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Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction (Review)

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[Intervention Review]

Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction

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ABSTRACT

Background

Beta-blockers and inhibitors of the renin-angiotensin aldosterone system improve survival and reduce morbidity in people with heart failure with reduced left ventricular ejection fraction. There is uncertainty whether these treatments are beneficial for people with heart failure with preserved ejection fraction and a comprehensive review of the evidence is required.

Objectives

To assess the effects of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction.

Search methods

We searched CENTRAL, MEDLINE, Embase and two clinical trial registries on 25 July 2017 to identify eligible studies. Reference lists from primary studies and review articles were checked for additional studies. There were no language or date restrictions.

Selection criteria

We included randomised controlled trials with a parallel group design enrolling adult participants with heart failure with preserved ejection fraction, defined by a left ventricular ejection fraction of greater than 40 percent.

Data collection and analysis

Two review authors independently selected studies for inclusion and extracted data. The outcomes assessed included cardiovascular mortality, heart failure hospitalisation, hyperkalaemia, all-cause mortality and quality of life. Risk ratios (RR) and, where possible, hazard ratios (HR) were calculated for dichotomous outcomes. For continuous data, mean difference (MD) or standardised mean difference (SMD) were calculated. We contacted trialists where neccessary to obtain missing data.

Main results

37 randomised controlled trials (207 reports) were included across all comparisons with a total of 18,311 participants.

Ten studies (3087 participants) investigating beta-blockers (BB) were included. A pooled analysis indicated a reduction in cardiovascular mortality (15% of participants in the intervention arm versus 19% in the control arm; RR 0.78; 95% confidence interval (CI) 0.62 to 0.99;

number needed to treat to benefit (NNTB) 25; 1046 participants; 3 studies). However, the quality of evidence was low and no effect on cardiovascular mortality was observed when the analysis was limited to studies with a low risk of bias (RR 0.81; 95% CI 0.50 to 1.29; 643 participants; 1 study). There was no effect on all-cause mortality, heart failure hospitalisation or quality of life measures, however there is uncertainty about these effects given the limited evidence available.

12 studies (4408 participants) investigating mineralocorticoid receptor antagonists (MRA) were included with the quality of evidence assessed as moderate. MRA treatment reduced heart failure hospitalisation (11% of participants in the intervention arm versus 14% in the control arm; RR 0.82; 95% CI 0.69 to 0.98; NNTB 41; 3714 participants; 3 studies; moderate-quality evidence) however, little or no effect on all-cause and cardiovascular mortality and quality of life measures was observed. MRA treatment was associated with a greater risk of hyperkalaemia (16% of participants in the intervention group versus 8% in the control group; RR 2.11; 95% CI 1.77 to 2.51; 4291 participants; 6 studies; high-quality evidence).

Eight studies (2061 participants) investigating angiotensin converting enzyme inhibitors (ACEI) were included with the overall quality of evidence assessed as moderate. The evidence suggested that ACEI treatment likely has little or no effect on cardiovascular mortality, all-cause mortality, heart failure hospitalisation, or quality of life. Data for the effect of ACEI on hyperkalaemia were only available from one of the included studies.

Eight studies (8755 participants) investigating angiotensin receptor blockers (ARB) were included with the overall quality of evidence assessed as high. The evidence suggested that treatment with ARB has little or no effect on cardiovascular mortality, all-cause mortality, heart failure hospitalisation, or quality of life. ARB was associated with an increased risk of hyperkalaemia (0.9% of participants in the intervention group versus 0.5% in the control group; RR 1.88; 95% CI 1.07 to 3.33; 7148 participants; 2 studies; high-quality evidence).

We identified a single ongoing placebo-controlled study investigating the effect of angiotensin receptor neprilysin inhibitors (ARNI) in people with heart failure with preserved ejection fraction.

Authors' conclusions

There is evidence that MRA treatment reduces heart failure hospitalisation in heart failure with preserverd ejection fraction, however the effects on mortality related outcomes and quality of life remain unclear. The available evidence for beta-blockers, ACEI, ARB and ARNI is limited and it remains uncertain whether these treatments have a role in the treatment of HFpEF in the absence of an alternative indication for their use. This comprehensive review highlights a persistent gap in the evidence that is currently being addressed through several large ongoing clinical trials.

PLAIN LANGUAGE SUMMARY

Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction

Review question

We investigated the effects of beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and angiotensin receptor neprilysin inhibitors (ARNI) on survival, hospital admissions for heart failure, quality of life and potassium levels in people with heart failure with preserved ejection fraction.

Background

Heart failure is a common condition that occurs when the function of the heart muscle is impaired that is associated symptoms of breathlessness and fatigue, and a reduction in survival. In around half of cases where there is reduced contraction (heart failure with reduced ejection fraction, HFrEF), several treatments are known to be effective at improving survival and reducing hospitalisation. In the remaining cases where relaxation is impaired (heart failure with preserved ejection fraction, HFpEF), it is not clear whether the same drug treatments are also effective at improving outcomes.

Selection criteria

We sought to investigate whether HFrEF treatments are also effective in HFpEF. We conducted a comprehensive search for all trials investigating BB, MRA, ACEI, ARB or ARNI (evidence current to 25 July 2017).

Results and conclusions

We included 10 studies with 3087 randomised participants for BB, 12 studies with 4408 randomised participants for MRA, eight studies with 2061 randomised participants for ACEI and eight studies with 8755 randomised participants for ARB. We combined the evidence in a pooled analysis for each drug class and for each of the outcomes assessed. Not all included studies are part of each analysis.

We found that beta-blockers may improve cardiovascular mortality, however the evidence quality was low due to small trials and uncertainty about the methods used. For MRA, the results suggest a reduction in heart failure hospitalisation and have little or no effect on cardiovascular and all-cause mortality, however the evidence quality was only moderate. For ACEI, treatment probably has little or

no effect on the outcomes of cardiovascular mortality, all-cause mortality and heart failure hospitalisation, however the evidence quality was only moderate. We found high quality evidence for ARB treatment and the results suggest little or no effect from this treatment. No completed studies were available for ARNI. Treatment with MRA and ARB was found to increase the risk of high potassium in the blood.

In conclusion, BB may improve outcomes in patients with HFpEF however this remains uncertain. MRA was found to result in a slight reduction in the risk of hospitalisation due to heart failure. Treatment with ACEI probably has no effect, however this remains uncertain. The evidence suggested that treatment with ARB is of little or no benefit in people with HFpEF.

Quality of the evidence

The quality of evidence ranged from high to low across the outcomes and drug classes studied. With the exception of ARB, there was a lack of large scale trials in HFpEF for the interventions and outcomes tested.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Beta-blockers compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Beta-blockers compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: beta-blockers
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with Beta-blockers				
Cardiovascular mortality (RR) follow-up: range 21 months to 3.2 years	Study population		RR 0.78 (0.62 to 0.99)	1046 (3 RCTs)	⊕⊕⊖⊖ LOW [1 2]	Three additional studies (ELANDD; SWEDIC; Takeda 2004) reported that no deaths occurred
	173 per 1000	135 per 1000 (107 to 171)				
Heart failure hospitalisation (RR) follow-up: range 6 months to 3.2 years	Study population		RR 0.73 (0.47 to 1.13)	449 (4 RCTs)	⊕⊖⊖⊖ VERY LOW [1 3 4]	Follow-up unclear for SWEDIC. ELANDD reported that no hospitalisation due to heart failure occurred
	117 per 1000	86 per 1000 (55 to 133)				
Hyperkalaemia				245 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 7]	J-DHF reported one participant in the intervention group (N = 120) experienced hyperkalaemia but did not report on this outcome for the control group. No further data were available from any of the other studies.
All-cause mortality (RR) follow-up: range 21 months to 3.2 years	Study population		RR 0.82 (0.67 to 1.00)	1105 (4 RCTs)	⊕⊕⊖⊖ LOW [1 2]	Follow-up unclear for Adamyan 2010. ELANDD, SWEDIC and Takeda 2004 reported that no deaths occurred
	243 per 1000	199 per 1000 (163 to 243)				
Quality of life (Minnesota) Scale from: 0 to 105 follow-up: mean 6 months	Mean quality of life (Min-	MD 1 lower (9.05 lower to 7.05 higher)	-	93 (1 RCT)	⊕⊖⊖⊖ VERY LOW [5 6]	Lower = better, 5 point difference considered to be clinically meaningful

	nesota) was 24

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level due to unclear selection bias in most studies.
[2] Downgraded by one level due to concerns about the smaller study being more precise than the larger study.
[3] Downgraded by one level due to large variation in size of effect.
[4] Downgraded by two levels due to few events and wide CI.
[5] Downgraded by two levels due to very small sample size.
[6] Suspected publication bias; this is a patient-relevant outcome that is not reported in most studies.
[7] Downgraded by two levels due to incomplete reporting.

Summary of findings 2. MRA compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

MRA compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: MRA
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with MRA				
Cardiovascular mortality (RR) follow-up: range 12 months to 3.3 years	Study population		RR 0.90 (0.74 to 1.11)	4070 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Two additional trials (RAAM-PEF, Kurrelmeyer 2014) reported that no deaths occurred
	88 per 1000	79 per 1000 (65 to 97)				

Heart failure hospitalisation (RR) follow-up: range 24 weeks to 3.3 years	Study population 136 per 1000	112 per 1000 (94 to 134)	RR 0.82 (0.69 to 0.98)	3714 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Three additional trials (ALDO-DHF ,Kurrelmeyer 2014, Upadhya 2017) reported that no hospitalisation due to heart failure occurred
Hyperkalaemia follow-up: range 24 weeks to 3.3 years	Study population 83 per 1000	175 per 1000 (146 to 208)	RR 2.11 (1.77 to 2.52)	4291 (6 RCTs)	⊕⊕⊕⊕ HIGH	Two trials defined hyperkalaemia ≥ 5.5 mEg/L
All-cause mortality follow-up: range 9 months to 3.3 years	Study population 133 per 1000	121 per 1000 (104 to 141)	RR 0.91 (0.78 to 1.06)	4207 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Two additional trials (RAAM-PEF, Kurrelmeyer 2014) reported that no deaths occurred
Quality of life (Minnesota) Scale from: 0 to 105 follow-up: range 9 months to 12 months	Mean quality of life (Minnesota) ranged from 20 to 25	MD 0.84 higher (2.30 lower to 3.98 higher)	-	511 (3 RCTs)	⊕⊕⊖⊖ LOW [2 3]	Lower = better, 5 points are considered a clinically significant difference We did not pre-specify which QoL scale was to be reported in the 'Summary of findings' table. To aid comparisons among 'Summary of findings' tables we chose to include the Minnesota Living with Heart Failure questionnaire and not the SMD across two scales

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level due to imprecision.
[2] Downgraded by one level because one trial was open label.
[3] Downgraded by one level due to small sample size.

Summary of findings 3. ACEI compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

ACEI compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: ACEI
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with ACEI				
Cardiovascular mortality (RR) follow-up: range mean 12 months to mean 26.2 months	Study population		RR 0.93 (0.61 to 1.42)	945 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]	One additional trial (Kitzman 2010) reported that no deaths occurred
	86 per 1000	81 per 1000 (53 to 123)				
Heart failure hospitalisation (RR) follow-up: range 6 months to 26.2 months	Study population		RR 0.86 (0.64 to 1.15)	1019 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
	13 per 1000	11 per 1000 (8 to 15)				
Hyperkalaemia				74 (1 RCTs)	⊕⊖⊖⊖ VERY LOW [1 3 4]	One trial (Zi 2003) reported 2 events in the intervention group (N = 36), 0 events in the control group (N = 38) (RR 5.27, 95% CI 0.26 to 106.16)
All-cause mortality (RR) follow-up: range mean 6 months to mean 26.2 months	Study population		RR 0.99 (0.71 to 1.38)	1079 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]	One additional trial (Kitzman 2010) reported that no deaths occurred
	119 per 1000	119 per 1000 (84 to 166)				
Quality of life (Minnesota) Scale from: 0 to 105 follow-up: mean 12 months	Mean quality of life (Minnesota) ranged from 10.9 to 29	MD 0.09 lower (3.66 lower to 3.48 higher)	-	154 (2 RCTs)	⊕⊕⊖⊖ LOW [2 3]	Scale: 0 to 105, lower = better, 5 point difference considered clinically relevant One trial (SNEGOVIK) reported mean change from baseline of -19.8 for intervention and -10.7 for control

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level due to wide CI.
[2] Downgraded by one level due to risk of bias (open label).
[3] Downgraded by one level due to low sample size.
[4] Downgraded by one level due to unclear selection bias.

Summary of findings 4. ARB compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

ARB compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: ARB
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with ARB				
Cardiovascular mortality (RR) follow-up: range mean 12 months to mean 49.5 months	Study population		RR 1.02 (0.90 to 1.14)	7254 (3 RCTs)	⊕⊕⊕⊕ HIGH	One additional trial (Parthasarathy 2009) reported that no deaths occurred
	131 per 1000	133 per 1000 (118 to 149)				
Heart failure hospitalisation (RR) follow-up: range mean 12 months to mean 49.5 months	Study population		RR 0.92 (0.83 to 1.02)	7254 (3 RCTs)	⊕⊕⊕⊕ HIGH	
	171 per 1,-000	157 per 1,-000 (142 to 174)				
Hyperkalaemia	Study population		RR 1.88 (1.07 to 3.33)	7148 (2 RCTs)	⊕⊕⊕⊕ HIGH	

follow-up: range 36.6 months to 49.5 months	3 per 1,000	5 per 1,000 (3 to 8)				
All-cause mortality (RR) follow up: range 1 years to 4.4 years	Study population		RR 1.01 (0.92 to 1.11)	7964 (4 RCTs)	⊕⊕⊕⊕ HIGH	One additional trial (Parthasarathy 2009) reported that no deaths occurred
	72 per 1000	73 per 1,-000 (66 to 80)				
Quality of life (Minnesota) scale from: 0 to 105 follow-up: range mean 13.8 weeks to mean 49.5 months	Mean quality of life (Minnesota) ranged from 10.9 to 31.6	MD 0.41 higher (0.86 lower to 1.67 higher)	-	3117 (3 RCTs)	⊕⊕⊕⊕ HIGH	Scale: 0 to 105, lower = better, 5 point difference considered clinically relevant

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Description of the condition

Heart failure is a clinical syndrome characterised by breathlessness and fatigue that results when abnormalities of cardiac structure and function lead to inadequate cardiac output, or elevated ventricular filling pressures, or both (Ponikowski 2016). Based on available data from the United States and Europe, the prevalence of heart failure is estimated from 1% to 12% of the adult population and is projected to increase with population aging and improved survival from cardiovascular disease (Roger 2013). Heart failure is a significant public health problem accounting for 5% of emergency hospital admissions in the United Kingdom, and is associated with significant mortality with five-year survival estimated at 50% (NICE 2010). Heart failure is classified according to the left ventricular ejection fraction (LVEF) into heart failure with reduced ejection fraction (HFrEF, typically considered as LVEF < 40%), and heart failure with preserved ejection fraction (HFpEF, typically LVEF > 40%). Recently, an intermediate subgroup was defined by the European Society of Cardiology as heart failure with mid-range ejection fraction (HFmrEF) defined as LVEF 40% to 49% (Ponikowski 2016). This was defined by the American College of Cardiology as borderline HFpEF, defined as LVEF 41% to 49% (Yancy 2013). In this review, we defined HFpEF as LVEF > 40% because completed and ongoing HFpEF trials have used a range of LVEF cut-offs between 40% and 50%. HFpEF accounts for approximately half of all cases of heart failure; mortality outcomes are similar to those for HFrEF (Gerber 2015).

