face-to-face) management with control (predominantly usual care) Absolute results not reported	OR 0.67 95% CI 0.36 to 1.26	⟷	Not significant
[19] Systematic review	1977 people 11 RCTs in this analysis	**Proportion of people admitted to hospital for heart failure** 183/959 (19%) with pharmacist care 238/1018 (23%) with no pharmacist care The review focused on the role of pharmacist care (both pharmacist-directed and pharmacist-as-	OR 0.69 95% CI 0.51 to 0.94	●○○	pharmacist care

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		sisted care) in the management of heart failure			
[20] Systematic review	4310 people 13 RCTs in this analysis	**Hospital admissions for heart failure** 424/2231 (19%) with remote patient monitoring 546/2079 (26%) with usual care	RR 0.71 95% CI 0.64 to 0.80 P <0.001	●○○	remote patient monitoring
[21] Systematic review	4269 people 13 RCTs in this analysis	**Hospital admissions for heart failure** 346/2102 (16%) with structured telephone support 462/2167 (21%) with usual care	RR 0.77 95% CI 0.68 to 0.87 P = 0.00004	●○○	structured telephone support
[21] Systematic review	1570 people 4 RCTs in this analysis	**Hospital admissions for heart failure** 189/844 (22%) with telemonitoring 207/726 (28%) with usual care	RR 0.79 95% CI 0.67 to 0.94 P = 0.008	●○○	telemonitoring
[22] RCT **3-armed trial**	1049 people hospitalised because of heart failure, New York Heart Association (NYHA) functional class II to IV The third arm assessed the effects of a basic support intervention (follow-up with specialised nurse and cardiologist)	**Rate of composite outcome of all-cause mortality or hospital re-admission as a result of heart failure , 18 months** 132/344 (38%) with intensive disease management programme 141/339 (42%) with usual care The intensive disease management programme involved specialised nursing care together with consultation with a cardiologist (353 people) Usual care involved follow-up with cardiologist alone (348 people)	HR 0.93 (intensive disease management *v* usual care) 95% CI 0.73 to 1.17 The results from this large RCT do not correlate with the results of the 6 systematic reviews reported (see further information on studies for details)	⟷	Not significant
[22] RCT **3-armed trial**	1049 people hospitalised because of heart failure, NYHA functional class II to IV The third arm assessed the effects of a basic support intervention (follow-up with specialised nurse and cardiologist)	**Proportion of people admitted to hospital for chronic heart failure , 18 months** 92/344 (27%) with intensive disease management programme 84/339 (25%) with usual care Primary outcome was a composite of all-cause mortality or all-cause hospital admission The intensive disease management programme involved specialised nursing care together with consultation with a cardiologist (353 people) Usual care involved follow-up with cardiologist alone (348 people)	Significance not assessed The results from this large RCT do not correlate with the results of the 6 systematic reviews reported (see further information on studies for details)		
[23] RCT	1518 people attending outpatients for stable chronic heart failure with mainly NYHA class II to III symptoms	**Hospital admission for heart failure , up to 1 year after completion of the trial** 174/760 (23%) with previous telephone monitoring 220/758 (29%) with previous usual care	RR 0.73 95% CI 0.60 to 0.90 P = 0.002	●○○	previous telephone monitoring

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The intervention of telephone monitoring by specialised nurses had ended 1 year earlier; both groups were getting routine follow-up			
[23] RCT	1518 people attending outpatients for stable chronic heart failure with mainly NYHA class II to III symptoms	**Hospital admission for heart failure , up to 3 years after completion of the trial** 217/760 (29%) with previous telephone monitoring 266/758 (35%) with previous usual care The intervention of telephone monitoring by specialised nurses had ended 3 years earlier; both groups were getting routine follow-up	RR 0.72 95% CI 0.60 to 0.87 P = 0.0004	●○○	previous telephone monitoring

No data from the following reference on this outcome. [16]

Functional improvement

No data from the following reference on this outcome. [15] [16] [17] [18] [19] [20] [21] [22] [23]

Quality of life

No data from the following reference on this outcome. [15] [16] [17] [18] [19] [20] [21] [22] [23]

Adverse effects

No data from the following reference on this outcome. [15] [16] [17] [18] [19] [20] [21] [22] [23]

Further information on studies

[15] The RCTs of multidisciplinary treatment were generally small, involving highly selected patient populations. Many lasted <6 months and were usually carried out in academic centres, and so the results may not generalise to longer-term outcomes based in smaller community centres.

[17] A multidisciplinary intervention was defined as one in which heart failure management was the responsibility of a team incorporating medical input and input from one or more other areas (specialist nurse, pharmacist, dietitian, or social worker).

[20] The systematic review also identified 6 cohort studies (1925 people). It found that remote patient monitoring significantly reduced all-cause mortality compared with usual care over the duration of the included studies (67/980 [7%] with remote patient monitoring *v* 123/945 [13%] with usual care; RR 0.53, 95% CI 0.29 to 0.96; P <0.001). It also found that remote patient monitoring significantly reduced all-cause hospital admissions (3 cohort studies, 819 people: 84/420 [20%] with remote patient monitoring *v* 153/399 [38%] with usual care; RR 0.52, 95% CI 0.28 to 0.96; P <0.001).

[22] One possible reason for the lack of observed benefit for the intensive disease management programme is that, during the course of the study, people in the usual-care group had a closer follow-up by the cardiologist than was anticipated before starting the study.

Comment: **Clinical guide:**
The multiple systematic reviews identified have suggested that disease management programmes may reduce mortality, all-cause hospital admissions, and hospital admission for heart failure. It is reassuring that, despite the lack of specific analysis of adverse effects, all-cause mortality and all-cause hospital re-admissions were reduced, suggesting that multidisciplinary treatment overall is beneficial and not associated with any clinically important adverse effects. The data at this time are supportive of the use of disease management programmes to treat people with heart failure, with the expectation that there will be a reduction in mortality and morbidity compared with usual care.

QUESTION What are the effects of exercise in people with heart failure?

OPTION EXERCISE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Exercise may reduce admissions to hospital due to heart failure in people with heart failure compared with usual care, although long-term benefits remain unclear.

Benefits and harms

Exercise versus usual care:

We found two systematic reviews (search date 2003, 30 parallel-group RCTs plus 9 crossover RCTs, 2387 people; [24] and search date 2008, 19 RCTs, 3647 people [25]) and one subsequent RCT. [26] The reviews identified 6 RCTs in common, however they presented different meta-analyses and so we report both reviews here.

Mortality

Compared with usual care Exercise seems no more effective at reducing mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[24] Systematic review	1197 people 14 RCTs in this analysis	**Rate of all-cause mortality , mean 5.9 months' follow-up** 26/622 (4%) with exercise 41/575 (7%) with control	OR 0.71 95% CI 0.37 to 1.02 Follow-up among RCTs ranged from 4 weeks to 192 weeks; about half the RCTs included in the review had a follow-up of 3 months or less	⟷	Not significant
[25] Systematic review	962 people 13 RCTs in this analysis	**Rate of all-cause mortality , up to 12 months' follow-up** 42/480 (8.8%) with exercise 41/482 (8.5%) with control	RR 1.02 95% CI 0.70 to 1.51 P = 0.90 Follow-up among RCTs ranged from 6 months to 12 months	⟷	Not significant
[25] Systematic review	2658 people 4 RCTs in this analysis	**Rate of all-cause mortality , >12 months' follow-up** 238/1319 (18%) with exercise 268/1339 (20%) with control	RR 0.88 95% CI 0.73 to 1.07 P = 0.21 Follow-up among RCTs ranged from 26 months to 75 months	⟷	Not significant

No data from the following reference on this outcome. [26]

Admission to hospital

Compared with usual care Exercise may be more effective than usual care at reducing hospital admissions caused by heart failure at up to 30 months' follow-up. However, we don't know whether exercise is more effective at reducing all-cause hospital admissions or composite outcomes including all-cause hospital admission (other outcomes in composites include emergency department admission, urgent transplant, and death) (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death or hospital admission					
[24] Systematic review	1197 people 14 RCTs in this analysis	**Rate of events (including hospital admission causing temporary or permanent withdrawal from exercise) , mean 5.9 months' follow-up** 30/622 (5%) with exercise 34/575 (6%) with control	OR 0.83 95% CI 0.50 to 1.39 Follow-up among RCTs ranged from 4 weeks to 192 weeks; about half the RCTs included in the review had a follow-up of 3 months or less	⟷	Not significant
[25] Systematic review	659 people 8 RCTs in this analysis	**Rate of all-cause hospital admissions , up to 12 months' follow-up** 47/329 (14%) with exercise 61/330 (18%) with control	RR 0.79 95% CI 0.58 to 1.07 P = 0.13 Follow-up among RCTs ranged from 6 months to 12 months	⟷	Not significant
[25] Systematic review	2658 people 4 RCTs in this analysis	**Rate of all-cause hospital admissions , >12 months' follow-up** 764/1319 (58%) with exercise 810/1339 (60%) with control	RR 0.96 95% CI 0.90 to 1.02 P = 0.15 Follow-up among RCTs ranged from 26 months to 75 months	⟷	Not significant
[25] Systematic review	569 people 7 RCTs in this analysis	**Rate of hospital admissions for heart failure , up to 30 months' follow-up** 44/286 (15%) with exercise 61/283 (22%) with control	RR 0.72 95% CI 0.52 to 0.99 P = 0.042	●○○	exercise

No data from the following reference on this outcome. [26]

Functional improvement

Compared with usual care Exercise may be more effective at increasing exercise time at 3 and 12 months, and at increasing distance walked on the 6-minute walk at 3 months, but we don't know whether it is more effective at increasing distance walked on the 6-minute walk at 6 or 12 months or at improving performance on the incremental shuttle walking test at 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Walking distance					
[27] RCT	173 people with heart failure and left ventricular ejection fraction (LVEF) 40% or less, New York Heart Association (NYHA) functional class II to IV In review [25]	**Change in distance on the 6-minute walk (change from baseline) , 6 months** From 1350 to 1422 with home-based exercise programme (a combination of aerobic and resistance exercise training) From 1324 to 1385 with usual care Units used to measure distance in this RCT is unclear	P = 0.275 The method of randomisation of the RCT is unclear	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[26] RCT	169 people with LVEF 40% or less and NYHA functional class II or more	**Change in the incremental shuttle walking test , 6 months** with home-based exercise training plus specialist heart failure nurse care with usual care (specialist heart failure nurse care alone) Absolute results not reported	Mean difference: +14.98 metres 95% CI –11.89 metres to +41.86 metres P = 0.1	⟷	Not significant
[28] RCT	1835 people with medically stable heart failure and LVEF <35% In review [25]	**Change in distance on the 6-minute walk (change from baseline) , 3 months** Median increase +20 metres (interquartile range [IQR] –15 metres to +57 metres) with exercise training Median increase +5 metres (IQR –28 to +37 metres) with usual care	P <0.001	○○○	exercise training
[28] RCT	1914 people with medically stable heart failure and LVEF <35% In review [25]	**Change in exercise time (change from baseline) , at 3 months** Median increase 1.5 minutes (IQR 0.3 minutes to 3.0 minutes) with exercise training Median increase +0.3 minutes (IQR –0.6 to +1.4 minutes) with usual care Absolute results not reported	P <0.001	○○○	exercise training
[28] RCT	1444 people with medically stable heart failure and LVEF <35% In review [25]	**Change in distance on the 6-minute walk (change from baseline) , 12 months** Median increase +13 metres (IQR –28 metres to +61 metres) with exercise training Median increase +12 metres (IQR –30 metres to +55 metres) with usual care	P = 0.26	⟷	Not significant
[28] RCT	1476 people with medically stable heart failure and LVEF <35% In review [25]	**Change in exercise time (change from baseline) , at 12 months** Median increase 1.5 minutes (IQR 0 minutes to 3.2 minutes) with exercise training Median increase +0.2 minutes (IQR –1.0 minutes to +1.7 minutes) with usual care	P <0.001	○○○	exercise

No data from the following reference on this outcome. [24] [25]

Quality of life

Compared with usual care We don't know how exercise impacts quality of life (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[26] RCT	169 people with left ventricular ejection fraction (LVEF) 40% or less and New York Heart Association (NYHA) functional class II or more	**Change in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) , 6 months** with home-based exercise training plus specialist heart failure nurse care with usual care (specialist heart failure nurse care alone) Absolute results not reported	Mean difference –2.53 95% CI –7.87 to +2.80 P = 0.3	⟷	Not significant
[26] RCT	169 people with LVEF 40% or less and NYHA functional class II or more	**Change in the MLHFQ , 12 months** with home-based exercise training plus specialist heart failure nurse care with usual care (specialist heart failure nurse care alone) Absolute results not reported	Mean difference –0.55 95% CI –5.87 to +4.76 P = 0.8	⟷	Not significant
[25] Systematic review	700 people 6 RCTs in this analysis	**Health-related quality of life with MLHFQ , up to 60 months' follow-up** with exercise with usual care Absolute results not reported	SMD –10.33 95% CI –15.89 to –4.77 P = 0.00027	◌◌◌	exercise
[25] Systematic review	3109 people 10 RCTs in this analysis	**Health-related quality of life with all questionnaires , up to 75 months' follow-up** with exercise with usual care Absolute results not reported	SMD –0.56 95% CI –0.82 to –0.30 P = 0.00002	◌◌◌	exercise

No data from the following reference on this outcome. [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] Systematic review	Number of people not clear	**Exercise-related mortality** with exercise with control The review found no reports of deaths directly related to exercise during >60,000 people-hours of exercise training			
[28] RCT	2331 people with medically stable heart failure and left ventricular ejection fraction of 35% or less In review [25]	**Proportion of people with at least 1 hospital admission as a result of an event during or within 3 hours after exercise** 37/1159 (3%) with exercise training 22/1171 (2%) with usual care	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The usual-care group did not undergo a formal exercise programme The RCT reported that exercise training was well tolerated and safe			

No data from the following reference on this outcome. [25] [26]

Further information on studies

Comment: **Clinical guide:**
The specific form of exercise training varied among trials, and the relative merits of each strategy are unknown. Adherence to home-based exercise programmes is typically low, which could result in underestimation of the beneficial effects of exercise training. The most recent RCT (HF-ACTION RCT) identified by review [25] is the largest (2331 people) study identified to date. [28] Results from this multicentre, international study may be more appropriately generalised to smaller community centres. The findings from HF-ACTION and overall by the second systematic review [25] support a prescribed exercise training programme for patients with heart failure in addition to other evidence-based treatments.

QUESTION What are the effects of drug treatments for heart failure?

OPTION ACE INHIBITORS FOR TREATING HEART FAILURE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- ACE inhibitors reduce mortality and hospital admissions from heart failure compared with placebo, with greater absolute benefits seen in people with more severe heart failure.
- Combined treatment with angiotensin II receptor blockers and ACE inhibitors may lead to a greater reduction in hospital admission for heart failure compared with ACE inhibitor treatment alone.

Benefits and harms

ACE inhibitors versus placebo:

We found two systematic reviews (search dates 1994 [29] and not reported [30]) of ACE inhibitors versus placebo in heart failure. The second review analysed long-term results from large RCTs comparing ACE inhibitors versus placebo. [30] Three RCTs identified by the review examined the effects of ACE inhibitors in people for 1 year after MI. We found one systematic review (search date 1999) that specifically examined the adverse effects of ACE inhibitors in people with heart failure. [31]

Mortality

Compared with placebo ACE inhibitors are more effective at reducing mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[29] Systematic review	7105 people, New York Heart Association (NYHA) functional class III or IV	**Rate of all-cause mortality** 611/3870 (16%) with ACE inhibitors 709/3235 (22%) with placebo	ARR 6% 95% CI 4% to 8% OR 0.77	●○○	ACE inhibitors

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	32 RCTs in this analysis Duration of identified RCTs was 3 to 42 months	The review reported that relative reductions in mortality were similar in different subgroups (stratified by age, sex, cause of heart failure, and NYHA functional class)	95% CI 0.67 to 0.88		
[30] Systematic review	12,763 people with left ventricular dysfunction or heart failure of mean duration 35 months 5 RCTs in this analysis	**Rate of all-cause mortality** 1467/6391 (23%) with ACE inhibitors 1710/6372 (27%) with placebo	OR 0.80 95% CI 0.74 to 0.87 See further information on studies for details of relative benefits of ACE inhibitors	●○○	ACE inhibitors
[30] Systematic review	5966 people at 1 year post-infarction 3 RCTs in this analysis	**Rate of all-cause mortality** 702/2995 (23%) with ACE inhibitors 866/2971 (29%) with placebo	OR 0.74 95% CI 0.66 to 0.83 See further information on studies for details of relative benefits of ACE inhibitors	●○○	ACE inhibitors

Admission to hospital

Compared with placebo ACE inhibitors are more effective at reducing hospital admissions for heart failure (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Heart failure-specific re-admission to hospital					
[30] Systematic review	12,763 people with left ventricular dysfunction or heart failure of mean duration 35 months 5 RCTs in this analysis	**Proportion of people admitted to hospital for heart failure causes** 876/6391 (14%) with ACE inhibitors 1202/6372 (19%) with placebo	OR 0.67 95% CI 0.61 to 0.74 See further information on studies for details of relative benefits of ACE inhibitors	●○○	ACE inhibitors
[30] Systematic review	5966 people at 1 year post-infarction 3 RCTs in this analysis	**Proportion of people admitted to hospital for heart failure causes** 355/2995 (12%) with ACE inhibitors 460/2971 (16%) with placebo	OR 0.73 95% CI 0.63 to 0.85 See further information on studies for details of relative benefits of ACE inhibitors	●○○	ACE inhibitors

No data from the following reference on this outcome. [29]

Functional improvement

No data from the following reference on this outcome. [29] [30]

Quality of life

No data from the following reference on this outcome. [29] [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal owing to adverse effects					
[31] Systematic review	18,234 people 22 RCTs in this analysis	**Proportion of people withdrawing because of an adverse effect , about 2 years** 1035/7487 (14%) with ACE inhibitor 661/7025 (9%) with control (placebo or non-ACE inhibitor treatments)	RR 1.54 95% CI 1.30 to 1.83	●○○	control
Adverse effects					
[31] Systematic review	11,989 people Number of RCTs in analysis not clear	**Risk of cough** 123/6191 (2%) with ACE inhibitor 34/5798 (1%) with control (placebo or non-ACE inhibitor treatments)	RR 3.19 95% CI 2.22 to 4.57	●●○	control
[31] Systematic review	11,989 people Number of RCTs in analysis not clear	**Risk of hypotension** 102/6191 (2%) with ACE inhibitor 45/5798 (1%) with control (placebo or non-ACE inhibitor treatments)	RR 1.95 95% CI 1.39 to 2.74	●○○	control
[31] Systematic review	11,989 people Number of RCTs in analysis not clear	**Risk of renal dysfunction** 59/6191 (0.9%) with ACE inhibitor 31/5798 (0.5%) with control (placebo or non-ACE inhibitor treatments)	RR 1.84 95% CI 1.20 to 2.81	●○○	control
[31] Systematic review	11,989 people Number of RCTs in analysis not clear	**Risk of dizziness** 92/6191 (1.4%) with ACE inhibitor 56/5798 (0.9%) with control (placebo or non-ACE inhibitor treatments)	RR 1.60 95% CI 1.15 to 2.23	●○○	control
[31] Systematic review	11,989 people Number of RCTs in analysis not clear	**Risk of impotence** 10/6191 (0.16%) with ACE inhibitor 1/5798 (0.02%) with control (placebo or non-ACE inhibitor treatments)	RR 6.46 95% CI 1.14 to 36.58	●●●	control

No data from the following reference on this outcome. [29] [30]

Difference doses of ACE inhibitors versus each other:

We found one large RCT comparing low-dose lisinopril versus high-dose lisinopril. [32]

Mortality

Different doses of ACE inhibitors compared with each other Low-dose and high-dose lisinopril seem equally effective at reducing mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[32] RCT	3164 people with New York Heart Association functional class II to IV heart failure	**Rate of mortality** 717/1596 (45%) with low-dose lisinopril (2.5 or 5.0 mg/day) 666/1568 (43%) with high-dose lisinopril (32.5 or 35.0 mg/day)	ARR 2.4% CI not reported HR 0.92 95% CI 0.80 to 1.03 P = 0.128	⟷	Not significant

Admission to hospital

Different doses of ACE inhibitors compared with each other Low-dose lisinopril seems less effective than high-dose lisinopril at reducing admissions for heart failure (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death or hospital admission					
[32] RCT	3164 people with New York Heart Association (NYHA) functional class II to IV heart failure	**Rate of combined outcome of death or hospital admission for any reason** 1338/1596 (84%) with low-dose lisinopril (2.5 or 5.0 mg/day) 1250/1568 (80%) with high-dose lisinopril (32.5 or 35.0 mg/day)	ARR 4.1% CI not reported HR 0.88 95% CI 0.82 to 0.96	●○○	high-dose lisinopril
Heart failure-specific re-admission to hospital					
[32] RCT	3164 people with NYHA functional class II to IV heart failure	**Proportion of people admitted to hospital for heart failure** 1576/1596 (99%) with low-dose lisinopril (2.5 or 5.0 mg/day) 1199/1568 (77%) with high-dose lisinopril (32.5 or 35.0 mg/day)	ARR 22.2% CI not reported P = 0.002	○○○	high-dose lisinopril

Functional improvement

No data from the following reference on this outcome. [32]

Quality of life

No data from the following reference on this outcome. [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[32] RCT	3164 people with New York Heart Association (NYHA) functional class II to IV heart failure	**Proportion of people withdrawing from RCT** 18% with low-dose lisinopril (2.5 or 5.0 mg/day)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		17% with high-dose lisinopril (32.5 or 35.0 mg/day) Absolute numbers not reported			
Adverse effects					
[32] RCT	3164 people with NYHA functional class II to IV heart failure	**Proportion of people with dizziness** 12% with low-dose lisinopril (2.5 or 5.0 mg/day) 19% with high-dose lisinopril (32.5 or 35.0 mg/day) Absolute numbers not reported	Significance not assessed		
[32] RCT	3164 people with NYHA functional class II to IV heart failure	**Proportion of people with hypotension** 7% with low-dose lisinopril (2.5 or 5.0 mg/day) 11% with high-dose lisinopril (32.5 or 35.0 mg/day) Absolute numbers not reported	Significance not assessed		
[32] RCT	3164 people with NYHA functional class II to IV heart failure	**Proportion of people with worsening renal function** 7% with low-dose lisinopril (2.5 or 5.0 mg/day) 10% with high-dose lisinopril (32.5 or 35.0 mg/day) Absolute numbers not reported	Significance not assessed		
[32] RCT	3164 people with NYHA functional class II to IV heart failure	**Proportion of people with significant change in serum potassium concentration** 7% with low-dose lisinopril (2.5 or 5.0 mg/day) 7% with high-dose lisinopril (32.5 or 35.0 mg/day) Absolute numbers not reported	Significance not assessed		
[32] RCT	3164 people with NYHA functional class II to IV heart failure	**Proportion of people with cough** 13% with low-dose lisinopril (2.5 or 5.0 mg/day) 11% with high-dose lisinopril (32.5 or 35.0 mg/day) Absolute numbers not reported	Significance not assessed		

ACE inhibitors versus angiotensin II receptor blockers:

See option on angiotensin II receptor blockers, p 22 .