Description of the intervention

Neurohumoral inhibition with beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEI), and mineralocorticoid receptor antagonists (MRAs) leads to improved survival and a reduction in hospitalisations for heart failure in people with HFrEF (CIBIS Investigators 1999; Consensus Trial Study Group 1987; Flather 2005; Hjalmarson 2000; Kotecha 2014; MERIT-HF Study Group 1999; Packer 1999; Packer 2002; Packer 2001; Pitt 1999; Ponikowski 2016; SOLVD Investigators 1991; SOLVD Investigators 1992; Zannad 2011). Where ACEI or MRA are contra-indicated or not tolerated, angiotensin receptor antagonists (ARB) are recommended as an alternative for either, although evidence is limited (Granger 2003). Angiotensin receptor neprilysin inhibitors (ARNI) are recommended as an alternative to ACEI with superior efficacy in people with HFrEF who remain symptomatic despite optimal therapy (McMurray 2014). Although neurohumoral activation is observed in HFpEF (Hogg 2005), comparatively fewer clinical trials of neurohumoral inhibitor therapies have been performed in this population. The existing evidence from individual trials of BB, MRA, ACEI, ARB or MRAs in people with HFpEF does not support a reduction in mortality with these treatments (Ponikowski 2016). However, limited evidence indicates that candesartan (an ARB) (Yusuf 2003) and spironolactone (an MRA) (Pitt 2014) may be effective in reducing numbers of people hospitalised with heart failure.

This review sought to determine whether neurohumoral inhibition with therapies that improve mortality and morbidity in those with HFrEF (BB, MRA, ACEI, ARB, and ARNI) have similar benefit in people with HFpEF.

How the intervention might work

In people with HFpEF, inadequate cardiac function triggers compensatory neurohumoral responses similar to those observed in HFrEF (Hogg 2005). Activation of the renin-angiotensin aldosterone system (RAAS) and increased tone of the sympathetic nervous system may be adaptive in the short term; however, chronic activation is likely to be detrimental. Pre-clinical disease models of HFpEF suggest that RAAS activation leads to maladaptive hypertrophy and fibrosis (Sharma 2014). ACEIs, ARBs or MRAs inhibit components of the RAAS system to counter the over activation that occurs in people with heart failure. ARNIs combine inhibition of RAAS with an ARB (valsartan) with augmentation of the natriuretic peptide system by inhibition of neprilysin (sacubitril). Neprilysin is a neutral endopeptidase that degrades a number of endogenous vasoactive peptides serving to counteract some of the effects of RAAS activation (McMurray 2014). The beneficial effects of beta-blocker therapy in people with HFrEF are likely to be mediated by a reduction in the detrimental effects of increased sympathetic tone that may include increased heart rate, adverse myocardial energetics, and stimulation of RAAS (Sackner-Bernstein 1995). These mechanisms may also be important in HFpEF and the effect of beta-blockers to increase diastolic filling time may be particularly important (Sharma 2014). The population of people with HFpEF is heterogeneous, both with respect to disease aetiology and comorbidity. However, it is possible that neurohumoral activation represents a common pathophysiological mechanism that could be successfully targeted to improve clinical outcomes in people with heart failure across the spectrum of LVEF.

Why it is important to do this review

There is uncertainty as to whether beta-blockers or RAAS inhibitors are effective at reducing mortality and heart failure hospitalisation and improving quality of life in people with HFpEF. Guidelines offer no specific treatment recommendations regarding the use of these therapies beyond the management of comorbidities, aside from a recommendation for the use of ARBs to reduce hospitalisations (IIb recommendation, Yancy 2013) and for the use of MRAs (weak recommendation; moderate-quality evidence, Ezekowitz 2017). The UK's National Institute for Health and Care Excellence (NICE) highlighted a review of the evidence as a research priority (NICE 2010).

A recent systematic review and meta-analysis of pharmacotherapy in HFpEF included beta-blockers and RAAS inhibitors (ACEI, ARB and MRA) and suggested a reduction in cardiovascular and all-cause mortality with beta-blocker therapy (Zheng 2017). An updated review with a more comprehensive search strategy is needed to inform new guideline recommendations and to inform the conduct of further clinical trials.

OBJECTIVES

To assess the effects of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with parallel group design. We excluded cross-over trials because we considered these to be inappropriate for our review question due to the progressive nature of heart failure.

Studies published in full-text or as abstracts, or available only as unpublished data, were eligible for inclusion.

Types of participants

We included studies with adult participants (aged ≥ 18 years) with HFpEF defined by a left ventricular ejection fraction of greater than 40 percent (LVEF > 40%). It was recognised there was likely to be significant heterogeneity between study populations relating to the disease definition and a narrative summary is included in the Discussion. We contacted study authors to obtain data on the subgroup of interest for studies with mixed populations in relation to ejection fraction.

Types of interventions

We performed separate meta-analyses of studies that compared BB, MRA, ACEI, or ARB, in addition to standard care, with placebo or no treatment control. We did not perform a meta-analysis of ARNI because no trials were identified.

Types of outcome measures

Primary outcomes

1. Cardiovascular mortality.
2. Heart failure hospitalisation.
3. Hyperkalaemia.

Secondary outcomes

1. All-cause mortality.
2. Quality of life (measured using either the Minnesota Living With Heart Failure Questionnaire or Kansas City Cardiomyopathy Questionnaire).
3. Withdrawal due to adverse event (hypotension, hyperkalaemia or renal impairment).

Reporting one of more of the listed outcomes in the trial was not an inclusion criterion for the review. We assessed outcomes at the longest reported follow-up.

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases on 25 July 2017:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Wiley, Issue 6, June 2017);
2. MEDLINE (Ovid, 1946 to July Week 2 2017);
3. MEDLINE In-Process & Other Non-Indexed Citations, Epub Ahead of Print (Ovid, 24 July 2017); and
4. Embase and Embase Classic (embase.com, 1974 to 25 July 2017).

The search strategies used are included in Appendix 1. We applied the Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) to the main segment of MEDLINE (Ovid) (point 2 above) but did not use the filter when searching the MEDLINE Epub and In-Process database segments. We used the multi-term Embase filter with the best optimisation of sensitivity and specificity (Wong 2006) translated from Ovid to embase.com syntax.

We did not impose any restriction on language of publication.

Searching other resources

We searched ClinicalTrials.gov (https://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/) on 25 July 2017 to identify ongoing and unpublished trials. Search terms for the trials registers are also listed in Appendix 1.

We checked all primary references of included studies and systematic reviews for additional references. For any studies identified as eligible from clinical trial register records, we searched for the trials registry number on PubMed for publications about this study.

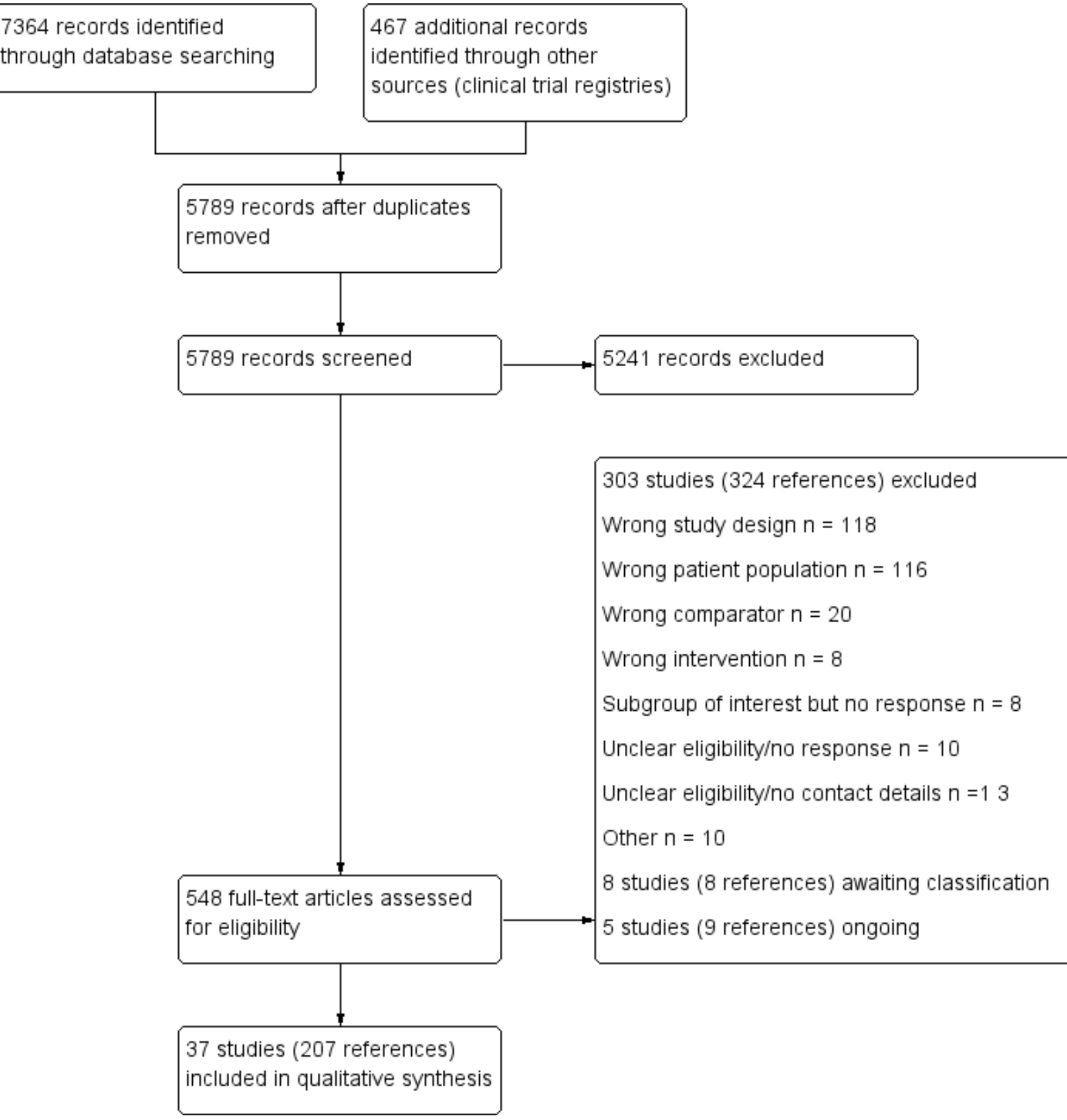
We contacted study authors to clarify details or obtain additional information not included in the published reports.

Data collection and analysis

Selection of studies

Two review authors (KM and NM) independently screened titles and abstracts of all records identified in our search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. In the event of disagreement, a third review author was asked to arbitrate (TL). We then retrieved the full-text study reports for records identified as eligible, potentially eligible or unclear. Two review authors (KM and NM) independently screened the full-text and identified studies for inclusion. We recorded reasons for exclusion of ineligible studies. We resolved any disagreement by consensus or consulted a third review author (TL). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram (Figure 1) and Characteristics of excluded studies table.

Figure 1. Study flow diagram



Data extraction and management

We used a data collection form to record study characteristics and outcome data from included studies, which had been piloted on two studies in the review (PEP-CHF; TOPCAT). Some modifications were made after the pilot phase. Two review authors (NM and TL) extracted study characteristics from included studies as follows:

1. Methods: study design, duration of follow-up, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and start/end date of enrolment.
2. Participants: N randomised/withdrawn/lost to follow-up/ analysed, mean age/age range, % male, inclusion criteria, exclusion criteria, systolic blood pressure, heart rate, body mass index, serum creatinine, B-type natriuretic peptide, NT pro B-type natriuretic peptide, LVEF, New York Heart Association (NYHA) class, comorbidity (hypertension, diabetes, atrial fibrillation, hospitalisation for heart failure, coronary heart disease, stroke, medications at baseline).
3. Interventions: intervention, comparison, concomitant medications (diuretic, digoxin, BB, ACEI, ARB, MRA).
4. Outcomes: planned and reported.
5. Notes: sources of funding, and notable conflicts of interest of trial authors.

Two review authors (NM and TL) independently extracted outcome data from included studies. Disagreements were resolved by consensus. One review author (NM) transferred data into the Review Manager (RevMan 2014) file. One review author (TL) double-checked that data were entered correctly by comparing the data presented in the systematic review with the data extraction sheet.

Assessment of risk of bias in included studies

Two review authors (NM and TL) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Disagreements were resolved by consensus. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We judged each potential source of bias as high, low or unclear and provided quotes from study reports together with justification for our judgment in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects in the pooled analysis, we accounted for risk of bias for the studies that contributed to each outcome tested.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported protocol deviations in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RR) with 95% confidence intervals (CI) and continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% CIs. We analysed mortality data as hazard ratios (HR). We used SMD for one analysis when combining quality of life data reported for two different scales. We entered data presented as a scale with a consistent direction of effect.

Unit of analysis issues

We included one three-arm trial (Hong Kong DHF); because two intervention arms contributed to two separate comparisons, no unit of analysis issue arose.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We considered possible causes in cases of substantial heterogeneity ($I^2 \geq 50\%$).

Assessment of reporting biases

We pooled fewer than 10 trials for each comparison. Therefore, we did not examine funnel plots to explore possible small-study biases for the primary outcomes.

Data synthesis

We undertook meta-analyses only where this was meaningful, that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. We used a fixed-effect model in the absence of substantial heterogeneity ($I^2 < 50\%$) and a random-effects model when unexplained substantial heterogeneity was present ($I^2 \geq 50\%$). We applied a random-effects model for quality of life analyses for MRA to account the high heterogeneity observed for the Kansas City Cardiomyopathy Questionnaire (KCCQ) (Analysis 2.7; $I^2 = 86\%$) and to permit a combined analysis with outcome data from the Minnesota Living With Heart Failure Questionnaire (MLHFQ) (Analysis 2.6; $I^2 = 50\%$).

We considered two relevant quality of life scales: the MLHFQ or KCCQ. The MLHFQ score has a range from 0 to 105, lower scores indicate better quality of life. The KCCQ score has a range from 0 to 100, higher scores indicate better quality of life. To account for the difference in the direction of the scale of the KCCQ, the mean values were multiplied by -1 (*Cochrane Handbook for Systematic Reviews of Interventions*, section 9.2.3.2, Deeks 2011). For the purpose of interpretation, we considered a five point difference in score as clinically significant for the MLHFQ (Rector 1995) and KCCQ (Spertus 2005).

'Summary of findings' table

We created 'Summary of findings' tables for each of our four interventions and included the following outcomes: cardiovascular mortality, heart failure hospitalisation, all-cause mortality, quality of life (Minnesota Living with Heart Failure Questionnaire) and hyperkalaemia. We used the five GRADE considerations (study limitations, inconsistencies, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (GRADEpro GDT). Four review authors assessed the quality of evidence (TL, NM, KM, CD). We documented our justification for decisions to downgrade the quality of evidence using footnotes.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Age.
2. Sex.
3. Heart failure with mid-range ejection fraction (HFmrEF) LVEF 40% to 49% and preserved LVEF ≥ 50%.
4. Length of follow-up < 12 months and ≥ 12 months.

We were only able to perform a subgroup analysis based on length of follow-up because data for the prespecified subgroups were unavailable.

We used the outcomes cardiovascular mortality and hospitalisation for heart failure in subgroup analyses.

We used the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We performed a sensitivity analysis for risk of bias by performing a pooled analysis including only studies with a low risk of bias (where at least four of the six domains for bias assessment were judged to be low risk and no domain was at high risk of bias).

RESULTS

Description of studies

Results of the search

The database searches retrieved 7364 records and the search of clinical trial registries retrieved 467 records. After de-duplication, 5789 records were screened by title and abstract. Of these, 5241 records did not meet the inclusion criteria and were excluded. The remaining 548 records were assessed for eligibility in full-text and 303 studies (324 references) were excluded.

Included studies

We included 37 studies (207 reports) that involved a total of 18,311 participants.

Beta-blockers

We included 10 studies (3087 participants) that investigated beta-blockers for HFpEF. Of these, five studies compared beta-blockers versus placebo (ELANDD; Mittal 2017; Sahoo 2016; SENIORS; SWEDIC) and five versus usual care (Adamyan 2010; Aronow 1997; J-DHF; Shu 2005; Takeda 2004). Four studies investigated carvedilol: Adamyan 2010 (up to 50 mg daily), J-DHF (up to 10 mg twice daily), SWEDIC (up to 25 mg twice daily or 50 mg twice daily in people weighing over 85 kg), Takeda 2004 (up to 20 mg daily). Two studies used nebivolol: ELANDD (up to 10 mg daily) and SENIORS (up to 10 mg daily). One study used propranolol: Aronow 1997 (30 mg, 3 times daily); and two studies investigated metoprolol succinate: Mittal 2017; Sahoo 2016 (up to 100 mg daily). Shu 2005 investigated bisoprolol (up to 10 mg daily).

Numbers of participants randomised ranged from 40 (Mittal 2017; Takeda 2004) to 643 (SENIORS).

Four were multicentre studies. ELANDD was conducted across 12 centres in eight countries in Europe; J-DHF was assumed to have taken place in Japan; SENIORS took place in 11 countries (Czech Republic, France, Germany, Hungary, Italy, Netherlands, Romania, Spain, Switzerland, UK and Ukraine), and SWEDIC took place in 12 centres in Sweden. Mittal 2017 and Sahoo 2016 were each conducted in one centre in India. Adamyan 2010, Aronow 1997 and Shu 2005 did not report numbers of centres or countries, but we assumed that Adamyan 2010 likely took place in Armenia. Takeda 2004 was a single centre trial in Japan.

Three studies did not report LVEF of the included participants at baseline (Adamyan 2010; Shu 2005; SWEDIC). Six studies reported LVEF at baseline with a mean ranging from 56% to 63% (Aronow 1997; ELANDD; J-DHF; Mittal 2017; Sahoo 2016; Takeda 2004). SENIORS included participants with a "clinical history of chronic HF with at least 1 of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive HF or documented LVEF ≤ 35% within the previous 6 months". The SENIORS study reported a subgroup of participants with LVEF > 40% and these outcome data were used in our analysis (643 participants).

Most participants were NYHA class II (51% to 78%). Shu 2005 did not report participants' NYHA class at baseline. Participants' mean age ranged from 30 years to 81 years; six studies reported mean age less than 70 years (Adamyan 2010; ELANDD; Mittal 2017; Sahoo 2016; Shu 2005; SWEDIC) and four reported mean age above 70 years (Aronow 1997; J-DHF; SENIORS; Takeda 2004).

Three studies were funded by industry (ELANDD; SENIORS; SWEDIC); two studies were funded by not-for-profit organisations (J-DHF; Mittal 2017); and five did not report sources of funding (Adamyan 2010; Aronow 1997; Sahoo 2016; Shu 2005; Takeda 2004).

Mineralocorticoid receptor antagonists (MRA)

We included 12 studies that investigated MRAs for HFpEF. Of these, eight compared MRA versus placebo (ALDO-DHF; AREA IN-CHF; Kurrelmeyer 2014; Mottram 2004; RAAM-PEF; STRUCTURE; TOPCAT; Upadhya 2017) and four versus usual care (Karapysh 2015; Mak 2009; Orea-Tejeda 2007; Wang 2010). Nine studies investigated spironolactone (ALDO-DHF; Kurrelmeyer 2014; Mottram 2004; STRUCTURE; Upadhya 2017 (25 mg/d); Karapysh 2015; Orea-Tejeda 2007 (25 mg/d up-titrated if tolerated to 50 mg/d); TOPCAT (15 mg/

d, increased to a maximum of 45 mg/d); Wang 2010 (50 mg/d)). Two studies used eplerenone (Mak 2009; RAAM-PEF (25 mg/d to a maximum of 50 mg/d)). AREA IN-CHF investigated canrenone at a maximum dose of 50 mg/d.

Numbers of participants randomised ranged from 28 (Orea-Tejeda 2007) to 3445 (TOPCAT). Four were multicentre trials; ALDO-DHF included 10 centres in Germany and Austria; AREA IN-CHF was conducted in 46 centres in Italy; STRUCTURE had centres in Poland (the number is unclear but publication states "of each centre"); and TOPCAT was conducted across 233 sites in six countries (Argentina, Brazil, Canada, Georgia, Russia, USA). Two studies were single-centre trials in USA (Kurrelmeyer 2014; RAAM-PEF). Mottram 2004 was a single centre trial in Australia. Wang 2010 was a single centre trial in Taiwan. Mak 2009 was a single-centre trial but the country was unspecified. Three trials did not report on numbers of centres or countries (Karapysh 2015; Orea-Tejeda 2007; Upadhya 2017).

Two studies (Karapysh 2015; Mottram 2004) did not report participants' LVEF at baseline. AREA IN-CHF had a mean LVEF at baseline of 39.9% (intervention) and 39.7% (control) for the overall included participants (N = 467). However, we obtained outcome data for the subgroup of participants with LVEF > 40% (N = 225). The LVEF in the remaining seven studies ranged from 62% to 72%.

Most participants in five studies were NYHA class II (52% to 88%; ALDO-DHF; Mak 2009; RAAM-PEF; STRUCTURE; TOPCAT). Most participants in two studies were NYHA class III (58% to 64%; Kurrelmeyer 2014; Upadhya 2017). Three studies did not report NYHA class for participants eligible for inclusion in our review (AREA IN-CHF; Karapysh 2015; Mottram 2004). Orea-Tejeda 2007 reported that most participants in the intervention arm were NYHA class III (57.1%) and NYHA class I (75%) in the control arm.

Participants' mean age ranged from 54.5 years to 80 years; seven studies included participants whose mean age was less than 70 years (ALDO-DHF; AREA IN-CHF; Karapysh 2015; Mottram 2004; Orea-Tejeda 2007; STRUCTURE; TOPCAT). In four studies, participants' mean age was over 70 years (Kurrelmeyer 2014; Mak 2009; RAAM-PEF; Upadhya 2017).

AREA IN-CHF was industry funded; six studies were funded by not-for-profit organisations (ALDO-DHF; Kurrelmeyer 2014; RAAM-PEF; STRUCTURE; TOPCAT; Upadhya 2017). Five studies did not report sources of funding (Karapysh 2015; Mak 2009; Mottram 2004; Orea-Tejeda 2007; Wang 2010).

Angiotensin converting enzyme inhibitors (ACEI)

We included eight studies that investigated ACEIs for HFpEF. Of these, three compared ACEI with placebo (Kitzman 2010; PEP-CHF; Zi 2003), and five versus usual care (Aronow 1993; Aronow 1998; Hong Kong DHF; SNEGOVIK; Yuksek 2012). Two studies investigated enalapril (Aronow 1993, up to 20 mg daily; Kitzman 2010, up to 10 mg daily). Aronow 1998 investigated benazepril (up to 40 mg/d). Two studies investigated perindopril (PEP-CHF, up to 4 mg daily; Yuksek 2012, up to 10 mg). Hong Kong DHF investigated ramipril in one of two active arms (maximum of 10 mg daily). Two studies investigated quinapril (SNEGOVIK, dose not reported; Zi 2003, up to 40 mg daily).

Numbers of participants randomised ranged from 21 (Aronow 1993) to 850 (PEP-CHF). Two studies were reportedly multicentre trials (Hong Kong DHF; PEP-CHF). Hong Kong DHF did not report details on the number of centres. PEP-CHF was conducted at 53 centres in Bulgaria (3), Czech Republic (5), Hungary (10), Ireland (1), Poland (26), Russia (1), Slovakia (2), and the UK (5). Zi 2003 took place at one hospital in the UK and Yuksek 2012 was conducted in Turkey. The countries or number of centres were not reported in four studies (Aronow 1993; Aronow 1998; Kitzman 2010; SNEGOVIK).

The mean LVEF of the included participants at baseline was not reported by two studies (SNEGOVIK; Zi 2003). LVEF ranged from 61% to 69% in five studies (Aronow 1993; Aronow 1998; Hong Kong DHF; Kitzman 2010; PEP-CHF). Most participants were classified in NYHA class II in four studies (Hong Kong DHF; Kitzman 2010; PEP-CHF; Zi 2003) and in NYHA class III in one study (Aronow 1993). Two studies did not report participants' NYHA class at baseline (Aronow 1998; SNEGOVIK).

Participants' mean age ranged from 70 years to 82 years with all studies equal to or over a mean age of 70 years.

Four studies did not report funding sources (Aronow 1993; Aronow 1998; SNEGOVIK; Yuksek 2012). Three studies were industry funded (Hong Kong DHF; PEP-CHF; Zi 2003) and one study was funded by a not-for profit organisation (Kitzman 2010).

Angiotensin receptor blockers (ARB)

We included eight studies that investigated ARBs for HFpEF. Of these, five compared ARB versus placebo (CAN-DHF; CHARM-Preserved; I-PRESERVE; Kasama 2005; Parthasarathy 2009) and three compared ARB versus usual care (CandHeart; Hong Kong DHF; SUPPORT). Four studies investigated candesartan (CAN-DHF; CandHeart; CHARM-Preserved (up to 32 mg daily), Kasama 2005 (8 mg to 12 mg daily)). Two studies investigated irbesartan (one of the two active treatment arms in Hong Kong DHF (up to 75 mg daily), I-PRESERVE (up to 300 mg)). Parthasarathy 2009 investigated valsartan (80 mg daily). SUPPORT investigated olmesartan (up to 40 mg daily).

Numbers of participants randomised ranged from 22 (CAN-DHF) to 4128 (I-PRESERVE). Seven were multicentre trials: CAN-DHF was conducted at eight centres in Germany; CandHeart at 70 centres in Italy; CHARM-Preserved was conducted at 618 centres in 26 countries; I-PRESERVE involved 293 centres in 25 countries; Parthasarathy 2009 was conducted at five centres each in Germany and the UK; and SUPPORT was conducted at 17 centres in Japan. Hong Kong DHF was reported to be a multicentre trial but no details were provided on numbers of centres or countries. Kasama 2005 was reported to be a single-centre trial in Japan.

The mean LVEF of the included participants at baseline was not reported by CAN-DHF and ranged from 49% to 72% in seven studies (CandHeart; CHARM-Preserved; Hong Kong DHF; I-PRESERVE; Kasama 2005; Parthasarathy 2009; SUPPORT). Most participants were assessed as NYHA class II at baseline in five studies (CandHeart; CHARM-Preserved; Hong Kong DHF; Kasama 2005; SUPPORT); NYHA class III in I-PRESERVE; and was not reported by two studies (CAN-DHF; Parthasarathy 2009).

Participants' mean age ranged from 61 years to 75 years. Mean age was below 70 years in six studies (CAN-DHF; CandHeart; CHARM-Preserved; Kasama 2005; Parthasarathy 2009; SUPPORT) and over 70 years in two studies (Hong Kong DHF; I-PRESERVE).