ACE inhibitors alone versus ACE inhibitors plus angiotensin II receptor blockers:

See option on angiotensin II receptor blockers, p 22 .

ACE inhibitors versus beta-blockers:

See option on beta-blockers, p 28 .

Further information on studies

[30] The relative benefits of treatment with ACE inhibitors began soon after the start of treatment, persisted in the long term, and were independent of age, sex, and baseline use of diuretics, aspirin, and beta-blockers. Although there was a trend towards greater relative reduction in mortality or re-admission for heart failure in people with lower ejection fraction, benefit was apparent over the range examined.

Comment: The first systematic review found similar benefits with different ACE inhibitors. [29]

Clinical guide:
The relative benefits of ACE inhibitors were similar in different subgroups of people with heart failure. Most RCTs evaluated left ventricular function by assessing left ventricular ejection fraction, but some studies defined heart failure clinically, without measurement of left ventricular function in people at high risk of developing heart failure (soon after MI). It is unclear whether there are additional benefits from adding an ACE inhibitor to antiplatelet treatment in people with heart failure (see antiplatelet agents, p 48).

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS FOR TREATING HEART FAILURE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Angiotensin II receptor blockers reduce mortality and hospital admissions from heart failure compared with placebo, with greater absolute benefits seen in people with more severe heart failure.
- Combined treatment with angiotensin II receptor blockers and ACE inhibitors may lead to a greater reduction in hospital admission for heart failure compared with ACE inhibitor treatment alone.

Benefits and harms

Angiotensin II receptor blockers versus placebo:

We found one systematic review (search date 2003, 24 RCTs, 38,080 people with New York Heart Association (NYHA) functional class II–IV, follow-up 4 weeks to 2.7 years). [34]

Mortality

Compared with placebo Angiotensin II receptor blockers are more effective at reducing all-cause mortality at 4 weeks to 2.7 years (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[34] Systematic review	4623 people 9 RCTs in this analysis	**Rate of mortality** 299/2821 (11%) with angiotensin II receptor blockers (ARBs) 319/1802 (18%) with placebo	OR 0.83 95% CI 0.69 to 1.00	●○○	ARBs

Admission to hospital

Compared with placebo Angiotensin II receptor blockers are more effective at reducing hospital admissions for heart failure (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Heart failure-specific re-admission to hospital					
[34] Systematic review	2590 people 3 RCTs in this analysis	**Proportion of people admitted to hospital for heart failure** 230/1340 (17%) with angiotensin II receptor blockers (ARBs) 314/1250 (25%) with placebo	OR 0.64 95% CI 0.53 to 0.78	●○○	ARBs

Functional improvement

No data from the following reference on this outcome. [34]

Quality of life

No data from the following reference on this outcome. [34]

Adverse effects

No data from the following reference on this outcome. [34]

Angiotensin II receptor blockers versus ACE inhibitors:

We found two systematic reviews (search date 2003, 10 RCTs, 25,739 people with New York Heart Association functional class II–IV, follow-up 4 weeks to 2.7 years; [34] and search date 2007, 5 RCTs [all of which were identified by the first review], 24,822 people [35]). The reviews differed in their inclusion criteria in minimum number of people enrolled and length of follow-up. The first review included RCTs of any size with a minimum length of follow-up of 4 weeks, [34] whereas the second review specified a minimum number of 500 people and at least 6 months' follow-up. [35] The reviews therefore included different RCTs in their analysis of all-cause mortality and so we report both reviews here.

Mortality

Angiotensin II receptor blockers compared with ACE inhibitors Angiotensin II receptor blockers and ACE inhibitors are equally effective at reducing all-cause mortality at 4 weeks to 2.7 years (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[34] Systematic review	5201 people 8 RCTs in this analysis	**Rate of mortality** 331/2889 (11%) with angiotensin II receptor blockers (ARBs) 295/2312 (13%) with ACE inhibitors	OR 1.06 95% CI 0.90 to 1.26	⟷	Not significant
[35] Systematic review	4310 people 3 RCTs in this analysis	**Rate of mortality** 317/2257 (14.0%) with ARBs 286/2053 (13.9%) with ACE inhibitors	RR 1.06 95% CI 0.56 to 1.62	⟷	Not significant

Admission to hospital

Angiotensin II receptor blockers compared with ACE inhibitors Angiotensin II receptor blockers and ACE inhibitors are equally effective at 4 weeks to 2.7 years at reducing hospital admissions for heart failure (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Heart failure-specific re-admission to hospital					
[34] [35] Systematic review	4310 people 3 RCTs in this analysis The reviews included the same three RCTs in their meta-analyses of hospital admission for heart failure, and both found the same result for this outcome Meta-analysis reported from 1 review [34]	**Proportion of people admitted to hospital with heart failure** 333/2257 (15%) with angiotensin II receptor blockers (ARBs) 321/2053 (16%) with ACE inhibitors	OR 0.95 95% CI 0.80 to 1.13	⟷	Not significant

Functional improvement

No data from the following reference on this outcome. [34] [35]

Quality of life

No data from the following reference on this outcome. [34] [35]

Adverse effects

No data from the following reference on this outcome. [34] [35]

Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone:

We found three systematic reviews (search date 2003, 7 RCTs, 8260 people with New York Heart Association functional class II–IV heart failure; [34] search date 2003, 4 RCTs; [36] and search date 2007, 3 RCTs, 7999 people [35]). All RCTs identified by the second and third reviews [36] [35] were identified by the first review. [34] However, there was variation among the reviews in their inclusion criteria and outcomes assessed and so we report all three reviews here. The first review included RCTs of any size with a minimum length of follow-up of 4 weeks, [34] whereas the second and third reviews specified at least 6 months' follow-up. [36] [35] The second review (4 RCTs identified by the first systematic review, [34] 7666 people) primarily assessed the effects of angiotensin II receptor blockers (ARBs) plus ACE inhibitors versus ACE inhibitors alone with and without beta-blockers. [36] The third review specified inclusion criteria of 500 or more people and 6 months' or longer follow-up. [35] The review found the same results as the other two reviews. [34] [36] We also found a fourth systematic review (search date 2006) that assessed only adverse effects. [33]

Mortality

Angiotensin II receptor blockers plus ACE inhibitors compared with ACE inhibitors alone We don't know whether angiotensin II receptor blockers plus ACE inhibitors are more effective than ACE inhibitors alone at reducing mortality or a composite outcome of mortality plus morbidity independent of whether people are taking beta-blockers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[34] Systematic review	8260 people 7 RCTs in this analysis	**Rate of all-cause mortality** 903/4265 (21%) with angiotensin II receptor blocker (ARB) plus ACE inhibitor 901/3995 (23%) with ACE inhibitor alone	OR 0.97 95% CI 0.87 to 1.08	⟷	Not significant
[36] Systematic review	Number of people not clear 2 RCTs in this analysis Subgroup analysis Subgroup analysis of people not taking beta-blockers	**Rate of mortality** with ARB plus ACE inhibitor (without beta-blockers) with ACE inhibitor alone Absolute results not reported	OR 0.93 95% CI 0.81 to 1.06	⟷	Not significant
[36] Systematic review	Number of people not clear 2 RCTs in this analysis Subgroup analysis Subgroup analysis of people taking beta-blockers	**Rate of mortality** with ARB plus ACE inhibitor (with beta-blockers) with ACE inhibitor alone Absolute results not reported	OR 1.08 95% CI 0.90 to 1.29 There was statistical heterogeneity between the RCTs (P <0.05)	⟷	Not significant
[35] Systematic review	7999 people 3 RCTs in this analysis	**Rate of mortality** 901/4119 (22%) with ARB plus ACE inhibitor 900/3980 (23%) with ACE inhibitor alone	RR 0.98 95% CI 0.84 to 1.15	⟷	Not significant
Mortality and morbidity					
[36] Systematic review	7666 people 4 RCTs in this analysis	**Rate of a composite outcome of mortality and morbidity** with ARB plus ACE inhibitor (with or without beta-blockers) with ACE inhibitor alone Absolute results not reported	OR 0.89 95% CI 0.81 to 0.98	●○○	ARB plus ACE inhibitor
[36] Systematic review	Number of people not clear 2 RCTs in this analysis Subgroup analysis Subgroup analysis of people not taking beta-blockers	**Rate of a composite outcome of mortality and morbidity** with ARB plus ACE inhibitor (without beta-blockers) with ACE inhibitor alone Absolute results not reported	OR 0.83 95% CI 0.73 to 0.94	●○○	ARB plus ACE inhibitor
[36] Systematic review	Number of people not clear 2 RCTs in this analysis Subgroup analysis	**Rate of a composite outcome of mortality and morbidity** with ARB plus ACE inhibitor (with beta-blockers) with ACE inhibitor alone	OR 0.94 95% CI 0.80 to 1.10 There was statistical heterogeneity between the RCTs (P <0.05)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Subgroup analysis of people taking beta-blockers	Absolute results not reported			

Admission to hospital

Angiotensin II receptor blockers plus ACE inhibitors compared with ACE inhibitors alone Angiotensin II receptor blockers plus ACE inhibitors are more effective at reducing hospital admissions for heart failure (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Heart failure-specific re-admission to hospital					
[34] Systematic review	8108 people 4 RCTs in this analysis	**Proportion of people admitted to hospital with heart failure** 688/4176 (16%) with angiotensin II receptor blocker (ARB) plus ACE inhibitor 819/3932 (21%) with ACE inhibitor alone	OR 0.77 95% CI 0.69 to 0.87	●○○	ARB plus ACE inhibitor
[35] Systematic review	7999 people 3 RCTs in this analysis The 3 RCTs in the meta-analysis were included in the meta-analysis of another reported review [34]	**Proportion of people admitted to hospital with heart failure** 686/4119 (17%) with ARB plus ACE inhibitor 818/3980 (21%) with ACE inhibitor alone	RR 0.83 95% CI 0.71 to 0.97	●○○	ARB plus ACE inhibitor

No data from the following reference on this outcome. [36]

Functional improvement

No data from the following reference on this outcome. [34] [36] [35]

Quality of life

No data from the following reference on this outcome. [34] [36] [35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Any adverse event					
[33] Systematic review	18,160 people with heart failure or left ventricular dysfunction 9 RCTs in this analysis	**Proportion of people experiencing any adverse event** 11% with angiotensin II receptor blocker (ARB) plus ACE inhibitor	RR 1.27 95% CI 1.15 to 1.40 P <0.00001	●○○	ACE inhibitor alone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		9% with ACE inhibitor alone Absolute numbers not reported	See further information on studies for methodological issues highlighted by the review		
Worsening renal function					
[33] Systematic review	18,160 people with heart failure or left ventricular dysfunction 9 RCTs in this analysis	**Proportion of people with worsening renal function** 2% with ARB plus ACE inhibitor 1% with ACE inhibitor alone Absolute numbers not reported See further information on studies for methodological issues highlighted by the review	RR 2.12 95% CI 1.30 to 3.46	●●○	ACE inhibitor alone
Hypotension					
[33] Systematic review	18,160 people with heart failure or left ventricular dysfunction 9 RCTs in this analysis	**Hypotension** 2% with ARB plus ACE inhibitor 1% with ACE inhibitor alone Absolute numbers not reported See further information on studies for methodological issues highlighted by the review	RR 1.91 95% CI 1.37 to 2.66 P = 0.0002	●○○	ACE inhibitor alone
Hyperkalaemia					
[33] Systematic review	18,160 people with heart failure or left ventricular dysfunction	**Proportion of people with hyperkalaemia** 0.87% with ARB plus ACE inhibitor 0.20% with ACE inhibitor alone Absolute numbers not reported See further information on studies for methodological issues highlighted by the review	RR 4.17 95% CI 2.31 to 7.53 P <0.00001	●●○	ACE inhibitor alone

No data from the following reference on this outcome. [34] [36] [35]

Further information on studies

[33] The review identified heterogeneity among studies and therefore conducted subgroup analyses using a statistical test of interaction. Subgroups analysed included the proportion of people with diabetes, sex, follow-up duration, and diuretic use. The only end point that showed significant interaction by subgroup was shorter trial duration leading to higher estimates of RR of renal failure for ARB plus ACE inhibitor relative to ACE inhibitor alone. This review also reported several other limitations. One limitation was that many included studies did not explain how adverse effects were defined; another limitation was that the initial search revealed and excluded some trials in which no adverse events were reported, and it is not clear whether there were actually no adverse events or simply that the investigators did not report them; finally the authors advise caution in interpreting meta-analytic results when the number of events per study are small, as is the case for many studies of adverse events.

Comment: **Clinical guide:**
Evidence suggests that, in people intolerant of ACE inhibitors, an ARB would be as effective at reducing mortality and morbidity. Furthermore, the evidence suggests that, for people with NYHA

functional class II–IV, an ARB should be added to treatment after ACE inhibition and beta-blocker treatment have been optimised, to further reduce both mortality and morbidity.

OPTION BETA-BLOCKERS

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Beta-blockers reduce mortality and hospital admissions from heart failure compared with placebo, with greater absolute benefits seen in people with more severe heart failure.

Benefits and harms

Beta-blockers versus placebo:

We found three systematic reviews (search date 2000, 22 RCTs, 10,315 people; [37] search date 2004, 28 RCTs, 7637 people; [38] and search date 2008, 23 RCTs, 19,209 people [39]) in people with any severity of heart failure. The reviews identified many RCTs in common, however they applied different inclusion criteria (e.g., in minimum number of people enrolled and length of follow-up) and reported on different outcomes. We found one systematic review (search date 2002, 9 RCTs, 14,594 people followed up for 6–24 months) that assessed adverse effects of beta-blockers in people with heart failure. [40]

Mortality

Compared with placebo (in people with any severity of heart failure) Beta-blockers seem more effective at reducing mortality in people with heart failure of any severity also receiving triple therapy, and in particular ACE inhibitors. (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[37] Systematic review	10,315 people with heart failure, most receiving triple therapy, and in particular ACE inhibitors 22 RCTs in this analysis	**Rate of mortality** 444/5273 (8%) with beta-blockers 624/4862 (13%) with placebo	OR 0.65 95% CI 0.53 to 0.80 This is equivalent to 3 fewer deaths per 100 people treated for 1 year The results were consistent for selective and non-selective beta-blockers Sensitivity analysis and funnel plots found that publication bias was unlikely	●○○	beta-blockers
[39] Systematic review	19,209 people with heart failure, most receiving ACE inhibitors and digoxin 23 RCTs in this analysis	**Rate of mortality** 1205/9820 (12%) with beta-blockers 1515/9389 (16%) with placebo	RR 0.76 95% CI 0.68 to 0.84 There was significant statistical heterogeneity among RCTs (P = 0.09)	●○○	beta-blockers

No data from the following reference on this outcome. [38]

Admission to hospital

Compared with placebo (in people with any severity of heart failure) Beta-blockers may be more effective at reducing hospital admissions in people with heart failure of any severity also receiving triple therapy, and in particular ACE inhibitors, and may be more effective at reducing a composite outcome of mortality and hospital admissions in older people (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause hospital admissions					
[37] Systematic review	10,315 people with heart failure, most receiving triple therapy, and in particular ACE inhibitors 22 RCTs in this analysis	**Proportion of people admitted to hospital for any cause** 540/5244 (10%) with beta-blockers 754/4832 (16%) with placebo	OR 0.64 95% CI 0.53 to 0.79 This is equivalent to 4 fewer hospital admissions per 100 people treated for 1 year The results were consistent for selective and non-selective beta-blockers Sensitivity analysis and funnel plots found that publication bias was unlikely	●○○	beta-blockers
Death or hospital admission					
[41] RCT	2128 older people with heart failure, mean age 76 years, mean left ventricular ejection fraction (LVEF) 36%, 35% of people had LVEF >35% In review [39]	**Rate of composite end point of all-cause mortality or cardiovascular hospital admission** 332/1067 (31%) with nebivolol 375/1061 (35%) with placebo	HR 0.86 95% CI 0.74 to 0.99	●○○	beta-blockers

No data from the following reference on this outcome. [38] [39]

Functional improvement

Compared with placebo (in people with any severity of heart failure) Beta-blockers seem more effective at increasing the proportion of people with an improvement in function (New York Heart Association functional classification) by at least one class, and at improving exercise time (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Change in NYHA class					
[38] Systematic review	7511 people with heart failure 25 RCTs in this analysis Of the people included, 95% had New York Heart Association (NYHA) class II or III heart failure and were randomised to receive either beta-blocker (4015 people) or placebo (3622 people)	**Proportion of people who improved NYHA class by at least 1 class** with beta-blockers with placebo Absolute results not reported	OR 1.80 95% CI 1.33 to 2.43 P <0.0001	●○○	beta-blockers
Exercise duration					
[38] Systematic review	1120 people with heart failure 10 RCTs in this analysis Of the people included, 95% had NYHA class II or III heart failure and	**Proportion of people with improved exercise time** with beta-blockers with placebo Absolute results not reported	Mean difference 44.19 seconds 95% CI 6.62 seconds to 81.75 seconds P = 0.021	○○○	beta-blockers

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	were randomised to receive either beta-blocker (574 people) or placebo (546 people)				

No data from the following reference on this outcome. [37] [39]

Quality of life

No data from the following reference on this outcome. [37] [38] [39]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal for any cause					
[40] Systematic review	14,594 people 9 RCTs in this analysis	**Proportion of people withdrawing from RCT for any cause** 1195/7458 (16%) with beta-blockers 1287/7136 (18%) with placebo The review did not report overall withdrawals owing to adverse effects	RR 0.89 95% CI 0.81 to 0.98	●○○	beta-blockers
Cardiac adverse effects					
[41] RCT	2128 older people with heart failure, mean age 76 years, mean left ventricular ejection fraction (LVEF) 36%, 35% of people had LVEF <35% In review [39]	**Proportion of people experiencing aggravated cardiac failure** 256/1067 (24%) with nebivolol 265/1061 (25%) with placebo	Significance not assessed		
[40] Systematic review	4439 people 4 RCTs in this analysis	**Proportion of people with worsening heart failure** 625/2379 (26%) with beta-blockers 691/2060 (34%) with placebo	RR 0.83 95% CI 0.71 to 0.98	●○○	beta-blockers
[40] Systematic review	13,796 people 7 RCTs in this analysis	**Proportion of people with bradycardia** 400/7057 (6%) with beta-blockers 118/6739 (2%) with placebo	RR 3.62 95% CI 2.48 to 5.28	●●○	placebo
Dizziness					
[40] Systematic review	10,082 people 4 RCTs in this analysis	**Proportion of people with dizziness** 1117/5196 (22%) with beta-blockers	RR 1.37 95% CI 1.09 to 1.71	●○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		810/4886 (17%) with placebo			
Hypotension					
[40] Systematic review	13,796 people 7 RCTs in this analysis	**Proportion of people with hypotension** 535/7057 (8%) with beta-blockers 409/6739 (6%) with placebo	RR 1.41 95% CI 0.96 to 2.06	⟷	Not significant
Fatigue					
[40] Systematic review	7793 people 3 RCTs in this analysis	**Proportion of people with fatigue** 953/4040 (24%) with beta-blockers 840/3753 (22%) with placebo	RR 1.04 95% CI 0.97 to 1.11	⟷	Not significant

No data from the following reference on this outcome. [37] [38] [39]

Beta-blockers versus placebo (in people with severe heart failure):

We found two systematic reviews (search dates not reported) assessing the effects of beta-blockers in people with severe heart failure, which identified 7 RCTs between them. [42] [43] The second systematic review (6 RCTs, 13,370 people with chronic heart failure [people with New York Heart Association functional class III or IV heart failure]) assessed the effects of beta-blockers in people with and without ACE inhibitors or angiotensin II receptor blockers (ARBs) at baseline. [43] We found one systematic review (search date 2002, 9 RCTs, 14,594 people followed up for 6 to 24 months) that assessed adverse effects of beta-blockers in people with heart failure. [40]

Mortality

Compared with placebo (in people with severe heart failure) Beta-blockers seem more effective at reducing mortality in people with severe heart failure who are also taking ACE inhibitors and diuretics with or without digitalis, but may be no more effective in those not taking ACE inhibitors or angiotensin II receptor blockers at baseline (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[42] Systematic review	635 people with New York Heart Association (NYHA) functional class IV heart failure, on ACE inhibitor and diuretic with or without digitalis 4 RCTs in this analysis	**Rate of mortality** 56/313 (18%) with beta-blockers 81/322 (25%) with placebo	RR 0.71 95% CI 0.52 to 0.96	●○○	beta-blockers
[43] Systematic review	12,728 people with chronic heart failure (people with NYHA functional class III or IV heart failure) 6 RCTs in this analysis Subgroup analysis	**Rate of mortality** 867/6496 (13%) with beta-blockers 1120/6232 (18%) with placebo	RR 0.76 95% CI 0.71 to 0.83	●○○	beta-blockers