Six studies were funded by industry (CAN-DHF; CandHeart; CHARM-Preserved; Hong Kong DHF; I-PRESERVE; Parthasarathy 2009). SUPPORT was funded by a not-for-profit organisation. Kasama 2005 did not report the source of funding.

Angiotensin receptor neprilysin inhibitors (ARNI)

We did not identify any completed trials that compared ARNI to placebo or no treatment control. However, one completed and two ongoing active controlled studies were identified investigating ARNI for HFpEF. Although people with HFpEF and co-existing hypertension are often treated with the active comparators used in these studies (ARB or ACEI), these therapies are not considered as usual care for HFpEF.

The PARAMOUNT study, which randomised participants with HFpEF defined as heart failure with LVEF ≥ 45%, investigated ARNI (sacubitril/valsartan), (N = 149) or matching ARB (valsartan), (N = 152) (Zile 2016). The primary outcome measure was change in N-terminal pro b-type natriuretic peptide (NT-proBNP), and secondary outcomes included echocardiographic parameters, NYHA class, and quality of life (KCCQ). During the 36-week follow-up, one death occurred in the ARNI group and two deaths in the ARB group. Hyperkalaemia and quality of life outcomes did not differ between groups (Solomon 2012). PERSPECTIVE (NCT02884206) is an ongoing RCT to examine the effect of LCZ696 compared to valsartan on cognitive outcomes in participants with HFpEF, defined as LVEF > 40%. NCT03066804 is a four-arm, parallel group study to compare the effects of sacubitril/valsartan, enalapril, valsartan and placebo in participants with HFpEF (LVEF ≥ 45%), with estimated enrolment of 2200 participants.

PARAGON-HF (NCT01920711) is a large active comparator RCT comparing sacubitril/valsartan with valsartan for a composite primary outcome of cardiovascular death and heart failure hospitalisation. The study is ongoing with 4822 participants enrolled, and an estimated study completion date of March 2019.

Excluded studies

We excluded 303 studies (324 references) based on full-text assessment. Details for the reasons for exclusion are provided in the Characteristics of excluded studies table. In summary we made exclusions based on:

- wrong population: n = 116;
- wrong intervention: n = 8;
- wrong comparator: n = 20;
- wrong study design: n = 118;
- subgroup of interest but no response to our enquiry for data: n = 8;
- unclear eligibility and no response to our enquiry for details: n = 10;
- unclear eligibility and no current contact details: n = 13;
- completed status in trial registry record but no published results and no response to our enquiry for data: n = 1;
- missing data and response that no details can be provided: n = 6;
- retraction: n = 1; and
- did not take place as planned: n = 2.

Studies awaiting classification

We identified eight studies that await classification (Anonymous 2003d; Botoni 2010; Dielievska 2015; Gao 2010; Liu 2006; Metra 1999; Rapezzi 1999; Zheng 2009; Characteristics of studies awaiting classification). We are waiting to retrieve the full-text (n = 4), responses from translators (n = 3) and response from the trialists to clarify eligibility (n = 1).

Ongoing studies

We identified five ongoing studies (EudraCT 2013-000867-10; IMPRESS-AF; NCT02901184; NCT03066804; Zhou 2010; Characteristics of ongoing studies). Three studies are investigating MRAs: spironolactone versus placebo (EudraCT 2013-000867-10; IMPRESS-AF); spironolactone versus usual care (NCT02901184). NCT03066804 is a four-arm trial comparing ARNI (sacubitril/valsartan), ACEI (enalapril), ARB (valsartan) and matching placebo. Zhou 2010 is testing a beta-blocker (metoprolol succinate) versus usual care.

Risk of bias in included studies

The risk of bias assessments are detailed in the Characteristics of included studies tables, and summarised in the text below and in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

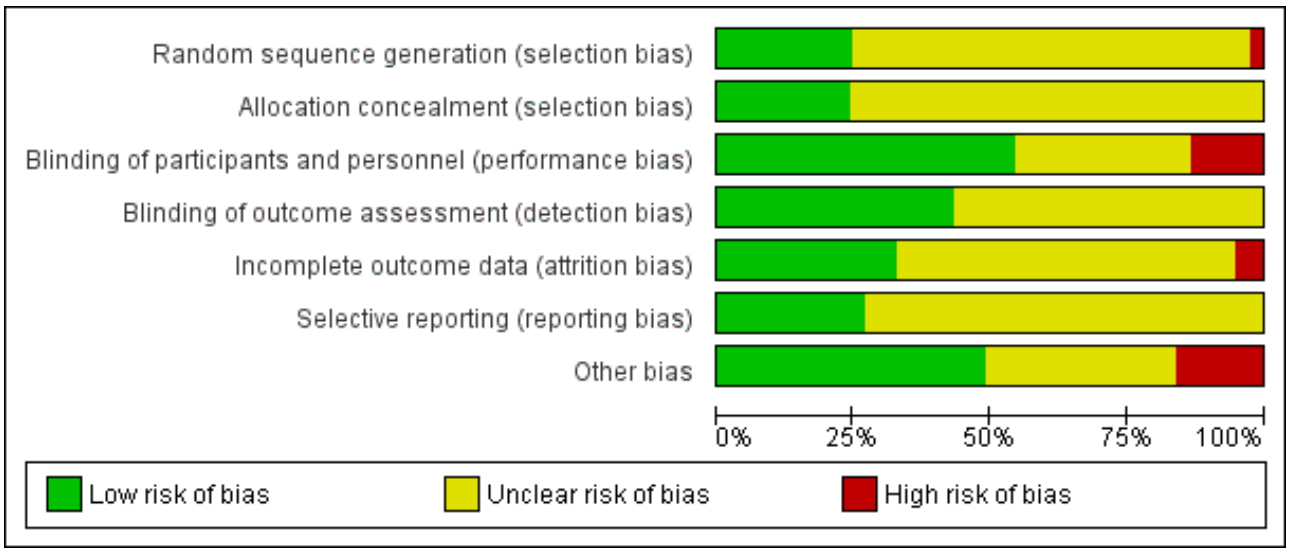


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

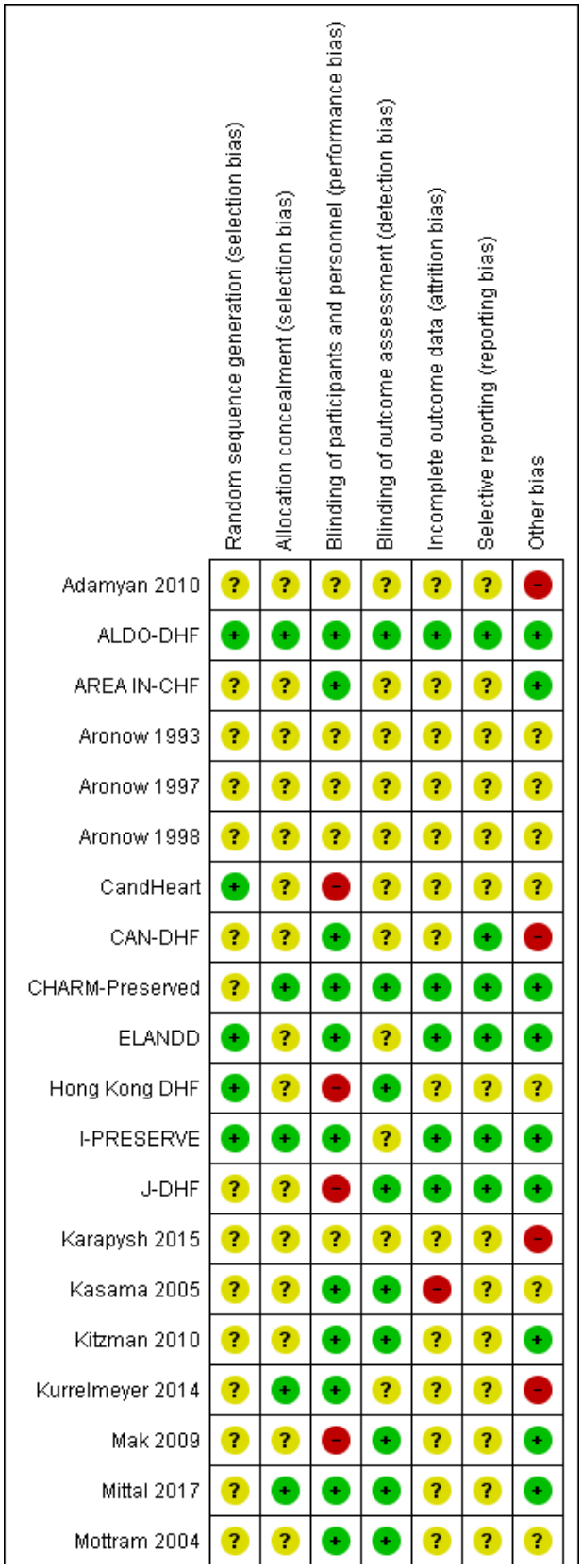
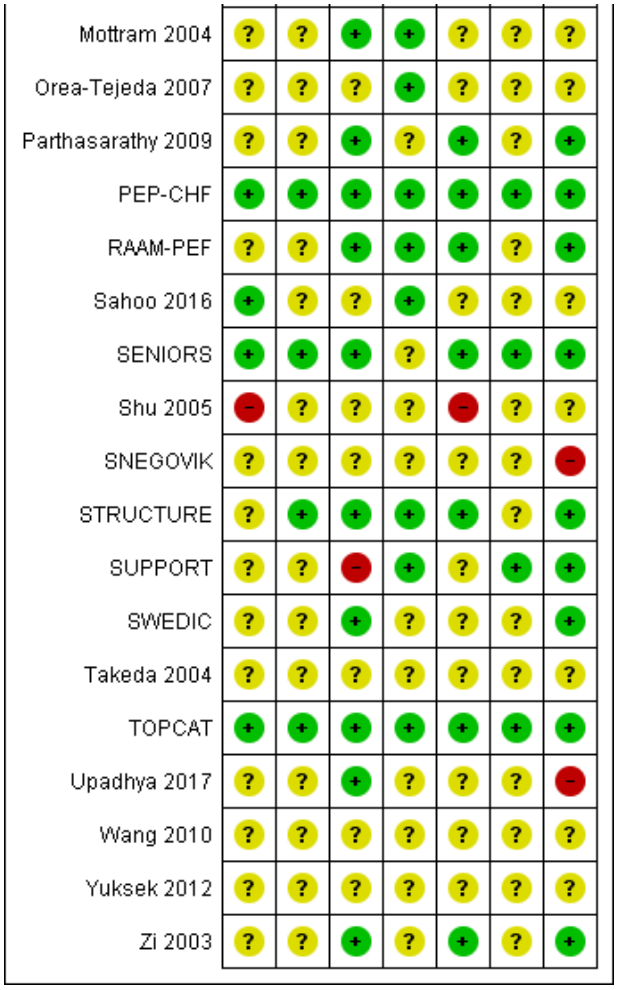


Figure 3. (Continued)



Allocation

Nine studies reported random sequence methods and were rated as low risk of bias (ALDO-DHF; CandHeart; ELANDD; Hong Kong DHF; I-PRESERVE; PEP-CHF; Sahoo 2016; SENIORS; TOPCAT). We assessed 28 studies at unclear risk of bias for this domain because no information was provided in study reports.

Nine studies used a method for allocation concealment that was judged to be of low risk of bias (ALDO-DHF; CHARM-Preserved; I-PRESERVE; Kurrelmeyer 2014; Mittal 2017; PEP-CHF; SENIORS; STRUCTURE; TOPCAT). We assessed 28 studies at unclear risk of bias for this domain because no information was provided in study reports.

Blinding

We assessed 20 studies as low risk of bias regarding blinding of participants and personnel (ALDO-DHF; AREA IN-CHF; CAN-DHF; CHARM-Preserved; ELANDD; I-PRESERVE; Kasama 2005; Kitzman 2010; Kurrelmeyer 2014; Mittal 2017; Mottram 2004; Parthasarathy 2009; PEP-CHF; RAAM-PEF; SENIORS; STRUCTURE; SWEDIC; TOPCAT; Upadhya 2017; Zi 2003). Five studies were open-label designs and therefore judged to be at high risk of bias for this domain (CandHeart; Hong Kong DHF; J-DHF; Mak 2009; SUPPORT).

The remaining 12 studies were assessed at unclear risk of bias because no information was provided.

Detection bias was judged to be at low risk in 16 studies (ALDO-DHF; CHARM-Preserved; Hong Kong DHF; J-DHF; Kasama 2005; Kitzman 2010; Mak 2009; Mittal 2017; Mottram 2004; Orea-Tejeda 2007; PEP-CHF; RAAM-PEF; Sahoo 2016; STRUCTURE; SUPPORT; TOPCAT). The remaining 21 studies did not provide information and were judged to be at unclear risk of detection bias.

Incomplete outcome data

Attrition bias was judged to be at low risk in 12 studies (ALDO-DHF; CHARM-Preserved; ELANDD; I-PRESERVE; J-DHF; Parthasarathy 2009; PEP-CHF; RAAM-PEF; SENIORS; STRUCTURE; TOPCAT; Zi 2003). We judged Kasama 2005 to be at high risk of bias for this domain because the study report did not indicate if losses to follow-up or withdrawals occurred. All other 25 studies were assessed as unclear risk of bias for attrition bias as no information was reported to allow judgement.

Selective reporting

We assessed 10 studies to be at low risk of reporting bias (ALDO-DHF; CAN-DHF; CHARM-Preserved; ELANDD; I-PRESERVE; J-DHF; PEP-CHF; SENIORS; SUPPORT; TOPCAT). These 10 studies reported

planned outcomes in either published protocols or clinical trial registers before enrolment started. We were unable to assess reporting bias in 27 studies because either no information was available in the form of protocols or clinical trial registry entries, or they were published/entered after enrolment was completed.

Other potential sources of bias

We judged 18 studies to be at low risk of other biases (mainly based on providing details on funding and declaring any conflict of interest by the authors) (ALDO-DHF; AREA IN-CHF; CHARM-Preserved; ELANDD; I-PRESERVE; J-DHF; Kitzman 2010; Mak 2009; Mittal 2017; Parthasarathy 2009; PEP-CHF; RAAM-PEF; SENIORS; STRUCTURE; SUPPORT; SWEDIC; TOPCAT; Zi 2003).