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Subgroup analysis of people taking ACE inhibitors or angiotensin II receptor blockers (ARBs) at baseline (95.2% of people in identified RCTs)				
[43] Systematic review	642 people with chronic heart failure (people with NYHA functional class III or IV heart failure) 6 RCTs in this analysis Subgroup analysis Subgroup analysis of people not taking ACE inhibitors or ARBs at baseline	**Rate of mortality** 50/347 (14%) with beta-blockers 62/295 (21%) with placebo	RR 0.73 95% CI 0.53 to 1.02	⟷	Not significant

Admission to hospital

Compared with placebo (in people with severe heart failure) Beta-blockers may be more effective at reducing the combined outcome of death and hospital admissions independent of whether people are taking ACE inhibitors or angiotensin II receptor blockers at baseline (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death or hospital admission					
[43] Systematic review	Number of people in analysis not clear (8988 people in 3 RCTs) 3 RCTs in this analysis Subgroup analysis Subgroup analysis of people taking ACE inhibitors or angiotensin II receptor blockers (ARBs) at baseline (95.2% of people in identified RCTs)	**Rate of composite outcome of death or hospital admission for heart failure** 26% with beta-blockers 33% with placebo Absolute numbers not reported	RR 0.78 95% CI 0.74 to 0.83	●○○	beta-blockers
[43] Systematic review	Number of people in analysis not clear (8988 people in 3 RCTs) 3 RCTs in this analysis Subgroup analysis Subgroup analysis of people not taking ACE inhibitors or ARBs at baseline	**Rate of composite outcome of death or hospital admission for heart failure** 28% with beta-blockers 35% with placebo Absolute numbers not reported	RR 0.81 95% CI 0.61 to 1.08	⟷	Not significant

No data from the following reference on this outcome. [42]

Functional improvement

No data from the following reference on this outcome. [42] [43]

Quality of life

No data from the following reference on this outcome. [42] [43]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal for any cause					
[40] Systematic review	14,594 people 9 RCTs in this analysis	**Proportion of people withdrawing from RCT for any cause** 1195/7458 (16%) with beta-blockers 1287/7136 (18%) with placebo The review did not report overall withdrawals owing to adverse effects	RR 0.89 95% CI 0.81 to 0.98	●○○	beta-blockers
Cardiac adverse effects					
[40] Systematic review	4439 people 4 RCTs in this analysis	**Proportion of people with worsening heart failure** 625/2379 (26%) with beta-blockers 691/2060 (34%) with placebo	RR 0.83 95% CI 0.71 to 0.98	●○○	beta-blockers
[40] Systematic review	13,796 people 7 RCTs in this analysis	**Proportion of people with bradycardia** 400/7057 (6%) with beta-blockers 118/6739 (2%) with placebo	RR 3.62 95% CI 2.48 to 5.28	●●○	placebo
Dizziness					
[40] Systematic review	10,082 people 4 RCTs in this analysis	**Proportion of people with dizziness** 1117/5196 (22%) with beta-blockers 810/4886 (17%) with placebo	RR 1.37 95% CI 1.09 to 1.71	●○○	placebo
Hypotension					
[40] Systematic review	13,796 people 7 RCTs in this analysis	**Proportion of people with hypotension** 535/7057 (8%) with beta-blockers 409/6739 (6%) with placebo	RR 1.41 95% CI 0.96 to 2.06	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[40] Systematic review	7793 people 3 RCTs in this analysis	**Proportion of people with fatigue** 953/4040 (24%) with beta-blockers 840/3753 (22%) with placebo	RR 1.04 95% CI 0.97 to 1.11	⟷	Not significant

No data from the following reference on this outcome. [42] [43]

Beta-blockers versus ACE inhibitors:

We found one RCT. [44]

Admission to hospital

Compared with ACE inhibitors The beta-blocker bisoprolol and the ACE inhibitor enalapril may be equally effective at reducing the composite outcome of all-cause mortality or hospital admission in people with heart failure (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death or hospital admission					
[44] RCT	1010 people with left ventricular ejection fraction (LVEF) 35% or less and not receiving ACE inhibitors, beta-blockers, or angiotensin II receptor blockers (ARBs)	**Rate of composite outcome of all-cause mortality or hospital admission , 6 months** 178/505 (35%) with bisoprolol (10 mg daily) 186/505 (37%) with enalapril (10 mg twice daily) Bisoprolol and enalapril were initially given for 6 months. After 6 months, they were combined for 6 to 24 months	HR 0.94 95% CI 0.77 to 1.16 In the intention-to-treat analysis, bisoprolol was found to be non-inferior compared with enalapril These data suggest that bisoprolol may be as safe and efficacious as enalapril for treating heart failure	⟷	Not significant

Mortality

No data from the following reference on this outcome. [44]

Functional improvement

No data from the following reference on this outcome. [44]

Quality of life

No data from the following reference on this outcome. [44]

Adverse effects

No data from the following reference on this outcome. [44]

Further information on studies

Comment:

Clinical guide

Fears that beta-blockers may cause excessive problems with worsening heart failure, bradyarrhythmia, or hypotension have not been confirmed. We found good evidence for beta-blockers in people with moderate symptoms (NYHA functional class II or III) receiving standard treatment, including ACE inhibitors. Data suggest that the magnitude of the prognostic benefit conferred by beta-blockers in the absence of ACE inhibitors or ARBs is similar to that of ACE inhibitors. [43] Therefore, evidence suggests that either ACE inhibitors or beta-blockers could be used as first-line treatment in systolic heart failure. The value of beta-blockers is uncertain in heart failure with preserved ejection fraction and in asymptomatic left ventricular systolic dysfunction. One RCT (1959 people) found that carvedilol reduced all-cause mortality compared with placebo in people with MI and LVEF 40% or less (AR for death: 12% with carvedilol *v* 15% with placebo; HR 0.77, 95% CI 0.60 to 0.98). [45]

Effect of magnitude of heart rate reduction:

One systematic review (search date 2008) examined the relationship between degree of heart rate reduction and death in people with heart failure treated with beta-blockers. [39] The review performed a meta-regression analysis of data from 17 RCTs (17,831 people) and found that, for every 5 beats/minute reduction in heart rate with beta-blocker treatment, the relative risk for death decreased by 18% (95% CI 6% to 29%). These data suggest that the magnitude of the heart rate reduction is significantly associated with the survival benefit, further supporting evidence that both non-selective and selective beta-blockers are effective for heart failure.

Effect of different doses of beta-blocker:

The review (search date 2008) also compared the effects of different dosing schedules of beta-blockers on mortality. It compared results from higher dose trials (trials where people received a target dose of 50% or more of the dose recommended in guidelines) with results from lower dose trials. [39] The review found no significant difference between dosing schedule and reduction in all-cause mortality (17 RCTs, 17,660 people; RR 1.02, 95% CI 0.93 to 1.10 per dose increment; P = 0.69). The review reported that the RR for death was 0.74 (95% CI 0.64 to 0.86) in 15 trials in which people received high-dose beta-blockers, and the RR was 0.78 (95% CI 0.63 to 0.96) in 7 trials in which people received low-dose beta-blockers.

Effects of different beta-blockers:

One systematic review (search date 2009, 4 RCTs, 3501 people) compared non-selective versus selective beta-blockers in people with heart failure. [46] It found that non-selective beta-blockers significantly reduced all-cause mortality compared with selective beta-blockers (538/1754 [31%] with non-selective *v* 625/1747 [36%] with selective; RR 0.86, 95% CI 0.78 to 0.94). It should be noted that one trial (the COMET trial) made up 96% of these results. [47] The analysis of indirect comparisons of non-selective beta-blockers and selective beta-blockers found similar effects on mortality with non-selective (RR 0.75, 95% CI 0.61 to 0.92; P = 0.005) and selective beta-blockers (RR 0.76, 95% CI 0.68 to 0.87). Similarly, the analysis of indirect comparisons found similar rates of vascular events (fatal and non-fatal strokes, fatal and non-fatal MI, fatal pulmonary embolisms, other venous thromboembolic events) with both non-selective (RR 0.88, 95% CI 0.64 to 1.00) and selective (RR 1.33, 95% CI 0.86 to 2.04) beta-blockers; neither class of beta-blocker significantly reduced vascular events. It must be noted that the vascular event rate was relatively low, especially in people receiving selective beta-blockers (84 events in total; only 3 RCTs included in the analysis). The non-selective (RR 0.82, 95% CI 0.70 to 0.95) and selective (RR 0.77, 95% CI 0.61 to 0.97) beta-blockers equally decreased the events of fatal or non-fatal worsening heart failure. Thus, the data would suggest that non-selective and selective beta-blockers that have been used in clinical trials are equally effective for the management of heart failure.

One RCT suggested that results for non-black people were consistent between the non-selective beta-blockers bucindolol and carvedilol. [48]

Effects in different populations:
The lack of observed benefit for black people in one RCT [48] raises the possibility that there may be race-specific responses to pharmacological treatment for cardiovascular disease. There may also be different responses in people with diabetes mellitus. A meta-analysis (6 RCTs, 13,129 people) examined whether beta-blockers in people with heart failure are as efficacious in those with as without diabetes mellitus. [49] It found that overall mortality was significantly increased in people with diabetes mellitus compared with people without diabetes mellitus, regardless of treatment (RR 1.25, 95% CI 1.15 to 1.36). Carvedilol has also been assessed in people with diabetes in a meta-analysis because it is believed that carvedilol has unique characteristics compared with other beta-blockers. [50] In this meta-analysis, 7 RCTs were examined (5757 people, 25% with diabetes mellitus) to determine whether the effects of carvedilol were similar in people with and without diabetes mellitus. There was no significant difference in mortality or the number needed to treat (NNT) to prevent one death for 1 year for people with or without diabetes (mortality in people with diabetes: carvedilol *v* placebo: RRR 28%, 95% CI 3% to 46%; P = 0.03; people without diabetes: RRR 37%, 95% CI 22% to 48%; P <0.001; difference between 2 groups reported as not significant; P value not reported; NNT 25, 95% CI 14 to 118 for people with diabetes mellitus *v* NNT 23, 95% CI 17 to 37 for people without diabetes mellitus). Although beta-blockers significantly reduced mortality compared with placebo in people with diabetes mellitus (RR 0.84, 95% CI 0.73 to 0.96), the magnitude of benefit was significantly lower than that in people who did not have diabetes mellitus (P = 0.023).

One systematic review (search date 2007) identified assessed whether the magnitude of the benefit of beta-blockers differs in ischaemic and non-ischaemic heart failure. [51] The review searched for RCTs that reported mortality data for people with ischaemic or non-ischaemic heart failure separately. In the RCTs identified by the review (4 RCTs, 7250 people), heart failure was associated with ischaemic aetiology in 4746 (65%) people included in the analysis and with non-ischaemic aetiology in 2504 (35%) people. The review found the risk reduction in mortality for non-ischaemic heart failure (75/1335 [6%] with beta-blocker *v* 108/1169 [9%] with placebo; RR 0.62, 95% CI 0.45 to 0.84; P = 0.002) to be similar to that of ischaemic heart failure (226/2457 [9%] with beta-blocker *v* 324/2289 [14%] with placebo; RR 0.62, 95% CI 0.52 to 0.75; P <0.00001).

We found one systematic review (search date not reported, 5 RCTs, 17,346 people) investigating whether beta-blockers are as effective in older people as in non-elderly people for chronic heart failure. [52] The cut-off points for older age ranges varied across trials (59–71 years). The review found that beta-blocker treatment significantly reduced all-cause mortality for non-elderly people (RR 0.66, 95% CI 0.52 to 0.85; P = 0.001; absolute numbers not reported) and for older people (RR 0.76, 95% CI 0.64 to 0.90; P = 0.002; absolute numbers not reported), without a statistically significant difference in mortality reduction between the two groups (P = 0.38). [52]

OPTION DIGOXIN

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Digoxin slows the progression of heart failure compared with placebo, but may not reduce mortality.

Benefits and harms

Digoxin versus placebo:

We found one systematic review (search date 2003, 13 RCTs with >7 weeks' follow-up, 7896 people in sinus rhythm). [53]

Mortality

Compared with placebo Digoxin seems no more effective at reducing mortality in people in sinus rhythm (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[53] Systematic review	7756 people 8 RCTs in this analysis	**Rate of mortality** with digoxin	OR 0.98 95% CI 0.89 to 1.09	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	All but 1 of the RCTs included in the review followed up people for 6 months or less	with placebo Absolute results not reported	See further information on studies for separate reporting of data from largest RCT in meta-analysis (6800 people)		

Admission to hospital

Compared with placebo Digoxin seems more effective at reducing all-cause hospital admissions in people receiving ACE inhibitors and diuretics (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission					
[53] Systematic review	7262 people 4 RCTs in this analysis All but 1 of the RCTs included in the review followed up people for 6 months or less	**Proportion of people admitted to hospital for any cause** with digoxin with placebo Absolute results not reported	OR 0.68 95% CI 0.61 to 0.75 See further information on studies for separate reporting of data from largest RCT in meta-analysis (6800 people)	●○○	digoxin

Functional improvement

No data from the following reference on this outcome. [53]

Quality of life

No data from the following reference on this outcome. [53]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Digoxin toxicity					
[54] RCT	6800 people In review [53]	**Proportion of people with digoxin toxicity** 12% with digoxin 8% with placebo Absolute numbers not reported	ARI 4% 95% CI 2% to 6% RR 1.50 95% CI 1.30 to 1.73	●○○	placebo
Cardiac adverse effects					
[54] RCT	6800 people In review [53]	**Proportion of people with ventricular fibrillation or tachycardia** 37/3397 (1.1%) with digoxin 27/3403 (0.8%) with placebo	ARI +0.3% 95% CI –0.1% to +1.0% RR 1.37 95% CI 0.84 to 2.24	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[54] RCT	6800 people In review [53]	**Proportion of people with supraventricular arrhythmia** 3% with digoxin 1% with placebo Absolute numbers not reported	ARI 1.3% 95% CI 0.5% to 2.4% RR 2.08 95% CI 1.44 to 2.99	●●○	placebo
[54] RCT	6800 people In review [53]	**Proportion of people with second- or third-degree atrioventricular block** 1.2% with digoxin 0.4% with placebo Absolute numbers not reported	ARI 0.8% 95% CI 0.2% to 1.8% RR 2.93 95% CI 1.61 to 5.34	●●○	placebo

No data from the following reference on this outcome. [53]

Further information on studies

[53] The largest RCT in the review, which dominated the meta-analysis (6800 people, 88% male, mean age 64 years, New York Heart Association [NYHA] functional class I to III, 94% already taking ACE inhibitors, 82% taking diuretics), compared blinded additional treatment with either digoxin or placebo for a mean of 37 months. [54] It found no significant difference between digoxin and placebo in all-cause mortality (1181/3397 [34.8%] with digoxin *v* 1194/3403 [35.1%] with placebo; ARR +0.3%, 95% CI –2.0% to +2.6%; RR 0.99, 95% CI 0.93 to 1.06). It found that digoxin significantly reduced admission rates for heart failure over 37 months compared with placebo and reduced the combined outcome of death or hospital admission caused by worsening heart failure (heart failure admissions: 910/3397 [27%] with digoxin *v* 1180/3403 [35%] with placebo; ARR 8%, 95% CI 6% to 10%; RR 0.77, 95% CI 0.72 to 0.83; NNT 13, 95% CI 10 to 17; death or hospital admission: 1041/3397 [31%] with digoxin *v* 1291/3403 [38%] with placebo; ARR 7%, 95% CI 5% to 9%; RR 0.81, 95% CI 0.75 to 0.87).

Comment: None.

OPTION POSITIVE INOTROPES OTHER THAN DIGOXIN

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Positive inotropic agents (other than digoxin) may increase mortality and should be used with caution, if at all, in people with systolic heart failure.

Benefits and harms

Positive inotropes (other than digoxin) versus placebo:

We found two systematic reviews [55] [56] and two additional RCTs [57] [58] on inotropic agents. The first systematic review (search date 2000, 21 RCTs, 632 people) assessed the effects of intravenous inotropic agents that act through the adrenergic pathway (beta-agonists and phosphodiesterase inhibitors) in people with heart failure. [55] The review identified 11 RCTs comparing inotropic agents (including dobutamine, dopexamine, toborinone, and milrinone) versus placebo or control. The second review (search date 2004, 21 RCTs, 8408 people) assessed the effects of phosphodiesterase inhibitors. [56]

Mortality

Compared with placebo Positive inotropic drugs other than digoxin (including intravenous inotropes acting through the adrenergic pathway, and phosphodiesterase III inhibitors) seem less effective at reducing mortality at 6 to 11 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[55] Systematic review	Number of people not clear 11 RCTs in this analysis	**Rate of mortality** with intravenous inotropes that act through the adrenergic path-way with placebo or control Absolute results not reported	OR 1.50 95% CI 0.51 to 3.92 See further information on studies for authors' conclusions	⟷	Not significant
[56] Systematic review	8408 people 21 RCTs in this analysis	**Rate of mortality** 897/5138 (17%) with phosphodi-esterase III inhibitors (PDIs) 478/3270 (15%) with placebo or control	RR 1.17 95% CI 1.06 to 1.30 See further information on studies for discussion of effects of PDIs	●○○	placebo or control
[57] RCT	3833 people with heart failure	**Rate of mortality , 9 months** 292/1275 (23%) with vesnarinone (a PDI) 60 mg daily 242/1280 (19%) with placebo	ARI 4% 95% CI 1% to 8% RR 1.21 95% CI 1.04 to 1.40	●○○	placebo
[58] RCT	1906 people with heart failure	**Rate of mortality , 11 months** 232/953 (24%) with ibopamine 193/953 (20%) with placebo	RR 1.26 95% CI 1.04 to 1.53	●○○	placebo

Admission to hospital

No data from the following reference on this outcome. [55] [56] [57] [58]

Functional improvement

No data from the following reference on this outcome. [55] [56] [57] [58]

Quality of life

No data from the following reference on this outcome. [55] [56] [57] [58]

Adverse effects

No data from the following reference on this outcome. [55] [56] [57] [58]

Further information on studies

[55] The authors of the review concluded that "intravenous inotropic agents acting through the adrenergic pathway are often used in people with worsening heart failure to achieve arbitrary haemodynamic targets. Our analyses show that there is very little evidence that such treatment improves symptoms or patient outcomes, and may not be safe". Of the 21 RCTs identified, 16 RCTs (474 people) were acute invasive haemodynamic studies of symptomatically severe heart failure, and 5 RCTs (158 people) were based on intermittent inotropic treatment in an outpatient setting. Included RCTs were often small.

[56] Considering mortality from all causes, the deleterious effects of PDIs were consistent, regardless of the severity of heart failure, use of background treatment, or type of PDI.

Comment: None.

OPTION ALDOSTERONE RECEPTOR ANTAGONISTS

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Aldosterone receptor antagonists (spironolactone, eplerenone, and canrenoate) may reduce all-cause mortality in people with heart failure, but increase the risk of hyperkalaemia.

Benefits and harms

Aldosterone receptor antagonists versus placebo:

We found one systematic review (search date 2008, 19 RCTs, 10,807 people) assessing the effectiveness of aldosterone receptor antagonists (spironolactone, eplerenone, and canrenoate) in people with symptomatic and asymptomatic left ventricular dysfunction, including heart failure and post MI with heart failure. [59] The review did not specify left ventricular ejection fraction (LVEF) for inclusion: two identified RCTs (58 people) recruited people with an LVEF >45%, and 5 RCTs (883 people) did not report LVEF of people included. Of the 19 RCTs identified, 15 RCTs included people with chronic heart failure (3395 people), and 4 RCTs included people who had previous MI and had heart failure (7412 people). Two RCTs (134 people) compared aldosterone receptor antagonists versus usual care rather than versus placebo and one RCT (105 people) assessed an active comparator (metoprolol) plus usual care.

Mortality

Compared with placebo Aldosterone receptor antagonists (spironolactone, eplerenone, and canrenoate) seem more effective at reducing all-cause mortality in people with heart failure and in people with heart failure after an MI (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[59] Systematic review	10,807 people 19 RCTs in this analysis	**Rate of mortality** 804/5565 (14%) with aldosterone receptor antagonists 994/5200 (19%) with control	RR 0.80 95% CI 0.74 to 0.87 The results of the review may not be generalisable to all people with heart failure (see further information on studies for more details)	●○○	aldosterone receptor antagonists
[59] Systematic review	3353 people with heart failure 15 RCTs in this analysis Subgroup analysis Subgroup analysis based on clinical condition	**Rate of mortality** 303/1858 (16%) with aldosterone receptor antagonists 404/1495 (27%) with control	RR 0.75 95% CI 0.67 to 0.84 The results of the review may not be generalisable to all people with heart failure (see further information on studies for more details)	●○○	aldosterone receptor antagonists

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[59] Systematic review	7412 people with heart failure after an MI 4 RCTs in this analysis Subgroup analysis Subgroup analysis based on clinical condition	**Rate of mortality** 501/3707 (14%) with aldosterone receptor antagonists 590/3705 (16%) with control	RR 0.85 95% CI 0.76 to 0.95 The results of the review may not be generalisable to all people with heart failure (see further information on studies for more details)	●○○	aldosterone receptor antagonists

Admission to hospital

Compared with placebo Aldosterone receptor antagonists (spironolactone, eplerenone, and canrenoate) seem more effective at reducing rate of hospital admission in people with heart failure (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission for any cause					
[59] Systematic review	8699 people 9 RCTs in this analysis	**Rate of all-cause hospital re-admission** with aldosterone receptor antagonists with placebo Absolute results not reported	RR 0.77 95% CI 0.68 to 0.87 The results of the review may not be generalisable to all people with heart failure (see further information on studies for more details)	●○○	aldosterone receptor antagonists

Functional improvement

No data from the following reference on this outcome. [59]

Quality of life

No data from the following reference on this outcome. [59]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hyperkalaemia					
[59] Systematic review	10,261 people 17 RCTs in this analysis	**Proportion of people with hyperkalaemia** 315/5314 (6%) with aldosterone receptor antagonists 148/4947 (3%) with control	Significance not assessed The results of the review may not be generalisable to all people with heart failure (see further information on studies for more details)		
Worsening renal failure					
[59] Systematic review	1613 people 11 RCTs in this analysis	**Proportion of people with worsening renal failure** 86/959 (9%) with aldosterone receptor antagonists	Significance not assessed The results of the review may not be generalisable to all people with heart failure (see further in-		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		11/654 (2%) with control	formation on studies for more details)		
Gynaecomastia					
[59] Systematic review	10,213 people 16 RCTs in this analysis	**Proportion of people with gynaecomastia** 88/5291 (2%) with aldosterone receptor antagonists 26/4922 (1%) with control	Significance not assessed The results of the review may not be generalisable to all people with heart failure (see further information on studies for more details)		

Further information on studies

[59] The two largest studies identified by the review (one assessing spironolactone including 1663 people [60] and one assessing eplerenone including 6632 people [61]) included people with only New York Heart Association (NYHA) functional class III or IV; therefore, these results cannot necessarily be generalised to people with milder heart failure. The RCT of eplerenone was limited to people who were post-MI with heart failure and therefore these results cannot necessarily be generalised to people with stable heart failure — that is, those without a recent MI and who have milder symptoms of heart failure. The contribution of these two large RCTs, which represent 76% (8295 people) of the people included in the analysis carried out by the review, should be considered when interpreting the results of the review.

Comment: A population-based time series analysis [62] examined the trends in the rate of spironolactone prescriptions and the rate of hospital admissions for hyperkalaemia in ambulatory patients before and after the publication of an RCT that demonstrated the benefits of spironolactone. [60] The spironolactone prescription rate significantly increased after publication of the RCT (rising from 34/1000 people to 149/1000 people; P <0.001). There was also a significant increase in the rate of hospital admission for hyperkalaemia (from 2.4/1000 people to 11.0/1000 people; P <0.001) and associated mortality (from 0.3/1000 people to 2.0/1000 people; P <0.001). The results of the study are important because they emphasise the need for appropriate monitoring of people treated with spironolactone.

OPTION AMIODARONE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- We don't know whether amiodarone is effective at reducing mortality.

Benefits and harms

Amiodarone versus placebo or conventional care:

We found two systematic reviews comparing amiodarone versus placebo in heart failure. [63] [64] The most recent review (search date 1997, 10 RCTs, 4766 people) included people with a wide range of conditions (symptomatic and asymptomatic heart failure, ventricular arrhythmia, recent MI, and recent cardiac arrest). [63] The earlier systematic review (search date not reported) found 8 RCTs (5101 people after MI) comparing prophylactic amiodarone versus placebo or usual care, and 5 RCTs (1452 people) in people with heart failure. [64]

Mortality

Compared with placebo or conventional treatment Amiodarone may be more effective at 3 to 24 months at reducing all-cause mortality (in people with a wide range of heart conditions such as symptomatic and asymptomatic heart failure, ventricular arrhythmia, recent MI, and recent cardiac arrest) and at reducing arrhythmic death or sudden death (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[63] Systematic review	4525 people 8 RCTs in this analysis	**Rate of mortality , 3 to 24 months** 436/2262 (19%) with amiodarone 507/2263 (22%) with placebo or conventional treatment	ARR 3.0% 95% CI 0.8% to 5.3% RR 0.86 95% CI 0.76 to 0.96	●○○	amiodarone
[64] Systematic review	6553 people 13 RCTs in this analysis	**Rate of annual mortality , mean follow-up of 16 months** 11% with amiodarone 12% with placebo or conventional treatment Absolute numbers not reported	Fixed effects model OR 0.87 95% CI 0.78 to 0.99 Random effects model OR 0.85 95% CI 0.71 to 1.02 The effect of amiodarone was significantly greater in RCTs comparing amiodarone versus usual care than in placebo-controlled RCTs		
[64] Systematic review	6553 people 13 RCTs in this analysis	**Rate of arrhythmic death or sudden death , mean follow-up of 16 months** with amiodarone with placebo or conventional treatment Absolute results not reported	OR 0.71 95% CI 0.59 to 0.85 The effect of amiodarone was significantly greater in RCTs comparing amiodarone versus usual care than in placebo-controlled RCTs	●○○	amiodarone
[64] Systematic review	1452 people with heart failure 5 RCTs in this analysis Subgroup analysis	**Rate of annual mortality , mean follow-up of 16 months** 20% with amiodarone 24% with placebo or conventional treatment Absolute numbers not reported	OR 0.83 95% CI 0.70 to 0.99 The effect of amiodarone was significantly greater in RCTs comparing amiodarone versus usual care than in placebo-controlled RCTs	●○○	amiodarone

Admission to hospital

No data from the following reference on this outcome. [63] [64]

Functional improvement

No data from the following reference on this outcome. [63] [64]

Quality of life

No data from the following reference on this outcome. [63] [64]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal because of adverse effects					
[64] Systematic review	Number of people and RCTs in analysis not clear	**Proportion of people permanently discontinuing study medication, primarily owing to adverse effects , 2 years** 41% with amiodarone 27% with placebo Absolute numbers not reported			
Adverse effects					
[64] Systematic review	Number of people in analysis not clear 10 RCTs in this analysis	**Odds of reporting adverse drug reactions** with amiodarone with placebo Absolute results not reported Nausea was the most common adverse effect	OR 2.22 95% CI 1.83 to 2.68	●●○	placebo
[64] Systematic review	Number of people and RCTs in analysis not clear	**Proportion of people reporting hypothyroidism** 7% with amiodarone 1% with placebo Absolute numbers not reported Hypothyroidism was the most common serious adverse effect			
[64] Systematic review	Number of people and RCTs in analysis not clear	**Proportion of people with hyperthyroidism** 1.4% with amiodarone 0.5% with placebo Absolute numbers not reported			
[64] Systematic review	Number of people and RCTs in analysis not clear	**Proportion of people with peripheral neuropathy** 0.5% with amiodarone 0.2% with placebo Absolute numbers not reported			
[64] Systematic review	Number of people and RCTs in analysis not clear	**Proportion of people with lung infiltrates** 2% with amiodarone 1% with placebo Absolute numbers not reported			
[64] Systematic review	Number of people and RCTs in analysis not clear	**Proportion of people with bradycardia** 2% with amiodarone 1% with placebo Absolute numbers not reported			
[64] Systematic review	Number of people and RCTs in analysis not clear	**Proportion of people with liver dysfunction** 1% with amiodarone 0.4% with placebo Absolute numbers not reported			

No data from the following reference on this outcome. [63]

Further information on studies

Comment: **Clinical guide:**
RCTs of amiodarone versus usual treatment found larger effects than placebo-controlled trials. [64] These findings suggest bias; unblinded follow-up may be associated with reduced usual care or improved adherence with amiodarone. Further studies are required to assess the effects of amiodarone treatment on mortality and morbidity in people with heart failure.

OPTION ANTIARRHYTHMICS OTHER THAN AMIODARONE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Evidence extrapolated from studies in people treated after an MI suggest that other antiarrhythmic drugs (apart from beta-blockers) may be associated with increased mortality in people with heart failure.

Benefits and harms

Antiarrhythmics other than amiodarone:

We found no systematic review or RCTs. Apart from beta-blockers, other antiarrhythmic drugs increase mortality in people at high risk (see class I antiarrhythmic agents [quinidine, procainamide, disopyramide, encainide, flecainide, and moracizine] in review on secondary prevention of ischaemic cardiac events).

Further information on studies

Comment: None.

OPTION ANTICOAGULATION

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- We don't know whether anticoagulants are effective at reducing mortality.

Benefits and harms

Anticoagulation versus placebo or no antithrombotic treatment:

We found one systematic review [65] (search date 2005, 1 RCT [66]), and one subsequent RCT. [67]

Mortality

Warfarin compared with placebo We don't know whether warfarin is more effective at 27 months than no antithrombotic treatment at reducing a combined outcome of death, MI, and stroke (very-low quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death, MI, or stroke					
[66] RCT **3-armed trial**	279 people, 70% with New York Heart Association (NYHA) functional class III In review [65] The third arm assessed the effects of aspirin (300 mg/day)	**Rate of combined outcome of death, MI, and stroke , mean follow-up of 27 months** 26% with warfarin (international normalised ratio [INR] 2.5) 27% with no antithrombotic treatment Absolute numbers not reported	Reported as not significant (warfarin *v* no antithrombotic treatment) P value not reported	⟷	Not significant
[67] RCT	197 people aged 20 to 75 years with NYHA class II to IV caused by either previous MI or idiopathic dilated cardiomyopathy Those with cardiomyopathy (82 people) were randomised to warfarin or placebo	**Incidence of primary outcome (composite of non-fatal stroke, peripheral or pulmonary embolism, MI, hospital admission, exacerbation of heart failure, or death from any cause) , mean follow-up of 27 months** 8.9/100 patient-years with warfarin 14.8/100 patient-years with placebo	Significance not assessed		

Admission to hospital

No data from the following reference on this outcome. [65] [66] [67]

Functional improvement

No data from the following reference on this outcome. [65] [66] [67]

Quality of life

No data from the following reference on this outcome. [65] [66] [67]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Haemorrhagic events					
[66] RCT **3-armed trial**	279 people, 70% with New York Heart Association (NYHA) functional class III In review [65] The third arm assessed the effects	**Rate of haemorrhagic events , mean follow-up of 27 months** with warfarin (international normalised ratio [INR] 2.5) with no antithrombotic treatment The RCT found 4 haemorrhagic events with warfarin and none with no antithrombotic treatment			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	of aspirin (300 mg/day)	(total number of people in each group not reported)			
[67] RCT	197 people aged 20 to 75 years with NYHA class II to IV caused by either previous MI or idiopathic dilated cardiomyopathy Those with cardiomyopathy (82 people) were randomised to warfarin or placebo	**Haemorrhagic event rate , mean follow-up of 27 months** 4.6/100 patient-years with warfarin 0/100 patient-years with placebo	Significance not assessed		

Anticoagulation versus antiplatelet agents:
See option on antiplatelet agents, p 48 .

Further information on studies

Comment:

The systematic review (search date 2005) [65] found three additional non-randomised trials. Meta-analysis of these trials and the RCT [66] found that anticoagulant significantly reduced death from all causes and cardiovascular event rates compared with control (death from all causes: 1087 people; OR 0.64, 95% CI 0.45 to 0.90; cardiovascular event rates: 1130 people; OR 0.26, 95% CI 0.16 to 0.43). [65] Meta-analysis of two non-randomised trials (645 people) found no significant difference in bleeding complications between warfarin and no warfarin (OR 1.52, 95% CI 0.56 to 4.10). The non-randomised controlled studies were performed in the early 1950s in hospitalised people with a high prevalence of rheumatic heart disease and atrial fibrillation, and the methods used may be considered unreliable today.

One retrospective analysis assessed the effect of anticoagulants used at the discretion of individual investigators in RCTs on the incidence of stroke, peripheral arterial embolism, and pulmonary embolism. [68] The first cohort was from one RCT (642 men with chronic heart failure) comparing hydralazine plus isosorbide dinitrate versus prazosin versus placebo. The second cohort was from another RCT (804 men with chronic heart failure) comparing enalapril versus hydralazine plus isosorbide dinitrate. All people were given digoxin and diuretics. The retrospective analysis found that, without treatment, the incidence of all thromboembolic events was low (2.7/100 patient-years in the first RCT; 2.1/100 patient-years in the second RCT) and that anticoagulation did not reduce the incidence of thromboembolic events (2.9/100 patient-years in the first RCT; 4.8/100 patient-years in the second RCT). In this group, atrial fibrillation was not associated with a higher risk of thromboembolic events.

A second retrospective analysis was from two large RCTs (2569 people with symptomatic and asymptomatic left ventricular dysfunction) comparing enalapril versus placebo. [69] The analysis found that people treated with warfarin at baseline had a significantly lower risk of death during follow-up (HR adjusted for baseline differences 0.76, 95% CI 0.65 to 0.89). Warfarin use was associated with a reduction in the combined outcome of death plus hospital admission for heart failure (adjusted HR 0.82, 95% CI 0.72 to 0.93). The benefit with warfarin use was not significantly influenced by the presence of symptoms, randomisation to enalapril or placebo, sex, presence of atrial fibrillation, age, ejection fraction, NYHA functional class, or cause of heart failure. Warfarin reduced cardiac mortality, specifically deaths that were sudden or associated with either heart failure or MI.

Neither of the retrospective studies was designed to determine the incidence of thromboembolic events in heart failure or the effects of treatment. Neither study included information about the intensity of anticoagulation or warfarin use. We found several additional cohort studies showing a reduction in thromboembolic events with anticoagulation, but they all reported on too few people to provide useful results. The two RCTs are of inadequate size to definitively conclude whether anticoagulation is of benefit in people with heart failure who are in sinus rhythm. [66] [67]

An RCT is still needed to compare anticoagulation versus no anticoagulation in people with heart failure.

OPTION ANTIPLATELET AGENTS

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- We don't know whether antiplatelets are effective at reducing mortality or hospital re-admission rates.

Benefits and harms

Antiplatelet agents versus no treatment:

We found two systematic reviews (search dates 2005), [65] [70] both of which identified the same three-arm RCT. [66]

Mortality

Aspirin compared with no treatment We don't know whether aspirin is more effective at 27 months than no antithrombotic treatment at reducing the combined outcome of death, MI, and stroke (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death, MI, and stroke					
[66] RCT **3-armed trial**	279 people, 70% with New York Heart Association (NYHA) functional class III In review [65] [70] The third arm assessed the effects of warfarin	**Rate of combined outcome of death, MI, and stroke , mean follow-up of 27 months** 29/91 (32%) with aspirin (300 mg/day) 26/99 (27%) with no antithrombotic treatment	Reported as not significant (aspirin *v* no antithrombotic treatment) P value not reported	⟷	Not significant

Admission to hospital

Aspirin compared with no treatment Aspirin may be less effective at reducing all-cause hospital re-admission rates at 27 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause hospital admissions					
[66] RCT **3-armed trial**	279 people, 70% with New York Heart Association (NYHA) functional class III In review [65] [70] The third arm assessed the effects of warfarin	**Rate of all-cause hospital admissions , mean follow-up of 27 months** with aspirin (300 mg/day) with no antithrombotic treatment Absolute results not reported	P <0.05 (aspirin *v* no antithrombotic treatment)	○○○	no antithrombotic treatment

Functional improvement

No data from the following reference on this outcome. [66]

Quality of life

No data from the following reference on this outcome. [66]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Haemorrhagic events					
[66] RCT **3-armed trial**	279 people, 70% with New York Heart Association (NYHA) functional class III In review [65] [70] The third arm assessed the effects of warfarin	**Rate of haemorrhagic events , mean follow-up of 27 months** with aspirin (300 mg/day) with no antithrombotic treatment Absolute results not reported The RCT reported 5 haemorrhagic events with aspirin and none with no antithrombotic treatment (total number of people in each group not reported)	Significance not assessed		
Serious adverse effects (unspecified)					
[70] Systematic review **3-armed trial**	279 people, 70% with NYHA functional class III Data from 1 RCT	**Total number of serious adverse effects** 198 with aspirin 163 with warfarin 178 with no antithrombotic treatment	P = 0.08 (among group difference)		

No data from the following reference on this outcome. [65]

Antiplatelet agents versus warfarin:

We found two RCTs comparing aspirin versus warfarin, [66] [67] and one RCT comparing aspirin versus clopidogrel versus warfarin. [71]

Mortality

Antiplatelet agents compared with warfarin We don't know whether antiplatelet agents (aspirin and clopidogrel) are more effective than warfarin at reducing mortality at 21 months or composite outcomes that include mortality (other outcomes in composite include MI, stroke, exacerbation of heart failure, and peripheral or pulmonary embolism) (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[71] RCT **3-armed trial**	1587 people with New York Heart Association (NYHA) class II to IV The third arm assessed the effects of clopidogrel	**Rate of mortality , median follow-up of 21 months** 94/523 (19%) with aspirin 92/540 (17%) with warfarin 1063 people in this analysis All-cause mortality was a secondary outcome: the primary	HR 0.98 (warfarin *v* aspirin) 95% CI 0.85 to 1.13 P = 0.75 The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		outcome assessed was a composite of death, non-fatal MI, or non-fatal stroke (see further information on studies for data on composite outcome)	may have been underpowered to detect a clinically important difference Results should be interpreted with caution		
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of aspirin	**Rate of mortality , median follow-up of 21 months** 96/524 (18%) with clopidogrel 92/540 (17%) with warfarin 1064 people in this analysis All-cause mortality was a secondary outcome: the primary outcome assessed was a composite of death, non-fatal MI, or non-fatal stroke (see further information on studies for data on composite outcome)	HR 0.92 (warfarin *v* clopidogrel) 95% CI 0.69 to 1.23 P = 0.58 The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and may have been underpowered to detect a clinically important difference Results should be interpreted with caution	⟷	Not significant
Death, MI, and stroke					
[66] RCT **3-armed trial**	279 people, 70% with NYHA functional class III The third arm assessed the effects of no antithrombotic treatment	**Rate of combined outcome of death, MI, and stroke , mean follow-up of 27 months** 29/91 (32%) with aspirin (300 mg/day) 23/89 (26%) with warfarin	Reported as not significant (aspirin *v* warfarin) P value not reported	⟷	Not significant
Composite outcome including all-cause mortality					
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of clopidogrel	**Rate of composite outcome of death, non-fatal MI, or non-fatal stroke** 108/523 (21%) with aspirin 106/540 (20%) with warfarin	HR (warfarin *v* aspirin) 0.98 95% CI 0.86 to 1.12 P = 0.77	⟷	Not significant
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of aspirin	**Rate of composite outcome of death, non-fatal MI, or non-fatal stroke** 113/524 (22%) with clopidogrel 106/540 (20%) with warfarin	HR (warfarin *v* clopidogrel) 0.89 95% CI 0.68 to 1.16 P = 0.39	⟷	Not significant
[67] RCT	197 people aged 20 to 75 years with NYHA class II to IV caused by either previous MI or idiopathic dilated cardiomyopathy Those with previous MI (115 people) were randomised to either aspirin or warfarin	**Time to the primary combined outcome of non-fatal stroke, peripheral or pulmonary embolism, MI, hospital admission, exacerbation of heart failure, or death from any cause** 14.9/100 patient-years with aspirin 15.7/100 patient-years with warfarin	Significance not assessed		

Admission to hospital

Antiplatelet agents compared with warfarin Aspirin may be less effective at reducing all-cause hospital re-admission rates at 21 to 27 months, but we don't know whether clopidogrel is more effective than warfarin at reducing all-cause hospital re-admission rates at 21 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause hospital admissions					
[66] RCT **3-armed trial**	279 people, 70% with New York Heart Association (NYHA) functional class III The third arm assessed the effects of no antithrombotic treatment	**Rate of all-cause hospital admissions , mean follow-up of 27 months** with aspirin (300 mg/day) with warfarin Absolute results not reported	P <0.05 (aspirin *v* warfarin)	○○○	warfarin
Admission to hospital for heart failure-specific causes					
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of clopidogrel	**Proportion of people admitted to hospital with worsening heart failure , median follow-up of 21 months** 116/523 (22%) with aspirin 89/540 (16%) with warfarin 1063 people in this analysis Hospital admission for worsening heart failure was a secondary outcome: the primary outcome assessed was a composite of death, non-fatal MI, or non-fatal stroke (see further information on studies for data on composite outcome)	P <0.02 (aspirin *v* warfarin) The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and may have been underpowered to detect a clinically important difference Results should be interpreted with caution	○○○	warfarin
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of aspirin	**Proportion of people admitted to hospital with worsening heart failure , median follow-up of 21 months** 97/524 (19%) with clopidogrel 89/540 (16%) with warfarin 1064 people in this analysis Hospital admission for worsening heart failure was a secondary outcome: the primary outcome assessed was a composite of death, non-fatal MI, or non-fatal stroke (see further information on studies for data on composite outcome)	P = 0.38 (clopidogrel *v* warfarin) The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and may have been underpowered to detect a clinically important difference Results should be interpreted with caution	⟷	Not significant

No data from the following reference on this outcome. [67]

Functional improvement

No data from the following reference on this outcome. [66] [67] [71]

Quality of life

No data from the following reference on this outcome. [66] [67] [71]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Haemorrhagic events					
[66] RCT **3-armed trial**	279 people, 70% with New York Heart Association (NYHA) functional class III In review [65] [70] The third arm assessed the effects of no antithrombotic treatment	**Rate of haemorrhagic events , mean follow-up of 27 months** with aspirin (300 mg/day) with warfarin Absolute results not reported The first RCT reported 5 haemorrhagic events with aspirin compared with 4 with warfarin (total number of people in each group not reported)	Significance not assessed		
[67] RCT	197 people age 20 to 75 years with NYHA class II to IV caused by either previous MI or idiopathic dilated cardiomyopathy Those with previous MI (115 people) were randomised to either aspirin or warfarin	**Haemorrhagic event rate** 0/100 patient-years with aspirin 4.6/100 patient-years with warfarin	Significance not assessed		
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of clopidogrel	**Proportion of people with major haemorrhage , median follow-up of 21 months** 19/523 (4%) with aspirin 28/540 (5%) with warfarin 1063 people in this analysis	P = 0.2184 (aspirin *v* warfarin) The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and may have been underpowered to detect a clinically important difference Results should be interpreted with caution	⟷	Not significant
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of clopidogrel	**Proportion of people with minor bleed , median follow-up of 21 months** 123/523 (24%) with aspirin 155/540 (29%) with warfarin 1063 people in this analysis	P = 0.0544 (aspirin *v* warfarin) The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and may have been underpowered to detect a clinically important difference Results should be interpreted with caution	⟷	Not significant
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of aspirin	**Proportion of people with major haemorrhage , median follow-up of 21 months** 11/524 (2%) with clopidogrel 28/540 (5%) with warfarin 1064 people in this analysis	P <0.01 (clopidogrel *v* warfarin) The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and may have been underpowered to detect a clinically important difference Results should be interpreted with caution	○○○	clopidogrel

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[71] RCT **3-armed trial**	1587 people with NYHA class II to IV The third arm assessed the effects of aspirin	**Proportion of people with minor bleed , median follow-up of 21 months** 119/524 (23%) with clopidogrel 155/540 (29%) with warfarin 1064 people in this analysis	P = 0.0254 (clopidogrel *v* warfarin) The RCT was terminated early because of slow enrolment (1587 people randomised rather than the planned 4500 people) and may have been underpowered to detect a clinically important difference Results should be interpreted with caution	○○○	clopidogrel

Further information on studies

Comment:

In people not taking ACE inhibitors:
We found no systematic review or RCTs. We found one retrospective cohort analysis within one RCT in 642 men with heart failure. [68] The RCT compared hydralazine plus isosorbide dinitrate versus prazosin versus placebo in men receiving digoxin and diuretics. Aspirin or dipyridamole, or both, were used at the discretion of the investigators. The number of thromboembolic events was low in both groups (1 stroke, and 0 peripheral and 0 pulmonary emboli in 184 person-years of treatment with antiplatelet agents *v* 21 strokes, and 4 peripheral and 4 pulmonary emboli in 1068 person-years of treatment without antiplatelet agents; 0.5 events/100 person-years with antiplatelet agents *v* 2.0 events/100 person-years without antiplatelet agents; P = 0.07).