We judged six studies to be at high risk of other bias. Kurrelmeyer 2014 was originally registered as an observational study and this detail was changed after completion of the trial but before the results were published. Five studies (Adamyan 2010; CAN-DHF; Karapysh 2015; SNEGOVIK; Upadhya 2017) were published as conference abstracts only; withholding the full results from publication may present a form of bias. The remaining 26 studies were judged to be at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Beta-blockers compared to placebo or no treatment for chronic heart failure with preserved ejection fraction; **Summary of findings 2** MRA compared to placebo or no treatment for chronic heart failure with preserved ejection fraction; **Summary of findings 3** ACEI compared to placebo or no treatment for chronic heart failure with preserved ejection fraction; **Summary of findings 4** ARB compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Beta-blockers versus placebo or no treatment

We included 10 studies that involved a total of 3087 participants that assessed beta-blockers versus placebo or no treatment. The main outcomes for this comparison are included in Summary of findings for the main comparison.

Cardiovascular mortality

Six studies reported cardiovascular mortality (Aronow 1997; ELANDD; J-DHF; SENIORS; SWEDIC; Takeda 2004). Three studies reported that no deaths occurred (ELANDD; SWEDIC; Takeda 2004). We included three studies in the meta-analysis (Aronow 1997; J-DHF; SENIORS) (15% of participants in the intervention arm versus 19% in the control arm; RR 0.78; 95% CI 0.62 to 0.99; NNTB 25; 1046 participants; I^2 = 0%; low-quality evidence; Analysis 1.1).

J-DHF reported cardiovascular mortality but with different numbers for events within the same table (Table 2 in the primary reference). We contacted the study authors to seek clarification but are yet to receive a response; we used the higher numbers in the analysis.

SENIORS reported a hazard ratio (HR 0.80; 95% CI 0.49 to 1.32; 643 participants).

Heart failure hospitalisation

We included five studies that reported heart failure hospitalisation (ELANDD; J-DHF; Shu 2005; SWEDIC; Takeda 2004). ELANDD reported that no hospitalisation occurred due to heart failure. Data from four studies (J-DHF; Shu 2005; SWEDIC; Takeda 2004) contributed to the meta-analysis (RR 0.73; 95% CI 0.47 to 1.13; 449 participants; I^2 = 22%; very low-quality evidence; Analysis 1.2).

Hyperkalaemia

J-DHF reported that one participant in the intervention group (N = 120) experienced hyperkalaemia but did not report on this outcome for the control group (very low-quality evidence). No further data were available from any other studies.

All-cause mortality

We included seven studies that reported all-cause mortality (Adamyan 2010; Aronow 1997; ELANDD; J-DHF; SENIORS; SWEDIC; Takeda 2004). Of these, three studies reported that no deaths occurred (ELANDD; SWEDIC; Takeda 2004). We included data from four studies in the meta-analysis (Adamyan 2010; Aronow 1997; J-DHF; SENIORS) (RR 0.82; 95% CI 0.67 to 1.00; 1105 participants; I^2 = 0%; low-quality evidence; Analysis 1.3).

J-DHF reported all-cause mortality but with different numbers for events within the same table (Table 2 in the primary reference). We contacted the study authors to seek clarification but are yet to receive a response. We used the higher number of deaths in the analysis.

SENIORS reported a hazard ratio (HR 0.92; 95% CI 0.61 to 1.36; 643 participants).

Quality of life

We included two studies that reported quality of life (ELANDD; Mittal 2017). Mittal 2017 reported quality of life using SF-36, which was not a scale we considered for our analysis. ELANDD reported end scores for the Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score and showed MD -1.00 between the treatment arms, favouring the intervention (95% CI -9.05 to 7.05; 93 participants; very low-quality evidence).

Withdrawal due to adverse event

We included five studies that reported withdrawals due to adverse events (Aronow 1997; ELANDD; J-DHF; Mittal 2017; Sahoo 2016). Mittal 2017 and Sahoo 2016 reported no withdrawals due to adverse events. Aronow 1997 reported 11 withdrawals due to "worsening CHF [chronic heart failure] in 7 patients and hypotension in 4 patients" but did not provide this information by intervention arm. Only two studies (ELANDD; J-DHF) contributed data for meta-analysis (9% of participants in the intervention arm versus 0% in the control arm, RR 18.07; 95% CI 2.45 to 133.04; 338 participants; I^2 = 0%; Analysis 1.5; number needed to harm (NNTH) 11).

Mineralocorticoid receptor antagonists (MRA) versus placebo or no treatment

We included 12 studies (4408 participants) that assessed MRA versus placebo or no treatment. The main outcomes for this comparison are included in Summary of findings 2. The findings for this comparison were driven by one trial (TOPCAT). Four trials (Karapysh 2015; Mottram 2004; Orea-Tejeda 2007; Wang 2010) did not contribute any outcome data of interest for this review.

Cardiovascular mortality

We included five studies that reported cardiovascular mortality (ALDO-DHF; AREA IN-CHF; Kurrelmeyer 2014; RAAM-PEF; TOPCAT). Of these, two studies reported that no deaths occurred (Kurrelmeyer 2014; RAAM-PEF). We included data from three studies in the meta-analysis (ALDO-DHF; AREA IN-CHF; TOPCAT) (RR 0.90; 95% CI 0.74 to 1.11; 4070 participants; I^2 = 0%; moderate-quality evidence; Analysis 2.1).

TOPCAT also reported a hazard ratio (HR 0.90; 95% CI 0.73 to 1.12; 3445 participants).

Heart failure hospitalisation

We included six studies that reported heart failure hospitalisation (ALDO-DHF; AREA IN-CHF; Kurrelmeyer 2014; RAAM-PEF; TOPCAT; Upadhya 2017). Of these, three studies reported no hospitalisations due to heart failure (ALDO-DHF; Kurrelmeyer 2014; Upadhya 2017). We included data from three studies in the meta-analysis (AREA IN-CHF; RAAM-PEF; TOPCAT) (11% of participants in the intervention arm versus 14% in the control arm, RR 0.82; 95% CI 0.69 to 0.98; 3714 participants; NNTB 41; I^2 = 22%; moderate-quality evidence; Analysis 2.2).

Hazard ratios for time to first heart failure hospitalisation were reported for two studies (AREA IN-CHF; TOPCAT) (HR 0.82; 95% CI 0.69 to 0.98; 3670 participants; I^2 = 59%; Analysis 2.3). The substantial heterogeneity was explained by differences in population characteristics (TOPCAT, LVEF ≥ 45%; AREA IN-CHF subgroup, LVEF 40% to 45%).

Hyperkalaemia

We included six studies that reported hyperkalaemia (ALDO-DHF; AREA IN-CHF; Kurrelmeyer 2014; RAAM-PEF; STRUCTURE; TOPCAT) (16% of participants in the intervention arm versus 8% in the control arm, RR 2.11; 95% CI 1.77 to 2.51; 4291 participants; I^2 = 0%; high-quality evidence; Analysis 2.4).

All-cause mortality

We included eight studies that reported all-cause mortality (ALDO-DHF; AREA IN-CHF; Kurrelmeyer 2014; Mak 2009; RAAM-PEF; STRUCTURE; TOPCAT; Upadhya 2017). Of these, three studies reported that no deaths occurred (Kurrelmeyer 2014; RAAM-PEF; STRUCTURE). The meta-analysis included data from five studies (ALDO-DHF; AREA IN-CHF; Mak 2009; TOPCAT; Upadhya 2017) (RR 0.91; 95% CI 0.78 to 1.06; 4207 participants; I^2 = 0%; moderate-quality evidence; Analysis 2.5).

TOPCAT also reported a hazard ratio (HR 0.91; 95% CI 0.77 to 1.08; 3445 participants).

Quality of life

We included six studies that reported quality of life (ALDO-DHF; Kurrelmeyer 2014; Mak 2009; RAAM-PEF; TOPCAT; Upadhya 2017). TOPCAT reported quality of life in a report by Lewis 2016, but the end scores per treatment arm were not provided. We contacted the investigators and await details.

Three studies (ALDO-DHF; Mak 2009; Upadhya 2017) reported total MLFHQ scores and were pooled for analysis (MD 0.84; 95% CI -2.30 to 3.98; 511 participants; I^2 = 0%; low-quality evidence; Analysis 2.8). Kurrelmeyer 2014 and RAAM-PEF reported Kansas City Cardiomyopathy Questionnaire (KCCQ) results and were pooled (MD -0.78; 95% CI -28.02 to 26.46; 92 participants; I^2 = 86%; Analysis 2.7). The substantial heterogeneity could not be explained.

All five studies that used MLHFQ and KCCQ were pooled (SMD 0.05; 95% CI -0.23 to 0.34; 603 participants; I^2 = 50%; Analysis 2.6). The substantial heterogeneity could not be explained.

Withdrawal due to adverse event

Four studies reported this outcome (ALDO-DHF; Kurrelmeyer 2014; TOPCAT; Upadhya 2017) and contributed to the meta-analysis (RR 1.10; 95% CI 1.00 to 1.21; 3986 participants; I^2 = 0%; Analysis 2.9).

Angiotensin converting enzyme inhibitors (ACEI) versus placebo or no treatment

We included eight studies that involved a total of 2061 participants that assessed ACEI versus placebo or no treatment. The main outcomes for this comparison are presented in Summary of findings 3. The findings for this comparison were driven by PEP-CHF. Two studies (Aronow 1993; Yuksek 2012) did not contribute any outcome data of interest for this review.

Cardiovascular mortality

Three studies reported cardiovascular mortality (Hong Kong DHF; Kitzman 2010; PEP-CHF). Kitzman 2010 reported that no deaths occurred. Hong Kong DHF and PEP-CHF contributed data to the meta-analysis (RR 0.93; 95% CI 0.61 to 1.42; 945 participants; I^2 = 0%; moderate-quality evidence; Analysis 3.1).

PEP-CHF also reported a hazard ratio (HR 0.98; 95% CI 0.63 to 1.52; 850 participants).

Heart failure hospitalisation

Three studies (Hong Kong DHF; PEP-CHF; Zi 2003) reported heart failure hospitalisation and were pooled for analysis (RR 0.86, 95% CI 0.64 to 1.15; 1019 participants; I^2 = 0%; moderate-quality evidence; Analysis 3.2).

PEP-CHF also reported a hazard ratio (HR 0.86, 95% CI 0.61 to 1.20; 850 participants).

Hyperkalaemia

Zi 2003 reported hyperkalaemia (RR 5.27; 95% CI 0.26 to 106.16; 74 participants; very low-quality evidence; Analysis 3.3).

All-cause mortality

We included five studies that reported all-cause mortality (Aronow 1998; Hong Kong DHF; Kitzman 2010; PEP-CHF; Zi 2003). Kitzman 2010 reported that no deaths occurred. Four studies (Aronow 1998; Hong Kong DHF; PEP-CHF; Zi 2003) contributed to the meta-analysis (RR 0.99; 95% CI 0.71 to 1.38; 1079 participants; I^2 = 0%; moderate-quality evidence; Analysis 3.4).

PEP-CHF also reported a hazard ratio (HR 1.09; 95% CI 0.75 to 1.58; 850 participants).

Quality of life

Three studies reported quality of life assessed using the MLHFQ scale (Hong Kong DHF; Kitzman 2010; SNEGOVIK). SNEGOVIK reported quality of life assessment based on the MLHFQ scale as

change from baseline per treatment arm (-18.9 for intervention, -10.7 for control). We were unsuccessful in our attempts to contact study authors to obtain scores at the end of follow-up. Two studies (Hong Kong DHF; Kitzman 2010) contributed to the meta-analysis (MD -0.09; 95% CI -3.66 to 3.48; 154 participants; I^2 = 4%; low-quality evidence; Analysis 3.5).

Zi 2003 assessed quality of life using the McMaster quality of life questionnaire and reported end scores at six months and reported 12.9 ± 3.1 for the intervention and 13.1 ± 4.7 for the control arm.

Withdrawal due to adverse event

Three studies (Hong Kong DHF; PEP-CHF; Zi 2003) reported this outcome and were pooled for analysis (RR 1.53; 95% CI 0.26 to 9.00; 1019 participants; I^2 = 59%; Analysis 3.6).

Angiotensin receptor blockers (ARB) versus placebo or no treatment

We included eight studies that involved a total of 8755 participants that assessed ARB versus placebo or no treatment. The main outcomes for this comparison are included in Summary of findings 4. The findings for this comparison were driven by two studies (CHARM-Preserved; I-PRESERVE). Three trials (CAN-DHF; CandHeart; Kasama 2005) did not contribute any outcome data of interest for this review.

Cardiovascular mortality

Four studies reported this outcome (CHARM-Preserved; Hong Kong DHF; I-PRESERVE; Parthasarathy 2009). Parthasarathy 2009 reported that no deaths occurred. Three studies (CHARM-Preserved; Hong Kong DHF; I-PRESERVE) contributed to the meta-analysis (RR 1.02; 95% CI 0.90 to 1.14; 7254 participants; I^2 = 0%; high-quality evidence; Analysis 4.1).

Two studies (CHARM-Preserved; I-PRESERVE) were also pooled for analysis (HR 1.00; 95% CI 0.89 to 1.13; 5087 participants; Analysis 4.2).

Heart failure hospitalisation

Three studies (CHARM-Preserved; Hong Kong DHF; I-PRESERVE) reported this outcome and were pooled for analysis (RR 0.92; 95% CI 0.83 to 1.02; 7254 participants; I^2 = 0%; high-quality evidence; Analysis 4.3).

Two studies (CHARM-Preserved; I-PRESERVE) were also pooled for analysis (HR 0.90; 95% CI 0.80 to 1.01; 7148 participants; Analysis 4.4).

Hyperkalaemia

Two studies reported this outcome and were pooled for analysis (CHARM-Preserved; I-PRESERVE) (0.9% of participants in the intervention group and 0.5% in the control group; RR 1.88; 95% CI 1.07 to 3.33; participants = 7148; high-quality evidence; Analysis 4.5).

All-cause mortality

Five studies reported this outcome (CHARM-Preserved; Hong Kong DHF; I-PRESERVE; Parthasarathy 2009; SUPPORT). Parthasarathy 2009 reported that no deaths occurred. Four studies (CHARM-Preserved; Hong Kong DHF; I-PRESERVE; SUPPORT) contributed to the meta-analysis (RR 1.01; 95% CI 0.92 to 1.11; 7964 participants; I^2 = 0%; high-quality evidence; Analysis 4.6). For the SUPPORT trial, data for participants with LVEF ≥ 50% were analysed according to the definition of HFpEF used in this trial.