In people taking ACE inhibitors:
We found no RCTs. We found two large retrospective cohort studies. [68] [72] The first retrospective analysis assessed the effect of antiplatelet agents used at the discretion of individual investigators on the incidence of stroke, peripheral arterial embolism, and pulmonary embolism within one RCT. [68] The RCT (804 men with chronic heart failure) compared enalapril versus hydralazine plus isosorbide dinitrate. It found that the incidence of all thromboembolic events was low without antiplatelet treatment and found no significant difference between groups (1.6 events/100 person-years with antiplatelet treatment *v* 2.1 events/100 person-years with no antiplatelet treatment; P = 0.48).

The second cohort analysis was from two large RCTs comparing enalapril versus placebo (2569 people with symptomatic and asymptomatic left ventricular dysfunction). It found that people treated with antiplatelet agents at baseline had a significantly lower risk of death (HR adjusted for baseline differences 0.82, 95% CI 0.73 to 0.92). [72] Subgroup analysis suggested that antiplatelet agents might have an effect in people randomised to placebo (mortality HR [for antiplatelet treatment at baseline *v* no antiplatelet treatment at baseline] 0.68, 95% CI 0.58 to 0.80), but not in people randomised to enalapril (mortality HR [for antiplatelet treatment *v* no antiplatelet treatment] 1.00, 95% CI 0.85 to 1.17). Both retrospective studies have important limitations common to studies with a retrospective cohort design. One study did not report on the proportions of people taking aspirin and other antiplatelet agents. [68] The other study noted that >95% of people took aspirin, but the dose and consistency of antiplatelet use was not recorded. [72] One retrospective non-systematic review (4 RCTs, 96,712 people) provided additional evidence about the effect of aspirin on the benefits of early ACE inhibitors in heart failure. [73] It found a similar reduction in 30-day mortality with ACE inhibitors versus control for those people not taking aspirin compared with those taking aspirin (aspirin: OR 0.94, 95% CI 0.89 to 0.99; no aspirin: OR 0.90, 95% CI 0.81 to 1.01). However, the analysis may not be valid because the people who did not receive aspirin were older and had a worse baseline prognosis than those taking aspirin. The effects of antiplatelet treatment in combination with ACE inhibitors in people with heart failure require further research.

OPTION CALCIUM CHANNEL BLOCKERS

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .

- Calcium channel blockers may increase mortality and should be used with caution, if at all, in people with systolic heart failure.
- Calcium channel blockers have been found to exacerbate symptoms of heart failure and increase mortality after MI in people who also have pulmonary congestion or left ventricular dysfunction.

Benefits and harms

Calcium channel blockers (for heart failure other than MI) versus placebo:

We found one systematic review (search date not reported, 18 RCTs, 3128 people with moderate to advanced heart failure for >2 months) of second-generation dihydropyridine calcium channel blockers, [74] one non-systematic review of all calcium channel blockers (3 RCTs, 1790 people with heart failure), [75] and one subsequent RCT. [76] For effects of calcium channel blockers after MI, see calcium channel blockers in review on myocardial infarction (ST-elevation).

Mortality

Compared with placebo Calcium channel blockers may be no more effective at reducing mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[74] Systematic review	1603 people 2 RCTs in this analysis	**Risk of mortality** with dihydropyridine calcium channel blockers with placebo Absolute results not reported	OR 0.94 95% CI 0.79 to 1.12	⟷	Not significant
[77] RCT	421 people with primary cardiomyopathy In review [75] Subgroup analysis This RCT was the largest RCT in the non-systematic review	**Rate of mortality , 14 months** 45/209 (22%) with amlodipine 74/212 (35%) with placebo	ARR 13% 95% CI 5% to 20% RR 0.62 95% CI 0.43 to 0.85	●○○	amlodipine
[77] RCT	People with heart failure caused by coronary artery disease (number of people not clear) In review [75] Subgroup analysis This RCT was the largest RCT in the non-systematic review	**Rate of mortality , 14 months** with amlodipine with placebo Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[76] RCT	2590 people with New York Heart Association (NYHA) functional class II to IV heart failure	**Rate of mortality** 350/1295 (27%) with mibefradil 319/1295 (25%) with placebo Mean follow-up of 1.5 years with mibefradil and 1.6 years with placebo	RR 1.10 95% CI 0.96 to 1.25	⟷	Not significant

Admission to hospital

Compared with placebo Calcium channel blockers seem no more effective at reducing the composite outcome of all-cause mortality and hospital admission for cardiovascular events (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death or hospital admission					
[77] RCT	1153 people with New York Heart Association (NYHA) functional class III or IV, left ventricular ejection fraction (LVEF) <0.30, using diuretics, digoxin, and ACE inhibitors In review [75] This RCT was the largest RCT in the non-systematic review	**Proportion of people with combined end point of all-cause mortality and hospital admission for cardiovascular events , 14 months** 222/571 (39%) with amlodipine 246/582 (42%) with placebo	ARR +3.4% 95% CI –2.3% to +8.8% RR 0.92 95% CI 0.79 to 1.06	⟷	Not significant
[75] Systematic review	186 people, idiopathic dilated cardiomyopathy, NYHA functional class I to III Data from 1 RCT	**Transplant-fee listing survival** with diltiazem with placebo Absolute results not reported The review found no evidence of a difference in survival between diltiazem and placebo in people who did not have a heart transplant, although people on diltiazem had improved cardiac function, exercise capacity, and subjective quality of life	Significance not assessed		
[75] Systematic review	451 people with mild heart failure, NYHA functional class II or III Data from 1 RCT	**Mortality** with felodipine with placebo Absolute results not reported The review reported that mortality for felodipine did not differ from that for placebo	Significance not assessed		

No data from the following reference on this outcome. [74] [76]

Functional improvement

No data from the following reference on this outcome. [74] [76] [77]

Quality of life

No data from the following reference on this outcome. [74] [76] [77]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[74] Systematic review		**Adverse effects** with dihydropyridine calcium channel blockers with placebo The review found that second-generation dihydropyridine calcium channel blockers did not cause significant adverse effects			
[75] Systematic review		**Adverse effects** with diltiazem with placebo Calcium channel blockers have been found to exacerbate symptoms of heart failure or increase mortality after MI in people who also have pulmonary congestion or left ventricular dysfunction (see calcium channel blockers in review on myocardial infarction [ST-elevation])			
[76] RCT	2590 people with New York Heart Association (NYHA) functional class II to IV heart failure	**Rate of mortality in people taking digoxin, class I or II antiarrhythmics, amiodarone, or drugs associated with torsade de pointes** with mibefradil with placebo Absolute results reported graphically Mean follow-up of 1.5 years with mibefradil and 1.6 years with placebo The RCT found that mibefradil significantly increased the risk of death in people taking digoxin, class I or II antiarrhythmics, amiodarone, or drugs associated with torsade de pointes compared with placebo	Reported as significant P value not reported	○○○	placebo

Further information on studies

Comment: Many of the RCTs were underpowered and had wide confidence intervals. One RCT of amlodipine in people with primary dilated cardiomyopathy is in progress.

OPTION HYDRALAZINE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Hydralazine plus isosorbide dinitrate may improve survival and quality-of-life scores compared with placebo in people with chronic congestive heart failure.

- We found no direct information from RCTs about the effects of hydralazine alone in the treatment of people with heart failure.

Benefits and harms

Hydralazine versus placebo:

We found no systematic review or RCTs.

Hydralazine plus isosorbide dinitrate versus placebo:

We found no systematic review but found two RCTs. [78] [79]

Mortality

Compared with placebo Hydralazine plus isosorbide dinitrate may be more effective at reducing cumulative mortality at 2 years and at reducing all-cause mortality at 6 months in people with heart failure also receiving standard treatment (very-low quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[78] RCT **3-armed trial**	642 men aged 18 to 75 years with stable chronic congestive heart failure (all participants were already receiving diuretics and digoxin) The third arm assessed the effects of prazosin	**Rate of cumulative mortality , 2 years** 78/186 (42%) with hydralazine plus isosorbide dinitrate 139/273 (51%) with placebo	Estimated cumulative reduction in mortality risk 34% (hydralazine plus isosorbide dinitrate *v* placebo) 95% CI 4% to 54% P <0.03 (hydralazine plus isosorbide dinitrate *v* placebo)	○○○	hydralazine plus isosorbide dinitrate
[79] RCT	1050 African-Americans with New York Heart Association (NYHA) class III or IV heart failure with dilated ventricles Before the start of the RCT, people were required to have been receiving standard treatment, as determined to be appropriate by their physician. This included diuretics, ACE inhibitors, angiotensin receptor blockers, beta-blockers, digoxin, and spironolactone	**Rate of mortality , 6 months** 6% with hydralazine plus isosorbide dinitrate 10% with placebo Absolute numbers not reported Mortality was a secondary outcome: primary end point was a composite score made up of weighted values for mortality from any cause, a first hospital admission for heart failure within 18 months, and change in quality of life at 6 months (see further information on studies for these data)	P = 0.02 The RCT was terminated early (after 10 months instead of 18 months) because mortality was higher with placebo	○○○	hydralazine plus isosorbide dinitrate

Quality of life

Compared with placebo Hydralazine plus isosorbide dinitrate may be more effective at 6 months at improving quality of life in people with heart failure also receiving standard treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[79] RCT	1050 African-Americans with New York Heart Association (NYHA) class III or IV heart failure with dilated ventricles Before the start of the RCT, people were required to have been receiving standard treatment, as determined to be appropriate by their physician. This included diuretics, ACE inhibitors, angiotensin receptor blockers, beta-blockers, digoxin, and spironolactone	**Quality-of-life score (measured on a scale where lower scores indicate better quality of life) , 6 months** –5.6 with hydralazine plus isosorbide dinitrate –2.7 with placebo Quality of life was a secondary outcome: primary end point was a composite score made up of weighted values for mortality from any cause, a first hospital admission for heart failure within 18 months, and change in quality of life at 6 months (see further information on studies for these data)	P = 0.02 (hydralazine plus isosorbide dinitrate *v* placebo) The RCT was terminated early (after 10 months instead of 18 months) because mortality was higher with placebo	○○○	hydralazine plus isosorbide dinitrate

No data from the following reference on this outcome. [78]

Admission to hospital

No data from the following reference on this outcome. [78] [79]

Functional improvement

No data from the following reference on this outcome. [78] [79]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache					
[78] RCT **3-armed trial**	642 men aged 18 to 75 years with stable chronic congestive heart failure (all participants were already receiving diuretics and digoxin) The third arm assessed the effects of prazosin	**Proportion of people with headache** 23/186 (12%) with hydralazine plus isosorbide dinitrate 1/273 (0.4%) with placebo Headache was one of the most common adverse effects leading to discontinuation of treatment	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[79] RCT	1050 African-Americans with New York Heart Association (NYHA) class III or IV heart failure with dilated ventricles Before the start of the RCT, people were required to have been receiving standard treatment, as determined to be appropriate by their physician. This included diuretics, ACE inhibitors, angiotensin receptor blockers, beta-blockers, digoxin, and spironolactone	**Proportion of people with headache , 6 months** 48% with hydralazine plus isosorbide dinitrate 19% with placebo Absolute numbers not reported	P <0.001 The RCT was terminated early (after 10 months instead of 18 months) because mortality was higher with placebo	○○○	placebo
Dizziness					
[78] RCT **3-armed trial**	642 men aged 18 to 75 years with stable chronic congestive heart failure (all participants were already receiving diuretics and digoxin) The third arm assessed the effects of prazosin	**Proportion of people with dizziness** 12/186 (6%) with hydralazine plus isosorbide dinitrate 5/273 (2%) with placebo Dizziness was one of the most common adverse effects leading to discontinuation of treatment	Significance not assessed		
[79] RCT	1050 African-Americans with NYHA class III or IV heart failure with dilated ventricles Before the start of the RCT, people were required to have been receiving standard treatment, as determined to be appropriate by their physician. This included diuretics, ACE inhibitors, angiotensin receptor blockers, beta-blockers, digoxin, and spironolactone	**Proportion of people with dizziness , 6 months** 29% with hydralazine plus isosorbide dinitrate 12% with placebo Absolute numbers not reported	P <0.001 The RCT was terminated early (after 10 months instead of 18 months) because mortality was higher with placebo	○○○	placebo

Further information on studies

[79] The primary end point was a composite score made up of weighted values for mortality from any cause, a first hospital admission for heart failure within 18 months, and change in quality of life at 6 months. The score could range from –6 to +2 with higher scores indicating improved outcomes. The RCT found that hydralazine plus isosorbide dinitrate significantly improved the composite end point compared with placebo (–0.1 with hydralazine-isosorbide dinitrate *v* –0.5 with placebo; P = 0.01).

Comment:

Clinical guide:

One systematic review has highlighted the potential risk of developing hydralazine-induced systemic lupus erythematous (SLE). [80] Although the risk is small because of lower doses used, people taking hydralazine should be monitored at each visit for signs and symptoms of SLE. A baseline antinuclear antibody (ANA) level should be determined before initiating hydralazine. However, it is not recommended to regularly check ANA levels. If any symptoms or signs of SLE develop, hydralazine treatment should be discontinued immediately because complications from the syndrome can be potentially fatal. [80]

Hydralazine plus isosorbide dinitrate could be used in combination with other medications for heart failure and in people intolerant to ACE inhibitors or angiotensin receptor blockers. The combination of hydralazine and isosorbide dinitrate would not be considered first-line treatment for heart failure.

QUESTION What are the effects of devices for treatment of heart failure?

OPTION IMPLANTABLE CARDIAC DEFIBRILLATORS

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Implantable cardiac defibrillators can reduce mortality in people with heart failure who are at high risk of ventricular arrhythmias.
- People with an implantable cardiac defibrillator are at risk of shocks from the device.

Benefits and harms

Implantable cardiac defibrillators versus usual care:

We found three systematic reviews. [81] [82] [83] The first systematic review (search date 2002, 8 RCTs, 4909 people at risk for sudden cardiac death or ventricular arrhythmia) compared implantable cardiac defibrillator (ICD) treatment versus usual care in the primary prevention (people at risk for sudden cardiac death or ventricular arrhythmia who had evidence of heart failure or coronary artery disease) or secondary prevention population (people who had survived sudden cardiac death or had unstable ventricular rhythm) of life-threatening arrhythmias and sudden cardiac death. [81] The second systematic review (search date 2004, 7 RCTs, 2110 people) compared ICD treatment versus usual care in people with heart failure caused by non-ischaemic cardiomyopathy, and analysed results separately for primary and secondary prevention RCTs. [82] The third systematic review (search date 2008, 5 RCTs, all included in the previous reviews) performed a subgroup analysis of women from the trials comparing ICD versus usual care (934 women with heart failure and reduced left ejection fraction). [83]

Mortality

Compared with usual care Implantable cardiac defibrillators seem more effective at reducing all-cause mortality and sudden cardiac death in people with heart failure when both men and women are analysed together. However, when women with heart failure are analysed alone, effects on mortality in this subgroup are unclear (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[81] Systematic review	4909 people 8 RCTs in this analysis	**Rate of mortality** 459/2428 (19%) with implantable cardiac defibrillator (ICD) 695/2481 (28%) with usual care	RR 0.74 95% CI 0.67 to 0.82	●○○	ICD
[81] Systematic review	2946 people with evidence of heart failure or coronary artery disease (primary prevention) 5 RCTs in this analysis	**Rate of mortality** 260/1494 (17%) with ICD 391/1452 (27%) with usual care	RR 0.72 95% CI 0.63 to 0.84 The magnitude of absolute-mortality benefit increased with increasing baseline risk of sudden cardiac death There was significant heterogeneity among RCTs because 3 RCTs were in people at high risk of heart failure and 2 RCTs were in	●○○	ICD

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
			people at moderate risk of heart failure		
[81] Systematic review	1963 people who had survived sudden cardiac death or had unstable ventricular rhythm (secondary prevention) 3 RCTs in this analysis	**Rate of mortality** 199/934 (21%) with ICD 304/1029 (30%) with usual care	RR 0.76 95% CI 0.65 to 0.89	●○○	ICD
[82] Systematic review	2110 people with heart failure caused by non-ischaemic cardiomyopathy 7 RCTs in this analysis	**Rate of mortality** with ICD with usual care Absolute results not reported	RR 0.69 95% CI 0.56 to 0.86	●○○	ICD
[82] Systematic review	1457 people with heart failure caused by non-ischaemic cardiomyopathy (primary prevention) 4 RCTs in this analysis	**Rate of mortality** with ICD with usual care Absolute results not reported	RR 0.74 95% CI 0.58 to 0.96	●○○	ICD
[82] Systematic review	256 people with previous resuscitated cardiac arrest or symptomatic ventricular tachycardia (secondary prevention) 2 RCTs in this analysis	**Rate of mortality** with ICD with usual care Absolute results not reported	RR 0.69 95% CI 0.39 to 1.24 The number analysed may have been too small to detect a significant difference	⟷	Not significant
[83] Systematic review	934 women with heart failure and reduced left ventricular ejection fraction 5 RCTs in this analysis	**Mortality** with ICD with usual care Absolute results reported graphically	HR 1.01 95% CI 0.76 to 1.33 P = 0.95	⟷	Not significant
Cardiac mortality					
[81] Systematic review	4909 people 8 RCTs in this analysis	**Rate of cardiac mortality** 124/2428 (5%) with ICD 339/2481 (14%) with usual care	RR 0.43 95% CI 0.35 to 0.53	●●○	ICD
[81] Systematic review	2946 people with evidence of heart failure or coronary artery disease (primary prevention) 5 RCTs in this analysis	**Rate of cardiac mortality** 57/1494 (4%) with ICD 177/1452 (12%) with usual care	RR 0.37 95% CI 0.27 to 0.50 The magnitude of absolute-mortality benefit increased with increasing baseline risk of sudden cardiac death There was significant heterogeneity among RCTs because 3 RCTs were in people at high risk of heart failure and 2 RCTs were in people at moderate risk of heart failure	●●○	ICD

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[81] Systematic review	1963 people who had survived sudden cardiac death or had unstable ventricular rhythm (secondary prevention) 3 RCTs in this analysis	**Rate of cardiac mortality** 67/934 (7%) with ICD 162/1029 (16%) with usual care	RR 0.50 95% CI 0.38 to 0.66	●●○	ICD

Admission to hospital

No data from the following reference on this outcome. [81] [82] [83]

Functional improvement

No data from the following reference on this outcome. [81] [82] [83]

Quality of life

No data from the following reference on this outcome. [81] [82] [83]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[81] Systematic review		**Adverse effects** with implantable cardiac defibrillator (ICD) with usual care Absolute results not reported The review found that complications associated with ICD treatment included perioperative infection (range 0.7–12.3%), lead fracture or device malfunction (range 0.8–14%), serious bleeding (range 1–6%), and pneumothorax (<1%)			

No data from the following reference on this outcome. [82] [83]

ICDs plus cardiac resynchronisation therapy versus usual care:
See option on cardiac resynchronisation therapy, p 63 .

ICDs plus cardiac resynchronisation therapy versus either device alone:
See option on cardiac resynchronisation therapy, p 63 .

Further information on studies

Comment:

Clinical guide:
The systematic reviews suggest that ICDs are more beneficial than drug treatment for secondary prevention of sudden cardiac death, and for primary prevention in certain high-risk groups. [81] [82] The third review [83] would suggest that women may not derive the same benefit from ICD treatment as do men. The decreased overall rate of sudden cardiac death with an increased rate of other competing causes of death leads to a smaller net benefit from ICDs in women with advanced heart failure and reduced left ventricular ejection fraction. There have been <1000 women studied in RCTs of ICD treatment and based on the event rate for women in these studies, >4000 women would need to be randomised to ICD or placebo to more definitively assess the benefit of ICD treatment. ICD treatment is expensive and must be used appropriately in people in whom indications for treatment clearly exist. Further research is required to develop accurate risk-stratification tools, to determine the impact of ICD treatment in different subgroups of people, and to evaluate quality-of-life issues.

People with ICDs are at risk of shocks from the device and this can adversely affect quality of life. An RCT has demonstrated that a combination of amiodarone plus a beta-blocker may be better to reduce the risk of shock compared with either sotalol (HR 0.43, 95% CI 0.22 to 0.85; P = 0.02) or beta-blocker alone (HR 0.27, 95% CI 0.14 to 0.52; P <0.001). [84] There was a trend for sotalol to reduce shocks compared with beta-blockers alone (HR 0.61, 95% CI 0.37 to 1.01; P = 0.05). There was a slightly greater incidence of adverse pulmonary and thyroid events, and of symptomatic bradycardia in people receiving amiodarone. As people with an ICD require some form of treatment to reduce the potential for shocks, therapeutic decisions should be individualised. The type of treatment used must take into consideration the possible improvements in quality of life, and small but increased risks of drug-related adverse effects.

OPTION CARDIAC RESYNCHRONISATION THERAPY

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Cardiac resynchronisation therapy can reduce mortality in people with heart failure who are at high risk of ventricular arrhythmias.
- However, studies evaluating cardiac resynchronisation therapy were performed in centres with considerable experience, which may have overestimated the benefits.