Two studies (I-PRESERVE; SUPPORT) were also pooled for analysis (HR 0.99; 95% CI 0.88 to 1.12; 4838 participants; Analysis 4.7).

Quality of life

Four studies reported this outcome (CHARM-Preserved; Hong Kong DHF; I-PRESERVE; Parthasarathy 2009). CHARM-Preserved reported quality of life (MLHF) in a study report (Lewis 2007): however, end scores per treatment arm were not provided. Three studies (Hong Kong DHF; I-PRESERVE; Parthasarathy 2009) contributed to the meta-analysis for MLHF (MD 0.41; 95% CI -0.86 to 1.67; 3117 participants; I^2 = 19%; high-quality evidence; Analysis 4.8).

Withdrawal due to adverse event

Four studies (CHARM-Preserved; Hong Kong DHF; I-PRESERVE; Parthasarathy 2009) reported this outcome and contributed to the meta-analysis (16% of participants in the intervention arm versus 13% in the control arm; RR 1.22; 95% CI 1.09 to 1.36; 7406 participants; I^2 = 0%; Analysis 4.9; NNTH 33).

Angiotensin receptor neprilysin inhibitors (ARNI) versus placebo or no treatment

We did not identify any completed trials that assessed ARNI.

Subgroup analyses

We were unable to perform a subgroup analysis for length of follow up for cardiovascular mortality as all included studies fell into one category of follow-up (≥ 12 months: Analysis 1.1; Analysis 2.1; Analysis 3.1; Analysis 4.1). Similarly, we were unable to perform a subgroup analysis for ARB and heart failure hospitalisation (Analysis 4.3).

Heart failure hospitalisation for the comparison of beta-blockers versus control (Analysis 1.2) showed no difference among the subgroups (< 12 months: RR 0.31; 95% CI 0.09 to 1.02; 67 participants; 1 study; versus ≥ 12 months: RR 0.79; 95% CI 0.48 to 1.31; 285 participants; studies = 2). SWEDIC did not report length of follow-up.

Heart failure hospitalisation for the comparison of MRA versus control (Analysis 2.2) showed a confirmation of the overall effect estimate (RR 0.82; 95% CI 0.69 to 0.98; 3714 participants; 3 studies) only in the subgroup for follow-up ≥ 12 months (RR 0.82; 95% CI 0.69 to 0.98; 3670 participants; 2 studies) while the much smaller study of shorter duration (< 12 months) showed RR 0.55; 95% CI 0.05 to 5.61; 44 participants.

Heart failure hospitalisation for the comparison of ACEI versus control (Analysis 3.2) showed no difference between subgroups (< 12 months: RR 0.42; 95% CI 0.09 to 2.04; 74 participants; 1 study; versus ≥ 12 months: RR 0.88; 95% CI 0.66 to 1.19; 945 participants; 2 studies).

Sensitivity analyses

We conducted a sensitivity analysis by only including studies assessed at low risk of bias. Across comparisons, the estimates were not significantly changed with the exception of beta-blockers where

no effect on cardiovascular mortality was observed (1 low risk of bias study (SENIORS): RR 0.81; 95% CI 0.50 to 1.29 versus overall analysis of 3 studies: RR 0.78; 95% CI 0.62 to 0.99).

DISCUSSION

Summary of main results

We examined the evidence for the effects of BB and RAAS inhibitors for the treatment of HFpEF. We included 37 trials, reported in 207 publications that involved a total of 18,311 participants. We identified five ongoing trials with treatment arms that include interventions assessed in this review. A further eight studies await assessment.

We performed a pooled analysis for the outcomes of cardiovascular and all-cause mortality, heart failure hospitalisation, quality of life and hyperkalaemia. We used data from the Minnesota Living with Heart Failure (MLHF) questionnaire for quality of life outcomes because this was most frequently reported instrument.

Withdrawals due to adverse events were inconsistently reported; these data could not be included in 'Summary of findings' tables.

We conducted a sensitivity analysis by including only studies assessed with overall low risk of bias. The effect estimates were not significantly changed except for beta-blockers.

Beta-blockers

A total of 10 included studies (3087 participants) assessed beta-blockers compared with placebo or no intervention. We performed meta-analyses including up to four studies and 1105 participants. The results suggested that treatment may improve cardiovascular mortality, however the quality of evidence was low due to imprecision and risk of bias. When we performed a sensitivity analysis by including only studies at low overall risk of bias, the effects on cardiovascular mortality did not persist. The two largest studies (J-DHF; SENIORS) reported high rates of study drug discontinuation due to intolerance rather than adverse events, which may have attenuated any true treatment effects. There is uncertainty about the effects of beta-blocker pharmacotherapy in people with HFpEF. A large, randomised, controlled, open label, clinical outcomes trial of metoprolol for HFpEF is ongoing (Zhou 2010, beta-PRESERVE).

Mineralocorticoid receptor antagonists (MRA)

A total of 12 studies (4408 participants) assessed MRA compared with placebo or no intervention. We combined evidence from up to six trials and 4291 participants in meta-analyses. We found that treatment with MRA reduces the risk of heart failure hospitalisation but found little or no effect on cardiovascular and all-cause mortality; however the quality of evidence was moderate and uncertainty remains over these treatment effects. As expected, MRA treatment was associated with an increased risk of hyperkalaemia; potassium monitoring is therefore required in people being treated using MRA. A large, registry-randomised clinical outcomes trial of spironolactone for HFpEF is ongoing and due to complete in 2022 (NCT02901184: Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction, SPIRRIT).

Angiotensin converting enzyme inhibitors (ACEI)

A total of eight included studies (2062 participants) assessed ACEI versus placebo or no intervention. We conducted a meta-analysis of data from four trials and 1079 participants. We found that there was probably little or no effect on cardiovascular mortality, all-cause mortality, heart failure hospitalisation or quality of life and data on hyperkalaemia were limited. No large clinical trials (>1000 participants) were available and the quality of evidence was assessed as moderate due to imprecision. The effectiveness of ACEI therapy in the treatment of people with HFpEF remains unclear.

Angiotensin receptor antagonists (ARB)

A total of eight included studies (8755 participants) assessed ARB therapy for people with HFpEF with the evidence quality assessed as high. We combined evidence from up to four trials and 7964 participants for meta-analysis and found little or no overall difference on the outcomes of cardiovascular mortality, all-cause mortality, heart failure hospitalisation or quality of life. The CHARM study found an effect on heart failure hospitalisation based on a time to event analysis, and the strength of this association was increased in a subsequent analysis based on recurrent events (Rogers 2014). As expected, ARB treatment was associated with an increased risk of hyperkalaemia; potassium monitoring is therefore required.

Overall completeness and applicability of evidence

This review provides the most comprehensive appraisal of the evidence to date. We included 37 studies (207 reports) that involved 18,311 participants. The included trials assessed beta-blockers (10 studies, 3087 participants), MRA (12 studies, 4408 participants), ACEI (8 studies, 2061 participants) and ARB (8 studies, 8755 participants).

We searched clinical trials registries and identified five ongoing clinical trials, several of which have potential to influence the review findings. We also identified eight studies that were classified as Studies awaiting classification, for which there was insufficient information to determine whether these studies met our inclusion criteria. These studies were mostly small and it is therefore unlikely that they would influence the results of this review. In total, we identified 207 reports of 37 trials, 8 studies awaiting classification, and 5 ongoing trials, compared with a total of 22 identified by Zheng 2017 for the same comparisons.

The LVEF threshold for defining the HFpEF trial populations varied among the included studies and may contribute to indirectness with implications for the applicability of the evidence. Nine studies included participants with an ejection fraction cut-off of 40%, 10 used 45%, 14 used 50%, and one used 55%. Adamyan 2010 included participants with preserved ejection fraction but did not specify the cut-off. SENIORS reported a subgroup of participants with LVEF > 40% and we obtained outcomes for a subgroup with LVEF > 40% for AREA IN-CHF. No trials reported outcomes for the subgroup in the 40% to 49% mid-range so we were unable to investigate this subgroup.

The included studies had enrolment start dates from 1997 to 2011. In more recent studies, B-type natriuretic peptides have been used as a key inclusion criterion to improve the specificity of the HFpEF population and enrich the trial populations for people at higher risk for clinical outcomes (e.g. CAN-DHF; Mak 2009; RAAM-PEF).

Similarly, new measures of diastolic function have been included in more recent studies to increase the specificity (e.g. ELANDD; J-DHF; PEP-CHF). We noted considerable clinical heterogeneity between study populations with respect to comorbidities and cardiovascular therapies at baseline, which may influence the applicability of the evidence.

Quality of the evidence

We used the GRADE method to assess evidence quality for the outcomes of cardiovascular mortality, all-cause mortality, heart failure hospitalisation, quality of life (assessed using the Minnesota Living with Heart Failure questionnaire), and hyperkalaemia. For beta-blockers, evidence quality for clinical outcomes (cardiovascular mortality, all-cause mortality and heart failure hospitalisation) ranged from low to very low. In the combined analysis, most participants were from a subgroup of a single large trial; the other included studies were small with high or unclear risk of bias.

For MRA, the TOPCAT study contributed the majority of participants to the meta-analysis for which the overall evidence quality for clinical outcomes was assessed as moderate. We noted differences in participant populations among the included studies (TOPCAT, LVEF > 40%; RAAM-PEF, LVEF ≥ 50%; AREA IN-CHF LVEF 40% to 45%) and it is reported that ejection fraction is a modifier of treatment effect for MRA (Solomon 2016). Notably, a post hoc analysis of the TOPCAT study reported important differences in the placebo event rates among participants enrolled from the Americas (Argentina, Brazil, Canada, USA) and participants enrolled from Russia and Georgia (Pfeffer 2015). Furthermore, a pharmacology substudy of participants at 12 months (206 participants from USA and Canada; 160 participants from Russia) found that drug metabolites were undetectable in a greater proportion of participants from Russia compared with participants from the USA and Canada (30% versus 3%, P < 0.001) (de Denus 2017). A geographical subgroup analysis suggested possible clinical benefit from spironolactone in HFpEF in participants who were enrolled in the Americas (United States, Canada, Brazil, Argentina; cardiovascular mortality HR 0.74, 95% CI 0.57 to 0.97; all-cause mortality HR 0.83, 95% CI 0.68 to 1.02; heart failure hospitalisation HR 0.82, 95% CI 0.67 to 0.99). These findings will be investigated further in the ongoing SPIRRIT study (NCT02901184).

For ARB, several large trials contributed a large number of events to the meta-analysis for the clinical outcomes of mortality and heart failure hospitalisation, and the evidence quality was high. For ACEI, fewer trials were included in the combined analysis, event numbers were low and the evidence quality was assessed as moderate. For beta-blockers, the quality of evidence was low due to small study sizes and risk of bias.

Potential biases in the review process

Although we conducted a comprehensive search of major databases, it is possible we missed studies on clinical trials registers, had not been reported, or both. Where information on relevant subgroups or outcomes were not reported, we attempted to contact the study authors however only a limited number of responses were received. Given the small number of included studies per analysis, we were unable to formally assess for the existence of publication bias.

Agreements and disagreements with other studies or reviews

Our results were largely consistent with those from the most recent comprehensive review of evidence for beta-blockers and RAAS inhibitors in people with HFpEF (Zheng 2017). However, important differences were noted. Our analysis included more studies for each comparison, but the additional studies were small and did not significantly alter the overall effect estimates. A further distinction is that we used a fixed-effect model rather than a random-effects model for meta-analysis given the low heterogeneity among studies for all comparisons. We found a reduction in cardiovascular mortality for beta-blocker therapy but this was not robust to a sensitivity analysis that included only studies assessed at low risk of bias. In contrast to Zheng 2017, we did not find an effect of beta-blocker treatment on all-cause mortality that achieved statistical significance.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence for the effects of treatment with beta-blockers, MRA, ACEI, ARNI for HFpEF was limited. Beta-blockers may improve cardiovascular mortality however the quality of evidence was low. The evidence for MRA suggests that treatment reduces the risk of HF hospitalisation; there was little or no effect on cardiovascular and all-cause mortality however the quality of evidence was only moderate due to imprecision. Treatment with ACEI probably has little or no effect on the outcomes of cardiovascular and all-cause mortality and heart failure hospitalisation, however evidence was limited. There is high quality evidence that ARB treatment has no beneficial effect on these outcomes. For all comparisons, no effect on quality of life was observed however the quality of evidence was low. The mainstay of pharmacological therapy in HFpEF remains the treatment of comorbid conditions such as hypertension that are implicated in aetiology and as triggers for decompensation.

Implications for research

This review highlights a persistent gap in the evidence for the role of beta-blockers, MRA, ACEI, ARNI in HFpEF. Large trials powered for clinical outcomes are under way for these interventions and these should provide greater certainty for the estimates of treatment effect. Substantial heterogeneity of study populations with respect to baseline LVEF, co-morbidity and medication was observed that may contribute to heterogeneity of treatment effects. Ultimately, a redefinition of HFpEF disease subtypes based on underlying disease mechanisms will likely be needed to enable the development of more effective therapeutic approaches. A stratified analysis of individual participant data from trials would enable the investigation of subgroups that may benefit most from beta-blockers or RAAS inhibition or both, and provide important insights to guide the design of future clinical trial. In addition, improved outcome measures that quantify the burden of disease, such as recurrent hospitalisations, may increase the power to detect any treatment effect.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adamyan 2010

Methods	**Study design**: four arm factorial RCT

Adamyan 2010 *(Continued)*

	Centres: not reported, assumed one, in Armenia
	Start of enrolment: not reported
	End of enrolment: not reported
	Mean follow-up: 12 months
	Run-in period: not reported
Participants	**Inclusion criteria**: "III NYHA class chronic ischemic heart failure (CHF) patients (pts) with normal cholesterol who have preserved LV ejection fraction (PEF) and restrictive diastolic filling pattern"
	Exclusion criteria: not reported
	Randomised (N): 118 in total, of interest are: carvedilol, no simvastatin (N = 31) versus no carvedilol, no simvastatin (N = 28)
	Withdrawn (N): not reported
	Lost to follow-up (N): not reported
	Analysed (N): not reported
	Age (years, mean, unspecified): 64.5, 0.3
	Sex (% men): not reported
	Ethnicity (%): not reported
	Systolic blood pressure: not reported
	Heart rate: not reported
	BMI: not reported
	Serum creatinine: not reported
	B-type natriuretic peptide (pg/mL): not reported
	NT pro B-type natriuretic peptide (pg/mL): not reported
	LVEF "preserved LV ejection fraction" but not defined
	NYHA class I (%): 0
	NYHA class II (%): 0
	NYHA class III (%): 100
	NYHA class IV (%): 0
	Hypertension: not reported
	Diabetes: not reported
	Atrial fibrillation: not reported
	Hospitalisation for heart failure: not reported
	Coronary heart disease: not reported
	Stroke: not reported
	Diuretic: not reported
	Digoxin: not reported

Adamyan 2010 *(Continued)*

	Beta-blockers: study drug **ACEI:** not reported **ARB:** not reported **MRA:** not reported
Interventions	**Intervention**: carvedilol (up to 50 mg), simvastatin, carvedilol and simvastatin **Comparator**: not receiving carvedilol or simvastatin **Concomitant medication**: "in addition to ACE inhibitors, aldosterone antagonists and diuretics"
Outcomes	**Planned**: not reported **Reported**: "prognosis, left ventricular (LV) diastolic function, plasma BNP level and inflammation status", "Assessment of relation of early (E) and late (A) diastolic filling velocities, deceleration time (DT) of E wave, levels of BNP, interleukin-6 (IL-6) and high sensitivity C-reactive protein (CRP)", mortality, hospitalisation
Notes	Two conference abstracts only. Comparison between carvedilol and no treatment was of interest for this review. No outcome data relevant to this review. Trialists were contacted; no response. Source of funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" but no details given
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	High risk	Published as conference abstracts only

ALDO-DHF

Methods	**Study design**: parallel RCT **Centres**: 10 centres in Germany and Austria **Start of enrolment**: March 2007 **End of enrolment**: April 2011 **Mean follow-up**: 11.6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "men and women aged 50 years or older were eligible to participate in the study if they had current heart failure symptoms consistent with New York Heart Association (NYHA) class II or III, left ventricular ejection fraction (LVEF) of 50% or greater, echocardiographic evidence of diastolic dysfunction (grade I) or atrial fibrillation at presentation, and maximum exercise capacity (peak VO2) of 25 mL/kg/min or less." **Exclusion criteria**: "Major exclusion criteria included prior documented reduced left ventricular ejection fraction (LVEF 40%), significant coronary artery disease (current angina pectoris or ischemia on stress tests; untreated coronary stenosis 50%), myocardial infarction or coronary artery bypass graft surgery 3 months or less prior to enrolment, clinically relevant pulmonary disease (vital capacity 80% or forced expiratory volume in 1 second 80% of reference values on spirometry), significant laboratory abnormalities (potassium 5.1 mmol/L; hemoglobin 11 g/dL; hematocrit 33%; serum creatinine 1.8 mg/dL; or estimated glomerular filtration rate [eGFR] 30 mL/min/1.73 m^2 , calculated using the Modification of Diet in Renal Disease formula: 186 [serum creatinine {in micromoles per liter}/ 88.4] 1.154 age [in years] 0.203 1.21 [if patient is black] 0.742 [if patient is female]), known contraindications for spironolactone or known intolerance to or therapy with a mineralocorticoid receptor antagonist within the last 3 months, concomitant therapy with a potassium-sparing diuretic (eg, triamterene, amiloride), or potassium supplementation." **Randomised** (N): 422 (213 intervention, 209 control) **Withdrawn** (N): for reasons other than death 16 (6 intervention, 10 control) **Lost to follow-up** (N): 5 (2 intervention, 3 control) **Analysed** (N): 422 (213 intervention, 209 control) **Age** (years, mean, SD): intervention: 67, 8; control: 67, 8 **Sex** (% men): intervention: 48; control: 47 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SD): intervention: 135, 18; control: 135, 18 **Heart rate** (beats/min, mean, SD): intervention: 66, 14; control: 64, 12 **BMI** (mean, SD): intervention: 28.9, 3.6; control: 28.9, 3.6 **Serum creatinine**: not reported **B-type natriuretic peptide**: not reported **NT pro B-type natriuretic peptide** (pg/mL, median, IQR): intervention: 179, 81 to 276; control: 148, 80-276 **LVEF** (%, mean, SD): intervention: 67, 8; control: 68, 7 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 85; control: 88

ALDO-DHF *(Continued)*

	NYHA class III (%): intervention: 15; control: 12 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 92; control: 91 **Diabetes** (%): intervention: 17; control: 16 Atrial fibrillation (%): intervention: 6; control: 4 **Hospitalisation for HF**: (%): intervention: 38; control: 36 **Coronary heart disease** (%): intervention: 43; control: 37 **Stroke** (%): not reported **Diuretic** (%); intervention: 55; control: 52 **Digoxin** (%): not reported **Beta-blocker** (%): intervention: 69; control: 75 **ACEI** (%): intervention: 78; control: 76 **ARB** (%): nor reported **MRA** (%): study drug
Interventions	**Intervention**: spironolactone "The study drug could be decreased temporarily to 25 mg every other day for a potassium level greater than 5.2 mmol/L or in the presence of other reversible, non–life-threatening adverse effects. For safety reasons, study medication was stopped for relevant hyperkalaemia (serum potassium 5.5 mmol/L) and/or hyperkalaemia-associated clinical symptoms, significant renal impairment (serum creatinine 2.5 mg/dL; eGFR 20 mL/min/1.73m^2), significant breast pain or gynaecomastia, or withdrawal of informed consent; rechallenge was encouraged wherever possible." "mean daily dose of spironolactone was 21.6 mg (95% CI, 20.8-22.3 mg)" **Comparator**: matching placebo **Concomitant medication**: "Standard therapies for risk factor and symptom control were at the discretion of treating physicians and required to be unchanged within the 2 weeks prior to randomization." "concomitant therapy with a potassium-sparing diuretic (eg, triamterene, amiloride), or potassium supplementation."
Outcomes	**Planned**: primary outcomes: exercise capacity, left ventricular end-diastolic pressure. **Reported**: all-cause mortality, QoL, diastolic function, exercise capacity, "changes in echocardiographic measures of cardiac function and remodeling, measures of submaximal and maximal exercise capacity, serum biomarkers, and quality of life. Clinical tolerability was assessed as the safety end point. Morbidity and mortality (all-cause and cardiovascular-specific) were also predefined exploratory end points."
Notes	Received outcome data for CV mortality, heart failure hospitalisation and hyperkalaemia from investigators.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Pocock minimisation algorithm".

ALDO-DHF *(Continued)*

Allocation concealment (selection bias)	Low risk	"The allocation sequence was implemented remotely via Internet/fax by the Coordination Center for Clinical Trials Leipzig."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, the investigator team, individuals performing the assessments, and data analysts remained blinded to the identity of treatment until after database lock".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients, the investigator team, individuals performing the assessments, and data analysts remained blinded to the identity of treatment until after database lock".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, except for QoL.
Selective reporting (reporting bias)	Low risk	primary outcomes reported as planned, some secondary outcomes not reported as planned, eg all-cause mortality, cardiovascular mortality.
Other bias	Low risk	"Production of identical matching placebo and quality control, packaging, labelling, storage, and dispensing of both spironolactone and placebo were performed by Allphamed PHARBIL." "This work was supported by the German-Austrian Heart Failure Study Group and the German Competence Network of Heart Failure. AldoDHF was funded by the Federal Ministry of Education and Research Grant 01GI0205 (clinical trial program Aldo-DHF [FKZ 01KG0506]). The University of Goettingen was the formal sponsor." "The sponsor and supporters of this study had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript."

AREA IN-CHF

Methods	**Study design**: RCT. **Centres**: 46 cardiology centres in Italy. **Start of enrolment**: September 2002. **End of enrolment**: July 2005. **Follow-up**: 12 months. **Run-in period**: not reported.
Participants	**Inclusion criteria**: aged 18 to 80 years, established evidence of NYHA class II HF, stable, optimised therapy according to European Society of Cardiology criteria, and an LV ejection fraction (EF) ≤ 45%, as measured locally up to 6 months before enrolment. **Exclusion criteria**: creatinine 2.5 mg/dL; K 5.0 mEq/L; valvular heart disease amenable to surgical treatment; congenital heart disease; unstable angina or acute myocardial infarction or coronary revascularisation procedure within 3 months before enrolment; intravenous therapy with inotropic drugs within 3 months before enrolment; treatment with lithium salts, Kþ-sparing diuretics, TNF-a antagonists, or MRA during the last 3 months; history of resuscitated ventricular arrhythmias (unless this occurred within 24 h of a previous acute myocardial infarction or in subjects with an implantable cardioverter defibrillator); other clinical or general conditions contraindicating participation in a clinical trial.

AREA IN-CHF *(Continued)*

	Randomised (N): 467 total (225 LVEF > 40%) (231 (116) intervention, 236 (109) control) **Withdrawn** (N): for reasons other than death 18 (14 intervention,4 control) **Lost to follow-up:** not reported **Analysed:** not reported **Age** (years, mean, SD): intervention: 62.3, 9.5; control: 62.7, 9.5 **Sex** (% men): intervention: 81.8; control: 85.2 **Ethnicity:** not reported **Systolic blood pressure** (mmHg, mean, SD): intervention: 127.9, 16.2; control: 128.0, 17.2 **Heart rate** (beats/min, mean, SD): intervention: 68.0, 11.8; control: 65.7, 10.7 **BMI** (mean, SD): intervention: 26.7, 3.5; control: 26.9, 3.6 **Serum creatinine** (mg/dL, mean, SD): intervention: 1.1, 0.3; control: 1.1, 0.2 **B-type natriuretic peptide:** not reported **NT pro B-type natriuretic peptide:** not reported **LVEF** (%, mean, SD): intervention: 39.9, 8.6; control: 39.7, 8.6 **NYHA class:** not reported **Hypertension** (%): intervention: 48.5; control: 42.4 **Diabetes** (%): intervention: 20.9; control: 19.9 **Chronic atrial fibrillation** (%): intervention: 7.4; control: 8.5 **Hospitalisation for heart failure** (%): intervention: 44.6; control: 49.2 **Coronary heart disease:** not reported **Stroke** (%): intervention: 1.7; control: 3 **Diuretic** (%); intervention: 67.8; control: 72 **Digoxin:** not reported **Beta-blocker** (%): intervention: 81.3; control: 77.5 **ACEI** (%): intervention: 84.9; control: 74.6 **ARB** (%): intervention: 12.1; control: 24.2 **MRA** (%): study drug
Interventions	**Intervention**: canrenone. "The dose of 25 mg/o.d. of canrenone at randomization was increased to 50 mg/o.d. after the first month, if serum Kþ was 5 mEq/L, and in the absence of deterioration in renal function. During follow-up, if serum Kþ increased up to 5 mEq/L and/or creatinine increased up to 2.5 mg/dL, the dosage of canrenone was reduced to 25 mg/o.d. Subjects requiring down-titration of study medications were asked to return to the outpatient clinic within 2 weeks for a supplemental visit to evaluate the effectiveness of this change in therapy. If serum Kþ remained .5.5 mEq/L, or if creatinine was 3 mg/dL or had increased by over 1 mg/dL, the study medication was discontinued and the patient managed with conventional treatment only." **Comparator**: placebo

AREA IN-CHF *(Continued)*

	Concomitant medication: "Aspirin, diuretics, digoxin, nitrates, antiarrhythmic agents, oral anticoagulants, and any other therapy were allowed when indicated by the local investigators."
Outcomes	**Planned**: unclear **Reported**: "The pre-specified primary endpoint was the change in echocardiographic LV end-diastolic volume (LVEDV) over 12 months, measured centrally at the Echocardiographic Reading Centre. Secondary endpoints included changes in EF, estimated diastolic filling pressure, NYHA class, BNP, cardiac mortality, hospitalization for cardiac causes, and the combination of cardiac mortality and hospitalization for cardiac causes"
Notes	Subgroup of participants of interest; response with outcome data for subgroup of participants LVEF > 40% received from trialists; baseline characteristics above are for all trial participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	double blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	echocardiography data were "read at the end of the study by one experienced independent observer who was blinded to all clinical data and treatment allocation" not reported for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT for all outcomes
Selective reporting (reporting bias)	Unclear risk	unable to assess as protocol and NCT record published/registered after enrolment completed
Other bias	Low risk	"The ANMCO Research Center coordinated the study, managed the data, and undertook analyses, under the supervision of the steering committee, who designed the AREA IN-CHF study. The funding source (Therabel GiEnne Pharma SpA) had no role in the trial design, conduct, data collection, analyses and data interpretation."