Benefits and harms

Cardiac resynchronisation therapy (CRT) alone versus usual care/control:

We found 4 systematic reviews (search date 2003, 9 RCTs, 3216 people, 85% with New York Heart Association [NYHA] functional class III or IV symptoms; [86] search date 2005, 8 RCTs, 3380 people; [87] search date 2006, 7 RCTs, 3889 people; [88] and search date 2006, 7 RCTs, 3164 people [89]). The reviews included different RCTs in their meta-analyses and so we report data from all 4 reviews. We also found one non-systematic review that combined the results from the three studies in the MIRACLE implantable cardioverter-defibrillator (ICD) programme (2078 people) to evaluate the safety of CRT implantation. [90]

Mortality

Compared with usual care Cardiac resynchronisation therapy may be more effective at reducing all-cause mortality and death from progressive heart failure and reducing the proportion of people classed as "worsened" on the heart failure clinical composite response (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[86] Systematic review	3203 people 8 RCTs in this analysis	**Rate of mortality** with cardiac resynchronisation therapy (CRT) with usual care Absolute results not reported	RR 0.79 95% CI 0.66 to 0.96 Some RCTs included in the analysis compared CRT plus implantable cardiac defibrillators (ICDs) versus ICDs alone	●○○	CRT
[87] Systematic review	3380 people 8 RCTs in this analysis	**Rate of mortality** 264/1847 (14%) with CRT 260/1533 (17%) with control (not further defined)	OR 0.72 95% CI 0.59 to 0.88 The review included RCTs in which ICDs were used in all people randomised	●○○	CRT
[88] Systematic review	2249 people 4 RCTs in this analysis	**Rate of mortality** 245/1283 (19%) with CRT 247/966 (26%) with usual care (medical treatment)	OR 0.67 95% CI 0.50 to 0.90 This analysis included those RCTs in which neither arm was treated with an ICD	●○○	CRT
[89] Systematic review	3164 people with heart failure 5 RCTs in this analysis	**All-cause mortality** 224/1664 (14%) with CRT 244/1364 (18%) with usual care	RR 0.70 95% CI 0.60 to 0.83	●○○	CRT
Cardiac mortality					
[86] Systematic review	1647 people 7 RCTs in this analysis	**Rate of death from progressive heart failure** with CRT with usual care Absolute results not reported	RR 0.60 95% CI 0.36 to 1.01 Some RCTs included in the analysis compared CRT plus ICDs versus ICDs alone	⟷	Not significant
[89] Systematic review	1716 people with heart failure 2 RCTs in this analysis	**Death from congestive heart failure** 98/1004 (9%) with CRT 92/712 (13%) with usual care	RR 0.79 95% CI 0.60 to 1.03	⟷	Not significant
[89] Systematic review	2085 people with heart failure 3 RCTs in this analysis	**Sudden cardiac death** 49/1191 (4%) with CRT 59/894 (7%) with usual care	RR 0.67 95% CI 0.46 to 0.96 P = 0.03	●○○	CRT

Admission to hospital

Compared with usual care Cardiac resynchronisation therapy may be more effective at reducing hospital admissions for heart failure or major cardiovascular events (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital for heart failure-specific causes					
[86] Systematic review	1642 people 6 RCTs in this analysis	**Rate of hospital admission for heart failure** with cardiac resynchronisation therapy (CRT) with usual care Absolute results not reported	RR 0.68 95% CI 0.41 to 1.12 Some RCTs included in the analysis compared CRT plus implantable cardiac defibrillators (ICDs) versus ICDs alone	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[86] Systematic review	People with New York Heart Association (NYHA) class III or IV symptoms (number of people in analysis not reported) 6 RCTs in this analysis	**Rate of hospital admission for heart failure** with CRT with usual care Absolute results not reported	RR 0.65 95% CI 0.48 to 0.88 Some RCTs included in the analysis compared CRT plus ICDs versus ICDs alone	●○○	CRT
[87] Systematic review	2455 people 7 RCTs in this analysis	**Proportion of people admitted to hospital for worsening heart failure** 174/1230 (14%) with CRT 282/1225 (23%) with control (not further defined)	OR 0.55 95% CI 0.44 to 0.68 The review included RCTs in which ICDs were used in all people randomised	●○○	CRT
[89] Systematic review	1892 people with heart failure 5 RCTs in this analysis	**Rate of hospital admission for heart failure** 181/950 (19%) with CRT 277/942 (29%) with usual care	RR 0.64 95% CI 0.50 to 0.80	●○○	CRT

No data from the following reference on this outcome. [88]

Functional improvement

Compared with usual care Cardiac resynchronisation therapy may be more effective at improving function (New York Heart Association functional classification) by at least one functional class (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Improvement in functional class					
[86] Systematic review	Number of people included in analysis not reported 4 RCTs in this analysis	**Proportion of people whose function improved by at least 1 New York Heart Association (NYHA) functional class** 58% with cardiac resynchronisation therapy (CRT) 37% with usual care Absolute numbers not reported	RR 1.6 95% CI 1.3 to 1.9 Some RCTs included in the analysis compared CRT plus implantable cardiac defibrillators (ICDs) versus ICDs alone	●○○	CRT

No data from the following reference on this outcome. [87] [88] [89]

Quality of life

Compared with usual care Cardiac resynchronisation therapy seems more effective at improving quality-of-life scores as assessed by the Minnesota Living with Heart Failure Questionnaire (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[86] Systematic review	2472 people 7 RCTs in this analysis	**Quality-of-life score on the Minnesota Living with Heart Failure Questionnaire (MLHFQ)** with cardiac resynchronisation therapy (CRT) with usual care Absolute results not reported	Weighted mean reduction: 7.6 points 95% CI 3.8 points to 11.5 points Some RCTs included in the analysis compared CRT plus implantable cardiac defibrillators (ICDs) versus ICDs alone	○○○	CRT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[87] Systematic review	3380 people 8 RCTs in this analysis	**Improved quality of life (assessed by the MLHFQ)** with CRT with control (not further defined) Absolute results not reported	WMD –7.1 95% CI –11.4 to –2.9 The review included RCTs in which ICDs were used in all people randomised	○○○	CRT

No data from the following reference on this outcome. [88] [89]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Implant safety					
[90] Non-systematic review	3078 people 3 RCTs in this analysis	**Implant safety and success** with cardiac resynchronisation therapy (CRT) with control Absolute results not reported The implant attempt succeeded in 1903/2078 (92%) of people overall Perioperative complication rate ranged from 9% for CRT implantation alone to 21% for the combined implantable cardiac defibrillator (ICD)/CRT implantation Postoperative complication rate ranged from 8.6% to 11.9% A total of 8% of people required re-operation to treat lead dislodgement, extracardiac stimulation, or infection over 6 months' follow-up There was 0.3% procedure-related mortality			
[86] Systematic review	3203 people 8 RCTs in this analysis	**Implant safety and success** with CRT with usual care Absolute results not reported The review found that 0.4% of people died during implantation (95% CI 0.2% to 0.7%) Over a median of 6 months' follow-up, leads dislodged in 9% of recipients (95% CI 7% to 10%) and mechanical malfunctions occurred in 7% (95% CI 5% to 8%)	Some RCTs included in the analysis compared CRT plus ICDs versus ICDs alone		

No data from the following reference on this outcome. [87] [88] [89]

CRT plus implantable cardiac defibrillator (ICD) versus usual care:

We found one systematic review (search date 2006, 7 RCTs, 3889 people), [88] which assessed the effects of CRT plus ICD.

Mortality

Cardiac resynchronisation therapy plus implantable cardiac defibrillator compared with usual care Cardiac resynchronisation therapy plus implantable cardiac defibrillator is more effective than medical therapy at reducing all-cause mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[88] Systematic review	903 people Data from 1 RCT	**Rate of mortality** 105/595 (18%) with cardiac resynchronisation therapy (CRT) plus implantable cardiac defibrillator (ICD) 77/308 (25%) with usual care (medical treatment)	OR 0.64 95% CI 0.46 to 0.90	●○○	CRT plus ICD

Admission to hospital

No data from the following reference on this outcome. [88]

Functional improvement

No data from the following reference on this outcome. [88]

Quality of life

No data from the following reference on this outcome. [88]

Adverse effects

No data from the following reference on this outcome. [88]

CRT plus ICD versus ICD alone:

We found two systematic reviews (search date 2006, 7 RCTs, 3889 people; [88] and search date 2009, 2 RCTs, 2430 people [85]), which assessed the effects of CRT plus ICD versus ICD alone.

Mortality

Cardiac resynchronisation therapy plus implantable cardiac defibrillator compared with implantable cardiac defibrillator alone Cardiac resynchronisation therapy plus implantable cardiac defibrillator may be no more effective than implantable cardiac defibrillator alone at reducing all-cause mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[88] Systematic review	1045 people 3 RCTs in this analysis	**Rate of mortality** 27/517 (5%) with cardiac resynchronisation therapy (CRT) plus implantable cardiac defibrillator (ICD) 33/528 (6%) with ICD alone	OR 0.81 95% CI 0.48 to 1.37	⟷	Not significant
[85] Systematic review	2430 people with heart failure 2 RCTs in this analysis	**All-cause mortality** with CRT plus ICD with ICD alone Absolute results not reported	OR 0.96 95% CI 0.67 to 1.37	⟷	Not significant

Functional improvement

No data from the following reference on this outcome. [88] [85]

Quality of life

No data from the following reference on this outcome. [88] [85]

Admission to hospital

Cardiac resynchronisation therapy plus implantable cardiac defibrillator compared with implantable cardiac defibrillator alone Cardiac resynchronisation therapy plus implantable cardiac defibrillator may be more effective than implantable cardiac defibrillator alone at reducing admissions to hospital (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital					
[85] Systematic review	2430 people with heart failure 2 RCTs in this analysis	**Heart failure events including hospital admission** with cardiac resynchronisation therapy (CRT) plus implantable cardiac defibrillator (ICD) with ICD alone Absolute results not reported	OR 0.57 95% CI 0.46 to 0.70	●○○	CRT plus ICD

No data from the following reference on this outcome. [88]

Adverse effects

No data from the following reference on this outcome. [88] [85]

CRT plus ICD versus CRT alone:

We found one systematic review (search date 2006, 7 RCTs, 3889 people), [88] which assessed the effects of CRT plus ICD versus CRT alone.

Mortality

Cardiac resynchronisation therapy plus implantable cardiac defibrillator compared with cardiac resynchronisation therapy alone Cardiac resynchronisation therapy plus implantable cardiac defibrillator is no more effective than cardiac resynchronisation therapy alone at reducing all-cause mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[88] Systematic review	1212 people Data from 1 RCT	**Rate of mortality** 105/595 (18%) with cardiac resynchronisation therapy (CRT) plus implantable cardiac defibrillator (ICD) 131/617 (21%) with CRT alone	OR 0.79 95% CI 0.60 to 1.06	⟷	Not significant

Functional improvement

No data from the following reference on this outcome. [88]

Quality of life

No data from the following reference on this outcome. [88]

Admission to hospital

No data from the following reference on this outcome. [88]

Adverse effects

No data from the following reference on this outcome. [88]

Further information on studies

[85] The review reported that the success rate for implantation was between 97% and 99%. It examined the complications related to placement of CRT devices in the two RCTs identified, but did not directly compare complication rates with combined CRT plus ICD versus ICD alone. Peri-implantation mechanical complications, including pneumothorax, coronary dissection, and pericardial tamponade occurred with a frequency of 1% to 2% in people receiving CRT. Left ventricular lead problems following implantation were reported in 4% of participants by 30 days and 7% of participants at 12 months of follow-up. Device-related infections occurred in 1% of participants within 30 days of implantation.

Comment: **Clinical guide:**
The results presented in the systematic reviews indicate beneficial effects with CRT. [86] [87] [88] [89] [85] People deriving benefit are those with the more severe symptoms of heart failure, although one systematic review suggests that cardiac resynchronisation therapy in people with milder symptoms of heart failure may have fewer heart failure events and reduction of cardiac remodelling. [85] Most people included in the studies were well selected, and procedures were performed in centres with experience. However, because in almost all RCTs people were randomly assigned to different modes of operation after placement of the pacemaker, the results may over-estimate the potential benefits of CRT. Furthermore, meta-analysis of RCTs comparing combination of CRT plus ICD versus either device alone found that the combination does not seem more effective than either ICD or CRT alone in reducing mortality. [88] [85]

QUESTION What are the effects of coronary revascularisation for treatment of heart failure?

OPTION CORONARY REVASCULARISATION New

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Coronary revascularisation may reduce mortality in people with heart failure and left ventricular dysfunction.
- However, very few people in the RCTs had clinical evidence of heart failure and the trials we found comparing coronary revascularisation with drug treatment were all conducted before ACE inhibitors, aspirin, beta-blockers, and statins were in routine use. Thus, the clinical relevance of the evidence to current clinical practice is unclear.

Benefits and harms

Coronary revascularisation versus drug treatment:

We found one systematic review (search date not reported), which performed a meta-analysis of individual patient data from 7 RCTs (2649 people with coronary artery disease, most with stable angina, 20% with left ventricular dysfunction [ejection fraction <49], 4% with clinical evidence of heart failure) comparing revascularisation (CABG surgery) versus drug treatment. [91] We also found two systematic reviews of observational studies, which did not meet *Clinical Evidence* inclusion criteria (see comments). [92] [93]

Mortality

Compared with drug treatment We don't know how coronary revascularisation and drug treatment compare with each other, at reducing all-cause mortality (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[91] Systematic review	549 people with left ventricular ejection fraction (LVEF) <50%, coronary artery disease, and deemed eligible for either CABG or drug treatment 7 RCTs in this analysis Subgroup analysis Analysis of individual patient data	**Mortality , 5 years** Not reported with CABG 25% with drug treatment Absolute numbers not reported 115/549 (21%) of people died overall (analysis of both groups)	OR 0.59 95% CI 0.39 to 0.91 P = 0.02	●○○	CABG

Admission to hospital

No data from the following reference on this outcome. [91]

Functional improvement

No data from the following reference on this outcome. [91]

Quality of life

No data from the following reference on this outcome. [91]

Adverse effects

No data from the following reference on this outcome. [91]

Coronary revascularisation versus non-drug treatment:
We found no systematic review or RCTs.

Coronary revascularisation versus devices:
We found no systematic review or RCTs.

Further information on studies

Comment:

We found two systematic reviews (search date 1999, 24 observational studies, 3088 people with coronary artery disease and left ventricular dysfunction, mean New York Heart Association (NYHA) functional class 2.8; [92] and search date not reported, 9 observational studies, all identified by the first review, 1244 people [93]), both of which evaluated the effects of myocardial viability on mortality. All the studies identified by the reviews were completed before ACE inhibitors, aspirin, beta-blockers, and statins were in routine use. Neither review assessed outcomes other than mortality.

The first review found that, in people with myocardial viability, annual mortality was 16% in those who received drug treatment compared with 3% in those treated with revascularisation (P <0.0001). [92] Retrospective, within-group meta-analysis found that annual mortality was 3% in people with myocardial viability who were revascularised compared with 8% in those without viability. [92] For people with myocardial viability who received drug treatment, annual mortality was 16%, compared with 6% in those without viability. [92] These findings suggest that the presence of viability is important when considering revascularisation of patients with coronary artery disease who have left ventricular dysfunction and heart failure.

The second review further supports this conclusion. [93] This review examined the same group of studies as the first review, [92] but only included studies that could contribute data from all 4 relevant parameters: presence or absence of viability, drug treatment, or revascularisation. In their meta-analysis the authors examined the interaction between myocardial viability and treatment allocation. The combined estimated interaction ratio for all 9 observational studies suggested that people who had left ventricular dysfunction, heart failure, and viable myocardium had a better result from revascularisation therapy than from drug treatment.

Clinical guide:
Although these reviews suggest that revascularisation of people with coronary artery disease, left ventricular dysfunction, and heart failure (especially in those with demonstrated myocardial viability) is better than drug treatment, there are several important limitations. The RCTs and observational studies examining this question were all conducted before treatments such as ACE inhibitors, aspirin, beta-blockers, and statins were routinely used. We found no RCTs solely in people with heart failure; all the evidence comes from subgroup analyses that represent a relatively small number of people. The other studies included in the meta-analyses were observational. Although meta-analysis is useful to increase the statistical power of small studies by pooling the data, [94] there are inherent flaws of this technique that can be amplified by deficiencies within the primary resources. [95] Thus, it cannot be definitively concluded that revascularisation is of benefit in our population of interest. There is currently an ongoing RCT that is designed to more definitively answer this question, the Surgical Treatment for Ischemic Heart Failure (STICH) trial. [96]

QUESTION What are the effects of drug treatments in people at high risk of heart failure?

OPTION ACE INHIBITORS IN PEOPLE AT HIGH RISK OF HEART FAILURE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- ACE inhibitors delay the onset of symptomatic heart failure, reduce cardiovascular events, and improve long-term survival in people with asymptomatic left ventricular systolic dysfunction compared with placebo.

Benefits and harms

ACE inhibitors versus placebo:

We found two systematic reviews, [97] [98] and three additional RCTs, [99] [100] [101] one of which [100] reported the 12-year follow-up of one of the RCTs [102] identified by the first review. The first review (search date not reported) identified three RCTs of people with vascular disease, but no heart failure or left ventricular systolic dysfunction (LVSD) (29,805 people), and 5 RCTs of people with LVSD or heart failure (12,763 people). [97] The second review (search date 2009) identified 6 RCTs, three identified by the previous review, of people with vascular disease, but no heart failure (32,210 people). [98] The reviews performed different analyses so we report both here.

Mortality

Compared with placebo ACE inhibitors seem more effective at reducing all-cause mortality and cardiovascular mortality in people with asymptomatic left ventricular systolic dysfunction, and in people with vascular disease without known evidence of left ventricular dysfunction or heart failure, and at reducing fatal MI in people with left ventricular systolic dysfunction (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[97] Systematic review	29,805 people with vascular disease 3 RCTs in this analysis	**Rate of mortality** 8% with ACE inhibitors 9% with control Absolute numbers not reported	OR 0.86 95% CI 0.79 to 0.94 P = 0.0004	●○○	ACE inhibitors
[97] Systematic review	12,763 people with left ventricular systolic dysfunction (LVSD) or heart failure 5 RCTs in this analysis	**Rate of mortality** 23% with ACE inhibitors 27% with control Absolute numbers not reported	OR 0.80 95% CI 0.74 to 0.87 P <0.0001	●○○	ACE inhibitors
[97] Systematic review	42,568 people 8 RCTs in this analysis Combined analysis of people with vascular disease but no heart failure and people with	**Rate of mortality** 12% with ACE inhibitors 14% with placebo Absolute numbers not reported	OR 0.83 95% CI 0.79 to 0.88 P <0.0001	●○○	ACE inhibitors

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	LVSD or heart failure				
[98] Systematic review	32,210 people with vascular disease 6 RCTs in this analysis	**All-cause mortality** 1188/16,123 (7%) with ACE inhibitors 1365/16,087 (8%) with placebo	RR 0.87 95% CI 0.81 to 0.94	●○○	ACE inhibitors
[98] Systematic review	31,750 people with vascular disease 5 RCTs in this analysis	**Cardiovascular mortality** 656/15,894 (4%) with ACE inhibitors 798/15,856 (5%) with placebo	RR 0.83 95% CI 0.70 to 0.98	●○○	ACE inhibitors
[100] RCT	5165 people followed up Further report of reference [102] The RCT was a 12-year follow-up of 1 of the RCTs identified by a review [97]	**Rate of mortality , 12 years** 1074/2111 (51%) with enalapril given for 3 to 4 years 1195/2117 (56%) with placebo	HR 0.86 95% CI 0.79 to 0.93	●○○	ACE inhibitors
[101] RCT	1749 people with MI and LVSD, ejection fraction 35% or less	**Rate of mortality , 12 years** with trandolapril given 3 to 7 days after MI with placebo Absolute results not reported	RR 0.89 95% CI 0.80 to 0.99 P = 0.03	●○○	ACE inhibitors
Cardiac mortality					
[99] RCT	2231 asymptomatic people after MI with documented LVSD	**Proportion of people with fatal MI** 56/1115 (5%) with captopril 80/1116 (7%) with placebo	RR 0.68 95% CI 0.49 to 0.96	●○○	ACE inhibitors
[100] RCT	5165 people followed up Further report of reference [102] The RCT was a 12-year follow-up of 1 of the RCTs identified by a review [97]	**Rate of cardiac mortality , 12 years** 736/2111 (35%) with enalapril given for 3 to 4 years 826/2117 (39%) with placebo	HR 0.85 95% CI 0.77 to 0.94	●○○	ACE inhibitors

Admission to hospital

Compared with placebo ACE inhibitors seem more effective at reducing all-cause hospital admissions, cardiovascular hospital admissions, and heart-failure hospital admissions in people with heart failure, asymptomatic left ventricular dysfunction, or other risk factors for heart failure (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital for any cause					
[101] RCT	1749 people with MI and left ventricular systolic dysfunction (LVSD), ejection fraction 35% or less	**Rate of hospital admission for any cause , 12 years** with trandolapril given 3 to 7 days after MI with placebo Absolute results not reported	RR 0.92 95% CI 0.88 to 0.96 P <0.001	●○○	ACE inhibitors

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital for heart failure-specific causes					
[97] Systematic review	29,805 people with vascular disease 3 RCTs in this analysis	**Rate of hospital admission for heart failure** 2% with ACE inhibitors 3% with control Absolute numbers not reported	OR 0.77 95% CI 0.67 to 0.90 P = 0.0007	●○○	ACE inhibitors
[97] Systematic review	12,763 people with LVSD or heart failure 5 RCTs in this analysis	**Rate of hospital admission for heart failure** 14% with ACE inhibitors 19% with control Absolute numbers not reported	OR 0.66 95% CI 0.60 to 0.74 P <0.0001	●○○	ACE inhibitors
[97] Systematic review	42,568 people 8 RCTs in this analysis Combined analysis of people with vascular disease but no heart failure and people with LVSD or heart failure	**Proportion of people admitted to hospital for heart failure** 5% with ACE inhibitors 7% with control Absolute numbers not reported	OR 0.70 95% CI 0.64 to 0.76 P <0.0001	●○○	ACE inhibitors
[101] RCT	1749 people with MI and LVSD, ejection fraction 35% or less	**Rate of cardiovascular hospital admissions , 12 years** with trandolapril given 3 to 7 days after MI with placebo Absolute results not reported	RR 0.95 95% CI 0.91 to 1.00 P = 0.047	●○○	ACE inhibitors
[101] RCT	1749 people with MI and LVSD, ejection fraction 35% or less	**Rate of hospital admission for heart failure , 12 years** with trandolapril given 3 to 7 days after MI with placebo Absolute results not reported	RR 0.85 95% CI 0.77 to 0.93 P <0.001	●○○	ACE inhibitors

No data from the following reference on this outcome. [98] [99] [100]

Cardiovascular events

Compared with placebo ACE inhibitors seem more effective at reducing non-fatal MIs in people at high risk of heart failure (people with asymptomatic left ventricular systolic dysfunction, and people with vascular disease without known evidence of left ventricular dysfunction or heart failure) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Non-fatal MI					
[97] Systematic review	42,568 people 8 RCTs in this analysis Combined analysis of people with vascular disease but no heart failure and people with left ventricular systolic dysfunction	**Proportion of people with non-fatal MI** 6% with ACE inhibitors 7% with control Absolute numbers not reported	OR 0.80 95% CI 0.74 to 0.87 P <0.0001	●○○	ACE inhibitors

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(LVSD) or heart failure				
[98] Systematic review	32,210 people with vascular disease 6 RCTs in this analysis	**Non-fatal MI** 813/16,123 (5%) with ACE inhibitors 981/16,087 (6%) with placebo	RR 0.83 95% CI 0.73 to 0.94	●○○	ACE inhibitors

No data from the following reference on this outcome. [99] [100] [101]

Functional improvement

No data from the following reference on this outcome. [97] [98] [99] [100] [101]

Quality of life

No data from the following reference on this outcome. [97] [98] [99] [100] [101]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[100] RCT	5165 people followed up Further report of reference [102] The RCT was a 12-year follow-up of 1 of the RCTs identified by a review [97]	**Proportion of people reporting an adverse effect , 40 months** 76% with enalapril given for 3 to 4 years 72% with placebo Absolute numbers not reported	Significance not assessed		
[100] RCT	5165 people followed up Further report of reference [102] The RCT was a 12-year follow-up of one of the RCTs identified by a review [97]	**Proportion of people with dizziness or fainting , 40 months** 46% with enalapril given for 3 to 4 years 33% with placebo Absolute numbers not reported	Significance not assessed		
[100] RCT	5165 people followed up Further report of reference [102] The RCT was a 12-year follow-up of 1 of the RCTs identified by a review [97]	**Proportion of people with cough , 40 months** 34% with enalapril given for 3 to 4 years 27% with placebo Absolute numbers not reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[100] RCT	5165 people followed up Further report of reference [102] The RCT was a 12-year follow-up of 1 of the RCTs identified by a review [97]	**Proportion of people with angio-oedema , 40 months** 1% with enalapril given for 3 to 4 years 1% with placebo Absolute numbers not reported	Significance not assessed		
[98] Systematic review	10,235 people with vascular disease 3 RCTs in this analysis	**Proportion of people who withdrew because of adverse effects** 732/5139 (14%) with ACE inhibitor 343/5096 (7%) with placebo	RR 2.30 95% CI 1.34 to 3.95	●○○	placebo
[98] Systematic review	10,974 people with vascular disease 3 RCTs in this analysis	**Proportion of people with hypotension** 38/5490 (0.7%) with ACE inhibitors 26/5484 (0.5%) with placebo	RR 1.79 95% CI 0.68 to 4.71	⟷	Not significant
[98] Systematic review	17,587 people with vascular disease 2 RCTs in this analysis	**Proportion of people with syncope** 203/8803 (2.3%) with ACE inhibitors 162/8784 (1.8%) with placebo	RR 1.24 95% CI 1.02 to 1.52	●○○	placebo
[98] Systematic review	18,915 people with vascular disease 3 RCTs in this analysis	**Proportion of people with cough** 1726/9476 (18%) with ACE inhibitors 1183/9439 (12%) with placebo	RR 1.67 95% CI 1.22 to 2.29	●○○	placebo
Discontinuation of treatment					
[100] RCT	5165 people followed up Further report of reference [102] The RCT was a 12-year follow-up of 1 of the RCTs identified by a review [97]	**Proportion of people permanently discontinuing treatment , 40 months** 8% with enalapril given for 3 to 4 years 5% with placebo Absolute numbers not reported	Significance not assessed		

No data from the following reference on this outcome. [97] [99] [101]

ACE inhibitors versus angiotensin II receptor blockers:

See option on angiotensin II receptor blockers, p 77 .

Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone:

See option on angiotensin II receptor blockers, p 77 .

Further information on studies

Comment: Asymptomatic LVSD is prognostically important, but we found no prospective studies that evaluated screening to detect its presence.

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS IN PEOPLE AT HIGH RISK OF HEART FAILURE N e w

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- Angiotensin II receptor blockers and ACE inhibitors seem equally effective at reducing all-cause mortality and cardiovascular mortality in people at high risk of heart failure.
- The combination of angiotensin II receptor blockers and ACE inhibitors seems no more effective than ACE inhibitors alone and causes more adverse effects.
- We don't know how angiotensin II receptor blockers as a class compare with placebo, as the evidence available assesses only telmisartan.

Benefits and harms

Angiotensin II receptor blockers versus placebo:

We found two RCTs comparing angiotensin II receptor blockers versus placebo in people with vascular disease at high risk of developing heart failure. [105] [106] In one of the RCTs the people were intolerant of ACE inhibitors. [105] One of the papers included a prespecified pooling of the data from both trials for two composite outcomes. [105]

Mortality

Compared with placebo We don't know how effective angiotensin II receptor blockers are at reducing mortality in high risk people (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[105] RCT	5926 people with vascular disease who were intolerant to ACE inhibitors	**Cardiovascular mortality** 227/2954 (7.7%) with telmisartan 223/2972 (7.5%) with placebo	HR 1.03 95% CI 0.85 to 1.24 P = 0.78	⟷	Not significant

No data from the following reference on this outcome. [106]

Admission to hospital

Compared with placebo We don't know how effective angiotensin II receptor blockers are at reducing admission to hospital (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital					
[105] RCT	5926 people with vascular disease who were intolerant to ACE inhibitors	**Hospital admission for heart failure** 134/2954 (4.5%) with telmisartan 129/2972 (4.3%) with placebo	HR 1.05 95% CI 0.82 to 1.34 P = 0.69	⟷	Not significant

No data from the following reference on this outcome. [106]

Functional improvement

No data from the following reference on this outcome. [105] [106]

Quality of life

No data from the following reference on this outcome. [105] [106]

Cardiovascular events

Compared with placebo We don't know how angiotensin II receptor blockers and placebo compare at reducing the composite outcome of cardiovascular mortality, MI, stroke, or hospital admission for heart failure in high risk people (very-low quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cardiovascular events					
[105] RCT	5926 people with vascular disease who were intolerant to ACE inhibitors	**Cardiovascular mortality, MI, stroke, or hospital admission for heart failure** 465/2954 (16%) with telmisartan 504/2972 (17%) with placebo	HR 0.92 95% CI 0.81 to 1.05 P = 0.22	⟷	Not significant
[105] RCT	5926 people with vascular disease who were intolerent to ACE inhibitors	**Cardiovascular mortality, MI, or stroke** 384/2954 (13%) with telmisartan 440/2972 (15%) with placebo	HR 0.86 95% CI 0.76 to 1.00 P = 0.045	●○○	telmisartan
[106] RCT	20,332 people with previous stroke and risk factors for vascular disease	**Cardiovascular mortality, MI, stroke, or worsening or new heart failure** 1367/10,146 (13.5%) with telmisartan 1463/10,186 (14.4%) with placebo	HR 0.94 95% CI 0.87 to 1.01	⟷	Not significant
[106] RCT	20,332 people with previous stroke and risk factors for vascular disease	**Cardiovascular mortality, MI, stroke, or worsening or new heart failure , within 6 months of randomisation** 474/10,146 (5%) with telmisartan 433/10,986 (4%) with placebo	HR 1.10 95% CI 0.97 to 1.26	⟷	Not significant
[106] RCT	20,332 people with previous stroke and risk factors for vascular disease	**Cardiovascular mortality, MI, stroke, or worsening or new heart failure , >6 months after randomisation** 893/10,146 (9%) with telmisartan 1030/10,186 (10%) with placebo	HR 0.87 95% CI 0.80 to 0.95	●○○	telmisartan
[105] RCT	26,258 people with vascular disease 2 RCTs in this analysis Pooled analysis of results from TRANSCEND [105]	**Cardiovascular mortality, MI, stroke, or hospital admission for heart failure** 1832/13,100 (14%) with telmisartan 1967/13,158 (15%) with placebo	OR 0.93 95% CI 0.86 to 0.99 P = 0.03	●○○	telmisartan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	and PRoFESS trials [106]				
[105] RCT	26,258 people with vascular disease 2 RCTs in this analysis Pooled analysis of results from TRANSCEND [105] and PRoFESS trials [106]	**Cardiovascular mortality, MI, stroke, or hospital admission for heart failure , within 6 months of randomisation** 546/13,100 (4.2%) with telmisartan 492/13,158 (3.7%) with placebo	OR 1.12 95% CI 0.99 to 1.27 P = 0.075	⟷	Not significant
[105] RCT	26,258 people with vascular disease Pooled analysis of results from TRANSCEND [105] and PRoFESS trials [106]	**Cardiovascular mortality, MI, stroke, or hospital admission for heart failure , >6 months after randomisation** 1286/12,484 (10%) with telmisartan 1475/12,575 (12%) with placebo	OR 0.86 95% CI 0.80 to 0.94 P <0.001	●○○	telmisartan

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[105] RCT	5926 people with vascular disease who were intolerant to ACE inhibitors	**Withdrawal for any cause** 1090/2954 (37%) with telmisartan 1143/2972 (39%) with placebo	P = 0.22	⟷	Not significant
[105] RCT	5926 people with vascular disease who were intolerant to ACE inhibitors	**Hypotensive symptoms** 29/2954 (1.0%) with telmisartan 16/2972 (0.5%) with placebo	P = 0.05	⟷	Not significant
[105] RCT	5926 people with vascular disease who were intolerant to ACE inhibitors	**Doubling of serum creatinine** 60/2954 (2.0%) with telmisartan 42/2972 (1.4%) with placebo	Significance not assessed		
[105] RCT	5926 people with vascular disease who were intolerant to ACE inhibitors	**Hyperkalaemia (potassium >5.5 mmol/L)** 111/2954 (4%) with telmisartan 49/2972 (2%) with placebo	Significance not assessed		
[106] RCT	20,332 people with previous stroke and risk factors for vascular disease	**Withdrawal because of adverse effects** 1450/10,146 (14%) with telmisartan 1127/10,186 (11%) with placebo	P <0.001	○○○	placebo
[106] RCT	20,332 people with previous stroke and risk factors for vascular disease	**Withdrawal because of hypotension** 393/10,146 (4%) with telmisartan 186/10,186 (2%) with placebo	P <0.001	○○○	placebo

Angiotensin II receptor blockers versus ACE inhibitors:

We found two RCTs comparing angiotensin II receptor blockers versus ACE inhibitors in people with vascular disease at high risk of developing heart failure. [103] [104] Both RCTs tested a non-inferiority hypothesis for angiotensin II receptor blockers compared with ACE inhibitors. The primary outcome for one of the RCTs was all-cause mortality. [103] The primary outcome for the other RCT was a composite of cardiovascular death, MI, stroke, or hospital admission for heart failure. [104]

Mortality

Angiotensin II receptor blockers compared with ACE inhibitors Angiotensin II receptor blockers and ACE inhibitors seem equally effective at reducing all-cause mortality and cardiovascular mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[103] RCT **3-armed trial**	9818 people with MI, clinical heart failure, left ventricular ejection fraction (LVEF) <0.40, around 15% with diagnosed heart failure The remaining arm evaluated captopril plus valsartan	**All-cause mortality** 979/4909 (19.9%) with valsartan 958/4909 (19.5%) with captopril	HR 1.00 97.5% CI 0.90 to 1.11 Non-inferiority satisfied (see further information on studies) P = 0.98	⟷	Not significant
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm evaluated telmisartan plus ramipril	**All-cause mortality** 989/8542 (11.6%) with telmisartan 1014/8576 (11.8%) with ramipril	RR 0.98 95% CI 0.90 to 1.07 Non-inferiority satisfied (see further information on studies)	⟷	Not significant
[103] RCT **3-armed trial**	9818 people with MI, LVEF <0.40, or clinical heart failure The remaining arm evaluated captopril plus valsartan	**Cardiovascular mortality** 827/4909 (16.8%) with valsartan 830/4909 (16.9%) with captopril	HR 0.98 97.5% CI 0.87 to 1.09 Non-inferiority satisfied (see further information on studies) P = 0.62	⟷	Not significant
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm evaluated telmisartan plus ramipril	**Cardiovascular mortality** 598/8542 (7.0%) with telmisartan 603/8576 (7.0%) with ramipril	RR 1.00 95% CI 0.89 to 1.12 Non-inferiority satisfied (see further information on studies)	⟷	Not significant

Admission to hospital

Angiotensin II receptor blockers compared with ACE inhibitors Angiotensin II receptor blockers seem less effective than ACE inhibitors at reducing admission to hospital (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital					
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm evaluated telmisartan plus ramipril	**Hospital admission for heart failure** 394/8542 (5%) with telmisartan 354/8576 (4%) with ramipril	RR 1.12 95% CI 0.97 to 1.29 Non-inferiority not satisfied (see further information on studies)	⟷	Not significant

No data from the following reference on this outcome. [103]

Cardiovascular events

Angiotensin II receptor blockers compared with ACE inhibitors Angiotensin II receptor blockers and ACE inhibitors seem equally effective at reducing cardiovascular events (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cardiovascular events					
[103] RCT **3-armed trial**	9818 people with MI, left ventricular ejection fraction (LVEF) <0.40, or clinical heart failure The remaining arm evaluated captopril plus valsartan	**Cardiovascular mortality or heart failure** 1326/4909 (27.0%) with valsartan 1335/4909 (27.2%) with captopril	HR 0.97 97.5% CI 0.90 to 1.05 Non-inferiority satisfied (see further information on studies) P = 0.51	⟷	Not significant
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm evaluated telmisartan plus ramipril	**Cardiovascular mortality, MI, stroke, or hospital admission for heart failure** 1423/8542 (16.7%) with telmisartan 1412/8576 (16.5%) with ramipril	RR 1.01 95% CI 0.94 to 1.09 Non-inferiority satisfied (see further information on studies)	⟷	Not significant
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm evaluated telmisartan plus ramipril	**Fatal and non-fatal MI** 440/8542 (5.2%) with telmisartan 413/8576 (4.8%) with ramipril	RR 1.07 95% CI 0.94 to 1.22 Non-inferiority not satisfied (see further information on studies)	⟷	Not significant

Functional improvement

No data from the following reference on this outcome. [103] [104]

Quality of life

No data from the following reference on this outcome. [103] [104]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[103] RCT **3-armed trial**	9818 people with MI, left ventricular ejection fraction (LVEF) <0.40, or clinical heart failure The remaining arm evaluated captopril plus valsartan	**Withdrawal because of adverse effects** 282/4885 (5.8%) with valsartan 375/4879 (7.7%) with captopril	P <0.05	○○○	valsartan
[103] RCT **3-armed trial**	9818 people with MI, LVEF <0.40, or clinical heart failure	**Withdrawal because of hypotension** 70/4885 (1.4%) with valsartan 41/4879 (0.8%) with captopril	P <0.05	○○○	valsartan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated captopril plus valsartan				
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm evaluated telmisartan plus ramipril	**Withdrawal because of hypotension** 229/8542 (3%) with telmisartan 149/8576 (2%) with ramipril	P <0.001	●○○	ramipril
[103] RCT **3-armed trial**	9818 people with MI, LVEF <0.40, or clinical heart failure The remaining arm evaluated captopril plus valsartan	**Withdrawal because of renal impairment** 53/4885 (1.1%) with valsartan 40/4879 (0.8%) with captopril	Reported as not significant P value not reported	⟷	Not significant
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm evaluated telmisartan plus ramipril	**Withdrawal because of renal impairment** 68/8542 (0.8%) with telmisartan 60/8576 (0.7%) with ramipril	P = 0.46	⟷	Not significant
[103] RCT **3-armed trial**	9818 people with MI, LVEF <0.40, or clinical heart failure The remaining arm evaluated captopril plus valsartan	**Withdrawal because of hyperkalaemia** 7/4885 (0.1%) with valsartan 4/4879 (0.1%) with captopril	Reported as not significant P value not reported	⟷	Not significant

Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone:

We found two RCTs comparing angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone in people with vascular disease at high risk of developing heart failure. [103] [104] Both RCTs tested a non-inferiority hypothesis for the combination of angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone. The primary outcome for one of RCTs was all-cause mortality. [103] The primary outcome for the other RCT was a composite of cardiovascular mortality, MI, stroke, or hospital admission for heart failure. [104]

Mortality

Angiotensin II receptor blockers plus ACE inhibitors compared with ACE inhibitors alone Angiotensin II receptor blockers plus ACE inhibitors seem no more effective at reducing all-cause mortality and cardiovascular mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[103] RCT **3-armed trial**	9794 people with MI, left ventricular ejection fraction (LVEF) <0.40, or clinical heart failure The remaining arm assessed valsartan alone	**All-cause mortality** 941/4885 (19.3%) with valsartan plus captopril 958/4909 (19.5%) with captopril alone	HR 0.98 97.5% CI 0.89 to 1.09 Non-inferiority satisfied (see further information about studies) P = 0.73	⟷	Not significant
[104] RCT **3-armed trial**	17,078 people with vascular disease The remaining arm assessed telmisartan alone	**All-cause mortality** 1065/8502 (12.5%) with telmisartan plus ramipril 1014/8576 (11.8%) with ramipril alone	RR 1.07 95% CI 0.98 to 1.16	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[103] RCT **3-armed trial**	9794 people with MI, LVEF <0.40, or clinical heart failure The remaining arm assessed valsartan alone	**Cardiovascular mortality** 827/4885 (16.9%) with valsartan plus captopril 830/4909 (16.9%) with captopril alone	HR 1.00 97.5% CI 0.89 to 1.11 P = 0.95	⟷	Not significant
[104] RCT **3-armed trial**	17,078 people with vascular disease The remaining arm assessed telmisartan alone	**Cardiovascular mortality** 620/8502 (7.3%) with telmisartan plus ramipril 603/8576 (7.0%) with ramipril alone	RR 1.04 95% CI 0.93 to 1.17	⟷	Not significant

Admission to hospital

Angiotensin II receptor blockers plus ACE inhibitors compared with ACE inhibitors alone We don't know how effective angiotensin II receptor blockers plus ACE inhibitors are compared with ACE inhibitors alone in reducing admission to hospital (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital					
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm assessed telmisartan alone	**Hospital admission for heart failure** 332/8502 (3.9%) with telmisartan plus ramipril 354/8576 (4.1%) with ramipril alone	RR 0.95 95% CI 0.82 to 1.10	⟷	Not significant

No data from the following reference on this outcome. [103]

Functional improvement

No data from the following reference on this outcome. [103] [104]

Quality of life

No data from the following reference on this outcome. [103] [104]

Cardiovascular events

Angiotensin II receptor blockers plus ACE inhibitors compared with ACE inhibitors alone Angiotensin II receptor blockers plus ACE inhibitors seem no more effective at reducing cardiovascular events (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cardiovascular events					
[103] RCT **3-armed trial**	9794 people with MI, left ventricular ejection fraction (LVEF) <0.40, or clinical heart failure	**Cardiovascular mortality or heart failure** 1331/4885 (27.2%) with valsartan plus captopril 1335/4909 (27.2%) with captopril alone	HR 1.00 97.5% CI 0.92 to 1.09 P = 0.94	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm assessed valsartan alone				
[104] RCT **3-armed trial**	17,078 people with vascular disease The remaining arm evaluated telmisartan alone	**Cardiovascular mortality, MI, stroke, or hospital admission for heart failure** 1386/8502 (16.3%) with telmisartan plus ramipril 1412/8576 (16.5%) with ramipril alone	RR 0.99 95% CI 0.92 to 1.07	⟷	Not significant
[104] RCT **3-armed trial**	17,078 people with vascular disease The remaining arm evaluated telmisartan alone	**Fatal and non-fatal MI** 438/8502 (5.2%) with telmisartan plus ramipril 413/8576 (4.8%) with ramipril alone	RR 1.08 95% CI 0.94 to 1.23	⟷	Not significant
Adverse events					
[103] RCT **3-armed trial**	9794 people with MI, LVEF <0.40, or clinical heart failure The remaining arm assessed valsartan alone	**Withdrawal because of adverse effects** 438/4862 (9%) with valsartan plus captopril 375/4879 (8%) with captopril alone	P <0.05	○○○	captopril alone
[103] RCT **3-armed trial**	9794 people with MI, LVEF <0.40, or clinical heart failure The remaining arm assessed valsartan alone	**Withdrawal because of hypotension** 90/4862 (2%) with valsartan plus captopril 41/4879 (1%) with captopril alone	P <0.05	○○○	captopril alone
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm assessed telmisartan alone	**Withdrawal because of hypotension** 406/8502 (5%) with telmisartan plus ramipril 149/8576 (2%) with ramipril alone	P <0.001	●●○	ramipril alone
[103] RCT **3-armed trial**	9794 people with MI, LVEF <0.40, or clinical heart failure The remaining arm assessed valsartan alone	**Withdrawal because of hyperkalaemia** 12/4862 (0.2%) with valsartan plus captopril 4/4879 (0.1%) with captopril alone		⟷	Not significant
[104] RCT **3-armed trial**	17,118 people with vascular disease The remaining arm assessed telmisartan alone	**Hyperkalaemia (potassium >5.6 mmol/L)** 480/8502 (6%) with telmisartan plus ramipril 283/8576 (3%) with ramipril alone	P <0.001	●●○	ramipril alone

Further information on studies

[103] [104] Both trials calculated that for non-inferiority to be satisfied, the upper confidence limit of the hazard ratio must be <1.13.

Comment: **Clinical guide:**

An angiotensin II receptor blocker seems as effective as an ACE inhibitor for reducing cardiovascular events in people with vascular disease who are at high risk of developing heart failure. Interestingly, the data for angiotensin II receptor blocker compared with placebo are not as robust with regards to showing benefit in patients with vascular disease. There has been no mortality benefit demonstrated in people with vascular disease. However, there have been benefits demonstrated for the composite cardiovascular outcome of cardiovascular death, MI, or stroke. The less robust findings in studies comparing angiotensin II receptor blocker versus placebo may have been in part due to reduced power in the studies because of event rates that were less than was expected at the start of the study and follow-up may have been too short. In fact, pooling of the data shows significant benefit for the composite outcome of cardiovascular death, MI, stroke, and hospital admission for heart failure. Furthermore, there is an interaction with time as demonstrated by a significant reduction in the composite outcome of cardiovascular death, MI, stroke, and hospital admission for heart failure occurring >6 months after randomisation compared with within 6 months of randomisation. In these studies, the finding of the lower rate of treatment discontinuation for the angiotensin II receptor blocker group is important with regards to life-long adherence to treatment. The combination of angiotensin II receptor blocker plus ACE inhibitor was not found to be superior to ACE inhibitor alone and there was a greater rate of adverse events for the combination treatment. Therefore, combination treatment would not be advisable in people with vascular disease in the absence of chronic symptomatic heart failure.

QUESTION What are the effects of treatments for diastolic heart failure?

OPTION ACE INHIBITORS OR ANGIOTENSIN II RECEPTOR BLOCKERS FOR DIASTOLIC HEART FAILURE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- ACE inhibitors or angiotensin II receptor blockers seem no more effective at reducing mortality or rate of hospital admissions for cardiovascular events in people with diastolic heart failure compared with placebo.

Benefits and harms

ACE inhibitors or angiotensin II receptor blockers versus placebo:

We found one systematic review (search date 2008) comparing renin-angiotensin inhibitors versus placebo, which identified three RCTs (8021 people) assessing the ACE inhibitor perindopril or the angiotensin II receptor blockers candesartan or irbesartan in people with diastolic heart failure. [107] The review did not assess adverse effects so we report the results from the individual trials it identified. [108] [109] [110]

Mortality

ACE inhibitors or angiotensin II receptor blockers compared with placebo ACE inhibitors or angiotensin II receptor blockers are no more effective at reducing all-cause mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[107] Systematic review	8021 people with diastolic heart failure 3 RCTs in this analysis	**All-cause mortality** 745/4005 (19%) with ACE inhibitors or angiotensin II receptor blockers 726/3996 (18%) with placebo	OR 1.03 95% CI 0.92 to 1.15 P = 0.62	⟷	Not significant

Admission to hospital

ACE inhibitors or angiotensin II receptor blockers compared with placebo ACE inhibitors or angiotensin II receptor blockers seem no more effective at reducing hospital admissions for heart failure (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admission to hospital for heart failure-specific causes					
[107] Systematic review	8021 people with diastolic heart failure 3 RCTs in this analysis	**Hospital admissions for heart failure** with ACE inhibitors or angiotensin II receptor blockers with placebo Absolute results not reported	OR 0.90 95% CI 0.80 to 1.02 P = 0.09	⟷	Not significant

Functional improvement

No data from the following reference on this outcome. [107]

Quality of life

No data from the following reference on this outcome. [107]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Discontinuation of treatment because of adverse effects					
[108] RCT	3023 people with New York Heart Association (NYHA) functional class II to IV heart failure and left ventricular ejection fraction (LVEF) >40%	**Proportion of people permanently discontinuing treatment caused by an adverse effect (hypotension, hyperkalaemia, and increase in plasma creatinine) or an abnormal laboratory value , median follow-up of 36.6 months** 270/1514 (18%) with candesartan 204/1509 (14%) with placebo	P = 0.001	○○○	placebo
[109] RCT	4128 people with NYHA II to IV heart failure symptoms and LVEF 45% or greater	**Proportion of people withdrawing because of an adverse effect , mean follow-up of 49.5 months** 331/2067 (16%) with irbesartan 288/2061 (14%) with placebo	P = 0.07	⟷	Not significant
Adverse effects					
[109] RCT	4128 people with NYHA II to IV heart failure symptoms and LVEF 45% or greater	**Proportion of people with hypotension , mean follow-up of 49.5 months** 60/2067 (2.9%) with irbesartan 62/2061 (3.0%) with placebo	P = 0.84	⟷	Not significant
[109] RCT	4128 people with NYHA II to IV heart failure symptoms and LVEF 45% or greater	**Proportion of people with renal dysfunction , mean follow-up of 49.5 months** 69/2067 (3.3%) with irbesartan 57/2061 (2.8%) with placebo	P = 0.29	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[109] RCT	4128 people with NYHA II to IV heart failure symptoms and LVEF 45% or greater	**Proportion of people with renal hyperkalaemia , mean follow-up of 49.5 months** 12/2067 (0.6%) with irbesartan 9/2061 (0.4%) with placebo	P = 0.34	⟷	Not significant
[110] RCT	850 people with NYHA functional class I to IV heart failure and LVEF >40%	**Proportion of people with a serious adverse effect (including oedema and hypotension)** 9/424 (2%) with perindopril 4 mg daily 4/426 (1%) with placebo	Significance not assessed		

Further information on studies

[107] Given the higher symptom severity in one of the trials (IPRESERVE) included in the review and the possibility that renin-angiotensin inhibition may not be as effective at reducing hospital admission for heart failure in more advanced disease, the meta-analysis was repeated excluding the IPRESERVE data. Excluding the results of IPRESERVE did not change the outcome for all-cause mortality (OR 1.04, 95% CI 0.87 to 1.24; P = 0.69) and resulted in only a non-significant trend towards reduced hospital admissions for heart failure (OR 0.85, 95% CI 0.72 to 1.00; P = 0.06).

Comment: **Clinical guide:**
The causes of diastolic dysfunction vary among people with diastolic heart failure. Current treatment is largely based on the results of small clinical studies and consists of treating the underlying cause and coexistent conditions with interventions optimised for individuals. [111] [112] The findings from this systematic review would not support the routine use of renin-angiotensin antagonists to reduce cardiovascular mortality or morbidity in this population.

OPTION TREATMENTS OTHER THAN ANGIOTENSIN II RECEPTOR BLOCKERS FOR DIASTOLIC HEART FAILURE

- For GRADE evaluation of interventions for Heart failure, see table, p 93 .
- We don't know whether treatments other than angiotensin II receptor blockers are beneficial in reducing mortality in people with diastolic heart failure as we found only one trial.

Benefits and harms

Treatments other than angiotensin II receptor blockers versus placebo:

We found no systematic review but found one RCT. [113]

Mortality

Treatments other than angiotensin II receptor blockers compared with placebo We don't know whether digoxin is more effective at reducing all-cause or cardiovascular mortality at a mean follow-up of 37 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[113] RCT	988 people with New York Heart Association (NYHA) functional class I to IV heart	**Rate of mortality , mean follow-up of 37 months** with digoxin with placebo	HR 0.99 95% CI 0.76 to 1.28 P = 0.92	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	failure and left ventricular ejection fraction (LVEF) >45% Subgroup analysis The RCT reported a post-hoc subgroup analysis of people with heart failure with preserved ejection fraction from the DIG Study	Absolute results not reported			
Cardiovascular mortality					
[113] RCT	988 people with NYHA functional class I to IV heart failure and LVEF >45% Subgroup analysis The RCT reported a post-hoc subgroup analysis of people with heart failure with preserved ejection fraction from the DIG Study	**Rate of cardiovascular mortality , mean follow-up of 37 months** with digoxin with placebo Absolute results not reported	HR 1.00 95% CI 0.73 to 1.36 P = 0.98	⟷	Not significant

Admission to hospital

Treatments other than angiotensin II receptor blockers compared with placebo We don't know whether digoxin is more effective at reducing the combined outcome of all-cause mortality and unplanned heart failure-related hospital admissions (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death or hospital admission					
[113] RCT	988 people with New York Heart Association (NYHA) functional class I to IV heart failure and left ventricular ejection fraction (LVEF) >45% Subgroup analysis The RCT reported a post-hoc subgroup analysis of people with heart failure with preserved ejection fraction from the DIG Study	**Rate of combined primary outcome of hospital admission for heart failure, or heart failure mortality , mean follow-up of 37 months** with digoxin with placebo Absolute results not reported	HR 0.82 95% CI 0.63 to 1.07 P = 0.136	⟷	Not significant

Functional improvement

No data from the following reference on this outcome. [113]

Quality of life

No data from the following reference on this outcome. [113]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[113] RCT	988 people with New York Heart Association (NYHA) functional class I to IV heart failure and left ventricular ejection fraction (LVEF) >45% Subgroup analysis The RCT reported a post-hoc subgroup analysis of people with heart failure with preserved ejection fraction from the DIG Study	**Rate of digoxin toxicity** 10% with digoxin 4% with placebo Absolute numbers not reported	P <0.001	○○○	placebo
[113] RCT	988 people with NYHA functional class I to IV heart failure and LVEF >45% Subgroup analysis The RCT reported a post-hoc subgroup analysis of people with heart failure with preserved ejection fraction from the DIG Study	**Proportion of people admitted to hospital with unstable angina** with digoxin with placebo Absolute results not reported	HR 1.37 95% CI 0.99 to 1.91 P = 0.06 Result was of borderline significance	⟷	Not significant

Further information on studies

Comment:

Clinical guide:
The causes of diastolic dysfunction vary among people with diastolic heart failure. Current treatment is largely based on the results of small clinical studies and consists of treating the underlying cause and coexistent conditions with interventions optimised for individuals. [111] [112] Further RCTs with clinically relevant outcome measures are needed to determine the benefits and harms of treatments in diastolic heart failure.

GLOSSARY

New York Heart Association functional classification Classification of severity by symptoms. Class I: no limitation of physical activity; ordinary physical activity does not cause undue fatigue or dyspnoea. Class II: slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue or dyspnoea. Class III: limitation of physical activity; comfortable at rest, but less than ordinary activity causes fatigue or dyspnoea. Class IV: unable to carry out any physical activity without symptoms; symptoms are present even at rest; if any physical activity is undertaken, symptoms are increased.

Usual or conventional care describes the comparator arm of some controlled trials. It refers to appropriate drug and non-drug treatment, in the absence of the intervention being examined in the active treatment arm of the trial.

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.

Minnesota Living with Heart Failure Questionnaire Scores range from 1 to 105, with higher scores reflecting a lower quality of life.

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

Coronary revascularisation New option added. [91] Categorised as Unknown effectiveness because evidence is insufficient to judge this intervention in heart failure.

Angiotensin II receptor blockers in people at high risk of heart failure New option added. [105] [106] [103] [104] Categorised as Likely to be beneficial.

ACE inhibitors in people at high risk of heart failure New evidence added. [98] [103] [104] Categorisation unchanged (Beneficial).

Angiotensin II receptor blockers for treating heart failure New evidence added. [33] Categorisation unchanged (Beneficial).

Beta-blockers New evidence added. [39] Categorisation unchanged (Beneficial).

Cardiac resynchronisation therapy New evidence added. [89] [85] Categorisation unchanged (Likely to be beneficial).

Exercise New evidence added. [25] Categorisation unchanged (Likely to be beneficial).

Implantable cardiac defibrillators New evidence added. [83] [85] Categorisation unchanged (Beneficial).

Multidisciplinary interventions New evidence added. [20] [21] [23] Categorisation unchanged (Beneficial).

ACE inhibitors or angiotensin II receptor blockers for diastolic heart failure New evidence added. [107] Categorisation changed from Unknown effectiveness to Unlikely to be beneficial.

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GRADE **Evaluation of interventions for Heart failure.**

Important outcomes		Admission to hospital, Cardiovascular events, Functional improvement, Mortality, Quality of life							
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of multidisciplinary interventions for heart failure?									
at least 32 (at least 9733) [15] [16] [17] [18] [19] [20] [21] [22] [23]	Mortality	Multidisciplinary interventions versus usual care	4	0	0	0	0	High	
at least 34 (at least 9588) [15] [17] [18] [19] [20] [21] [22] [23]	Admission to hospital	Multidisciplinary interventions versus usual care	4	0	0	0	0	High	
What are the effects of exercise in people with heart failure?									
at least 14 (at least 1197) [24] [25]	Mortality	Exercise versus usual care	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about relative merits of the various exercise strategies assessed
at least 14 (at least 1197) [24] [25]	Admission to hospital	Exercise versus usual care	4	0	0	−2	0	Low	Directness points deducted for use of composite outcome and uncertainty about the relative merits of the various exercise strategies assessed
3 (2256) [27] [26] [28]	Functional improvement	Exercise versus usual care	4	0	−1	−1	0	Low	Consistency point deducted for different results at different times. Directness point deducted for uncertainty about relative merits of the various exercise strategies assessed
11 (3278) [26] [25]	Quality of life	Exercise versus usual care	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for uncertainty about benefits of each strategy
What are the effects of drug treatments for heart failure?									
37 (19,868) [29] [30]	Mortality	ACE inhibitors versus placebo	4	0	0	0	0	High	
5 (12,763) [30]	Admission to hospital	ACE inhibitors versus placebo	4	0	0	0	0	High	
1 (3164) [32]	Mortality	Difference doses of ACE inhibitors versus each other	4	0	0	−1	0	Moderate	Directness point deducted for composite outcome in 1 RCT
1 (3164) [32]	Admission to hospital	Difference doses of ACE inhibitors versus each other	4	0	0	−1	0	Moderate	Directness point deducted for composite outcome in 1 RCT
9 (4623) [34]	Mortality	Angiotensin II receptor blockers versus placebo	4	0	0	0	0	High	
3 (2590) [34]	Admission to hospital	Angiotensin II receptor blockers versus placebo	4	0	0	0	0	High	
8 (5201) [34] [35]	Mortality	Angiotensin II receptor blockers versus ACE inhibitors	4	0	0	0	0	High	
3 (4310) [34] [35]	Admission to hospital	Angiotensin II receptor blockers versus ACE inhibitors	4	0	0	0	0	High	

Important outcomes		Admission to hospital, Cardiovascular events, Functional improvement, Mortality, Quality of life							
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
at least 7 (8260) [34] [36] [35]	Mortality	Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for use of composite outcome in some assessments
4 (8108) [34] [35]	Admission to hospital	Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone	4	0	0	0	0	High	
at least 23 (at least 19,209) [37] [39]	Mortality	Beta-blockers versus placebo	4	0	−1	0	0	Moderate	Consistency point deducted for heterogeneity between studies
23 (12,263) [37] [41]	Admission to hospital	Beta-blockers versus placebo	4	0	0	−2	0	Low	Directness points deducted for uncertainty of benefit in older people and use of composite outcome
28 (7637) [38]	Functional improvement	Beta-blockers versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 6 (at least 12,278) [42] [43]	Mortality	Beta-blockers versus placebo (in people with severe heart failure)	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of various co-interventions
3 (8988) [43]	Admission to hospital	Beta-blockers versus placebo (in people with severe heart failure)	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for composite outcome
1 (1010) [44]	Admission to hospital	Beta-blockers versus ACE inhibitors	4	0	0	−2	0	Low	Directness points deducted for composite outcome and low number of comparators
7 (7756) [53]	Mortality	Digoxin versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (7262) [53]	Admission to hospital	Digoxin versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 24 (at least 13,957) [55] [56] [57] [58]	Mortality	Positive inotropes (other than digoxin) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
19 (10,807) [59]	Mortality	Aldosterone receptor antagonists versus placebo	4	0	0	−1	0	Moderate	Directness point deducted for non-generalisability of results (inclusion of people with ejection fraction >40%)
9 (8699) [59]	Admission to hospital	Aldosterone receptor antagonists versus placebo	4	0	0	−1	0	Moderate	Directness point deducted for non-generalisability of results (inclusion of people with ejection fraction >40%)
13 (9626) [63] [64]	Mortality	Amiodarone versus placebo or conventional care	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for including people with a wide range of conditions and for bias
2 (361) [65] [66] [67]	Mortality	Anticoagulation versus placebo or no antithrombotic treatment	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for combined outcome and for not exclusively including people with heart failure

Important outcomes		Admission to hospital, Cardiovascular events, Functional improvement, Mortality, Quality of life							
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (190) [66]	Mortality	Antiplatelet agents versus no treatment	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and for incomplete reporting of results. Directness point deducted for composite outcome
1 (190) [66]	Admission to hospital	Antiplatelet agents versus no treatment	4	−2	0	0	0	Low	Quality points deducted for sparse data and for incomplete reporting of results
3 (1882) [66] [67] [71]	Mortality	Antiplatelet agents versus warfarin	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and for largest RCT being underpowered to detect a clinically important difference. Directness point deducted for composite outcomes
2 (1767) [66] [71]	Admission to hospital	Antiplatelet agents versus warfarin	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and for largest RCT being underpowered to detect a clinically important difference. Directness point deducted for composite outcome
5 (4614) [74] [77] [76]	Mortality	Calcium channel blockers (for heart failure other than MI) versus placebo	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for subgroup analysis
3 (1790) [77]	Admission to hospital	Calcium channel blockers (for heart failure other than MI) versus placebo	4	0	0	−1	0	Moderate	Directness point deducted for composite outcome
2 (1509) [78] [79]	Mortality	Hydralazine plus isosorbide dinitrate versus placebo	4	−1	0	−2	0	Very low	Quality point deducted for short follow-up. Directness points deducted for mortality measured as secondary outcome in largest RCT and for differences in disease severity
1 (1050) [79]	Quality of life	Hydralazine plus isosorbide dinitrate versus placebo	4	−1	0	−1	0	Low	Quality point deducted for short follow-up. Directness point deducted for quality of life measured as secondary outcome
What are the effects of devices for treatment of heart failure?									
at least 8 (at least 2110) [81] [82] [83]	Mortality	Implantable cardiac defibrillators versus usual care	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 14 (at least 7154) [86] [87] [88] [89]	Mortality	Cardiac resynchronisation therapy (CRT) alone versus usual care/control	4	0	0	−2	0	Low	Directness points deducted for inclusion of co-intervention in some analyses (implantable cardiac defibrillator) and for composite outcome
at least 12 (at least 4349) [86] [87] [89]	Admission to hospital	Cardiac resynchronisation therapy (CRT) alone versus usual care/control	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of co-intervention in some analyses (implantable cardiac defibrillator)
4 (number of people not reported) [86]	Functional improvement	Cardiac resynchronisation therapy (CRT) alone versus usual care/control	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of co-intervention in some analyses (implantable cardiac defibrillator)
7 (2472) [86] [87]	Quality of life	Cardiac resynchronisation therapy (CRT) alone versus usual care/control	4	0	0	−1	0	Moderate	Directness point deducted for uncertainty about generalisability of results

Important outcomes		Admission to hospital, Cardiovascular events, Functional improvement, Mortality, Quality of life							
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (903) [88]	Mortality	CRT plus implantable cardiac defibrillator (ICD) versus usual care	4	0	0	0	0	High	
5 (3475) [88] [85]	Mortality	CRT plus ICD versus ICD alone	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different conclusions from different studies
2 (2430) [85]	Admission to hospital	CRT plus ICD versus ICD alone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for composite outcome
1 (1212) [88]	Mortality	CRT plus ICD versus CRT alone	4	0	0	0	0	High	
What are the effects of coronary revascularisation for treatment of heart failure?									
7 (549) [91]	Mortality	Coronary revascularisation versus drug treatment	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and for subgroup analyses. Directness point deducted for inclusion of older trials that were completed before ACE inhibitors, aspirin, beta-blockers, and statins were in routine use
What are the effects of drug treatments in people at high risk of heart failure?									
8 (46,548) [97] [98] [99] [100] [101]	Mortality	ACE inhibitors versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (14,512) [97] [101]	Admission to hospital	ACE inhibitors versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 8 (at least 42,568) [97] [98]	Cardiovascular events	ACE inhibitors versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (5926) [105]	Mortality	Angiotensin II receptor blockers versus placebo	4	0	0	–2	0	Low	Directness points deducted for only including people intolerant of ACE inhibitors and because data only available for 1 angiotensin II receptor blocker
1 (5926) [105]	Admission to hospital	Angiotensin II receptor blockers versus placebo	4	0	0	–2	0	Low	Directness points deducted for only including people intolerant of ACE inhibitors and because data only available for 1 angiotensin II receptor blocker
2 (26,258) [105] [106]	Cardiovascular events	Angiotensin II receptor blockers versus placebo	4	0	−1	−2	0	Very low	Consistency point deducted for different results at different time points. Directness points deducted for composite outcome and because data only available for 1 angiotensin II receptor blocker
2 (26,936) [103] [104]	Mortality	Angiotensin II receptor blockers versus ACE inhibitors	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of people with diagnosed heart failure
1 (17,118) [104]	Admission to hospital	Angiotensin II receptor blockers versus ACE inhibitors	4	0	0	–1	0	Moderate	Directness point deducted for only 1 drug of each class in the analysis
2 (26,936) [103] [104]	Cardiovascular events	Angiotensin II receptor blockers versus ACE inhibitors	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people with clinical evidence of heart failure

Important outcomes		Admission to hospital, Cardiovascular events, Functional improvement, Mortality, Quality of life							
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (26,872) [103] [104]	Mortality	Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people with clinically evident heart failure
1 (17,118) [104]	Admission to hospital	Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone	4	0	0	–2	0	Low	Directness points deducted for inclusion of people with clinically evident heart failure and for only 1 drug of each class in the analysis
2 (26, 872) [103] [104]	Cardiovascular events	Angiotensin II receptor blockers plus ACE inhibitors versus ACE inhibitors alone	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of all people with clinically evident heart disease
What are the effects of treatments for diastolic heart failure?									
3 (8021) [107]	Mortality	ACE inhibitors or angiotensin II receptor blockers versus placebo	4	0	0	0	0	High	
3 (8021) [107]	Admission to hospital	ACE inhibitors or angiotensin II receptor blockers versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting
1 (988) [113]	Mortality	Treatments other than angiotensin II receptor blockers versus placebo	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for subgroup analysis
1 (988) [113]	Admission to hospital	Treatments other than angiotensin II receptor blockers versus placebo	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and for subgroup analysis. Directness point deducted for composite outcome

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.