Aronow 1993

Methods	**Study design**: parallel RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported

Aronow 1993 *(Continued)*

	Mean follow-up: 3 months **Run-in period**: 2 mornings of control period
Participants	**Inclusion criteria**: "New York Heart Association functional class III CHF associated with prior myocardial infarction and normal LV ejection fraction (>50%) who were able to perform a maximal treadmill exercise test were included in the study". **Exclusion criteria**: "No patient had valvular heart disease, systolic blood pressure ˜100 mm Hg, lung disease, hepatic disease or renal insufficiency." **Randomised** (N): 21 (10 intervention, 11 control) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, mean, SD): intervention: 80, 3; control: 79, 4 **Sex** (% men): 14.3 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SD): intervention: 126, 12; control: 127, 10 **Heart rate** (beats/min, mean, SD): intervention: 85, 6; control: 84, 3 **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 64, 9; control: 64, 7 **NYHA class I** (%): 0 **NYHA class II** (%): 0 **NYHA class III** (%): 100 **NYHA class IV** (%): 0 **Hypertension** not reported **Diabetes** not reported Atrial fibrillation not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** not reported **Stroke** not reported **Diuretic** (%): 100 **Digoxin** (%): 0 **Beta-blocker** (%): 0 **ACEI** study drug

Aronow 1993 *(Continued)*

	ARB not reported **MRA** not reported
Interventions	**Intervention**: enalapril. "The initial dose of enalapril was 2.5 mg/day, which was increased to 5 mg/day during week 2, to 10 mg/day (5 mg twice daily) during week 3, to 15 mg/day (7.5 mg twice daily) during week 4 and up to a maximum of 20 mg (10 mg twice daily) during week 5, tf tolerated. If the patient developed symptomatic hypotension or an increase in serum creatinine level, the dose of enalapril was reduced to the previous dose. At the time of the follow-up studies, 3 months after beginning enalapril, the dose of enalapril was 2.5 mg/day in 1 patient, 5 mg/day in 1 patient, 10 mg/day in 3 patients, 1.5 mg/day in 2 patients, and 20 mg/day in 3 patients." **Comparator**: no treatment **Concomitant medication**: "All patients received diuretic treatment with furosemide for ˜2 weeks before the beginning of the study and a constant dose of furosemide during the study. Digitalis and other cardiac drugs (except enalapril) were not administered to any patient during the study."
Outcomes	**Planned**: not reported **Reported**: NYHA class, blood pressure, heart rate, cardiothoracic ratio, treadmill exercise time, LVEF, peak mitral E/A ratio, left ventricular mass
Notes	no outcome data relevant for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Chest roentgenograms were interpreted by a radiologist who was unaware of the study medication. M-mode, 2- dimensional and pulsed-wave Doppler echocardiograms were interpreted by an experienced echocardiographer (IK) who was unaware of the study medication. Treadmill exercise tests were performed under the guidance of the senior author who was aware of which patients were receiving enalapril."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	not reported
Other bias	Unclear risk	unable to assess

Aronow 1997

Methods	**Study design**: parallel RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported **Mean follow-up**: 32 months (intervention), 31 months (control) **Run-in period**: not reported
Participants	**Inclusion criteria**: "≥ 62 years of age with New York Heart Association functional class II or III CHF, prior Qwave myocardial infarction, and a LV ejection fraction ≥ 40% after 2 months of treatment with diuretics and ACE inhibitors were included in the study." **Exclusion criteria**: "No patient had valvular heart disease, systolic blood pressure < 100 mm Hg, lung disease with bronchospasm, hepatic disease, renal insufficiency, sinus bradycardia, greater than first-degree atrioventricular block, or severe peripheral arterial disease." **Randomised** (N): 158 (79 intervention, 79 control) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): 158 (79 intervention, 79 control) **Age** (years, mean, SD): intervention: 81, 8; control: 81, 7 **Sex** (% men): intervention: 29; control: 30 **Ethnicity** (%): not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** (pg/mL): **LVEF** (%, mean, SD): intervention: 56, 11; control: 57, 11 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 53; control: 51 **NYHA class III** (%): intervention: 47; control: 49 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 67; control: 65 **Diabetes:** not reported **Atrial fibrillation** (%): intervention: 33; control: 34 **Hospitalisation for HF**: not reported **Coronary heart disease** (%): 100

Aronow 1997 *(Continued)*

	Stroke not reported **Diuretic** (%): 100 **Digoxin** (%): intervention: 33; control: 34 **Beta-blocker** study drug **ACEI** (%): 100 **ARB** not reported **MRA** not reported
Interventions	**Intervention**: propranolol. "The initial dose of propranolol was 10 mg/day. This dose was increased by 10-mg increments at 10-day intervals until a dose of 30 mg 3 times daily was given. All patients treated with propranolol received a final daily dose of propranolol of 30 mg 3 times daily." **Comparator**: no treatment **Concomitant medication**: "All patients continued diuretic and ACE inhibitor therapy during the study. Digoxin was administered only if the patient had atrial fibrillation."
Outcomes	**Planned**: no published protocol or clinical trial registry entry **Reported**: "total mortality and total mortality plus nonfatal myocardial infarction"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"LV ejection fraction and LV mass were interpreted by an experienced echocardiographer (IK) who was unaware of the study medications"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analyses
Selective reporting (reporting bias)	Unclear risk	not reported
Other bias	Unclear risk	funding not reported

Aronow 1998

Methods	**Study design**: RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported **Median follow-up**: 6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "with New York Heart Association functional class II or III CHF associated with prior Q-wave myocardial infarction, a normal LV ejection fraction (50%),7 and 30 ventricular premature complexes per hour detected by 24-hour ambulatory electrocardiograms were included in the study." **Exclusion criteria**: not reported **Randomised** (N): 60 (30 intervention, 30 control) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): 53 completed study (27 intervention, 26 control) **Age** (years, mean, SD): intervention: 82, 8; control: 82, 7 **Sex** (% men): intervention: 27; control: 23 **Ethnicity** (%): not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** not reported **LVEF** (%, median, IQR): intervention: 61, 7; control: 62, 6 **NYHA class** not reported **Hypertension** (%): intervention: 73; control: 70 **Diabetes** not reported Atrial fibrillation not reported **Hospitalisation for HF**: **Coronary heart disease** (%): 100 **Stroke** not reported **Diuretic** (%): 100 **Digoxin** not reported **Beta-blocker** not reported **ACEI** study drug

Aronow 1998 *(Continued)*

	ARB not reported **MRA** not reported
Interventions	**Intervention**: benazepril. up to 40 mg/day **Comparator**: no treatment **Concomitant medication**: not reported
Outcomes	**Planned**: unclear **Reported**: decrease in number of ventricular premature complexes/h, decrease in ventricular couplets/h, decrease in number of runs of ventricular tachycardia/24 h
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The cardiologists interpreting the 24-hour ambulatory electrocardiograms were blinded to the study medications"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	unable to assess as we are unaware of published protocol or pre-registered clinical trial registry entry
Other bias	Unclear risk	unable to assess

CAN-DHF

Methods	**Study design**: two-arm, individual, placebo-controlled RCT **Centres**: 8 sites in Germany **Start of enrolment**: January 2008 **End of enrolment**: December 2008 **Follow-up**: 24 weeks **Run-in period**: not reported

CAN-DHF *(Continued)*

Participants	**Inclusion criteria**: "Male or female patients of at least 45 years of age suffering from a non-insulin dependent diabetes mellitus type 2 orally treated for at least 3 months and showing normotension or controlled hypertension with sitting systolic blood pressure (sSBP) < 140 mmHg and/or sitting diastolic blood pressure (sDBP) < 90 mmHg. Evidence of an abnormal left ventricular relaxation, diastolic distensibility or diastolic stiffness confirmed by echocardiography under the prerequisite of a preserved Left ventricular ejection fraction (LVEF) ≥ 45%. NT-proBNP ≥ 250 pg/ml at baseline, NYHA class II or III in stable condition since 3 months, and standard HF- therapy with an ACE-inhibitor alone or with further preparations in a constant regimen since at least 1 month (3 months in terms of β-blockers). Signed written informed consent available." **Exclusion criteria**: The following criteria must not be met to enrol a single patient into the study: Impaired renal function (serum creatinine > 2.2 mg/dL or > 194 µmol/l), Known bilateral renal artery stenosis (RAS) or interventional treatment for RAS in the last year, State after kidney transplantation, Serum potassium > 5.5 mmol/l or HbA1C > 9.5 %, Cor pulmonale or primary pulmonary disease with dyspnea at rest, Known disposition to episodes of symptomatic hypotension or sSBP < 95 mmHg at baseline, Acute coronary syndrome or unstable angina pectoris and any coronary artery disease that was not stable during the last 3 months prior to inclusion, CABG or PTCA (incl. stent implantation) within 3 months before inclusion, Myocardial infarction or stroke within 6 months before inclusion, Patients who are dependent on a permanently paced pacemaker (i.e. a patient with a device that is not pacing during the echocardiographic examination can enter the study), Open heart surgery for other reasons than coronary revascularization, Tachycardia at rest > 100 bpm as confirmed by ECG-recordings, Known clinically relevant rhythm disorders (e.g. tachyarrhythmias, salves of supraventricular or ventricular extrasystoles or atrial fibrillation without ventricular rate control) or symptoms suggesting a significant rhythm disorder (e.g. recurrent syncopes), Primary valvular diseases and/or restrictive or obstructive cardiomyopathy - Existing ventricular assist devices, Relevant liver diseases (cholestasis or ALAT/ASAT > 2xULN or GT > 3xULN), History of primary hyperaldosteronism, of cancer in the last 5 years (exception: nonmetastasizing skin cancer) or of another wasting disease with life expectancy of < 2 years, Known hypersensitivity to Candesartan Cilexetil, Need for maintenance therapy with NSAIDs or Cox-2-inhibitors, Use of other ARBs throughout the entire study period, Any history of life-threatening diseases, History of drug addiction and/or an extensive use of alcohol, Female patients who are pregnant or breast feeding, Sexually active women of childbearing potential not consistently and correctly practicing highly effective birth control with a low failure rate (less than 1% / year) such as implants, injectables, combined oral contraceptives, hormonal intrauterine devices (IUDs), sexual abstinence or vasectomised partner, Psychological and/or emotional problems, which render the informed consent invalid or limit the ability of the patient to comply with the study requirements, Patient is an employee or at least in dependence of the investigator and/or the sponsor or of another institution directly involved in the study or other trials under the investigator's direction, Participation in another clinical investigation within 30 days prior to enrolment or for the course of the present study (incl. studies for compassionate use or experimental medical devices) **Randomised** (N): 22 (11 intervention, 11 control) **Withdrawn** (N): for reasons other than death 14 (intervention: 3 premature study termination, 3 adverse events, 1 randomisation /enrolment error, control: 4 premature study termination, 2 adverse events, 1 randomisation / enrolment error) **Lost to follow-up** (N): 0 **Analysed** (N): 22 (11 intervention, 11 control) **Age** (years, mean, SD): intervention: 67.0, 16.8; control: 69.0, 7.1 **Sex** (% men): intervention: 64; control: 55 **Ethnicity** (%): not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** (mean, SD): intervention: 31.4, 5.0; control: 30.0, 5.7 **Serum creatinine** not reported

CAN-DHF *(Continued)*

	B-type natriuretic peptide (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** not reported **NYHA class**: not reported **Hypertension** (%): not reported **Diabetes** (%): not reported Atrial fibrillation (%): not reported **Hospitalisation for heart failure**: not reported Myocardial infarction (%): not reported **Stroke** (%): not reported **Diuretic** (%): not reported **Digoxin** (%): not reported **Beta-blocker** (%): not reported **ACEI** (%): not reported **ARB** (%): study drug **MRA** (%): not reported
Interventions	**Intervention**: candesartan. 8-32mg as tolerated. "The treatment comprised a titration period of 6 weeks and a period of constant study therapy of at least 18 weeks" **Comparator**: placebo **Concomitant medication**: "in an "added" regimen to a constant background-HF-therapy with at least ACE-inhibitors (or further drugs) for the treatment of symptomatic heart failure with diastolic dysfunction in diabetic and hypertensive patients" exclusion criteria: use of other ARB
Outcomes	**Planned**: primary: mean change from baseline for NT-proBNP, secondary: QoL, kidney function, NYHA, body weight, BP and echocardiographic measures, adverse events, rate of premature withdrawals **Reported**: as planned except QoL
Notes	This trial was terminated prematurely and the results are available via a clinical trial registry entry only. No outcome data relevant to this review reported (confirmed by sponsor Takeda via Email).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias)	Low risk	"double-blind" but no detail

CAN-DHF *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	no information
Selective reporting (reporting bias)	Low risk	all outcomes reported as planned except QoL
Other bias	High risk	"the study was terminated prematurely as a whole by the sponsor in December 2008 since randomization of patients was very poor until that date (low and slow recruitment (N = 42) with a high number (N = 20) of screening failures)" Takeda funded the study. The study results are unpublished and only available via the clinical trial registry entry.

CandHeart

Methods	**Study design**: parallel RCT **Centres**: 70, Italy **Start of enrolment**: December 2005 **End of enrolment**: May 2008 **Mean follow-up**: 48 weeks **Run-in period**: not reported
Participants	**Inclusion criteria**: congestive HF, "Patients aged ≥18 years, of both genders, with stable symptomatic NYHA II-IV HF and any LVEF measured at screening visit, and who provided a written informed consent were eligible. Patients with LVEF > 40% had to be hospitalized for cardiovascular events during the past 12 months before randomization." **Exclusion criteria**: "Exclusion criteria were history of prior treatment with ARBs within 2 weeks from screening; severe or malignant hypertension (SBP/DBP > 180/110 mmHg); symptomatic hypotension; prior acute myocardial infarction, stroke or transient ischemic attack (TIA), percutaneous transluminal coronary angioplasty (PTCA) or coronary artery by-pass graft (CABG) within 1 month from screening; hemodynamically relevant arrhythmias or cardiac valvular defect; prior implant of pacemakers, cardiac resynchronization therapy or cardioverters within 6 months from randomization; constrictive pericarditis or active myocarditis; likelihood of cardiac surgical intervention during the overall treatment period; evidence of angina pectoris in the previous month; poorly controlled diabetes mellitus (blood glucose > 140 mg/mL or HbA1c > 8%); untreated thyroid dysfunction; renal artery stenosis; angio-edema of any etiology; significant liver (AST, ALT, total bilirubin or alkaline phosphatase > 2x the upper limit of normal range) or renal impairment (serum creatinine > 2.0 mg/dL or serum potassium > 5.0 mmol/L); anemia of any etiology (Hb <10.5 g/dL) or any other clinically relevant hematological disease; pregnant or lactating females or females at risk of pregnancy; any disease with malabsorption; presence of any non-cardiac disease that is likely to significantly shorten life expectancy; history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study subjects' compliance; known allergy, sensitivity or intolerance to study drugs and/or study drugs' formulation in-

CandHeart *(Continued)*

	gredients; patients unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study; participation in another trial in the month preceding study entry." **Randomised** (N): 128 **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, mean, SD): 66, 12 **Sex** (% men): 67.2 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SD): 134, 19 **Heart rate** (beats/min, mean, SD): 67, 14 **BMI** (mean, SD): 28.2, 4.5 **Serum creatinine** (mg/dL, mean, DS): 1.0, 0.3 **B-type natriuretic peptide** (pg/mL): 163, 202 **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): 48.7, 8.2 **NYHA class I** (%): 0 **NYHA class II** (%): 71.9 **NYHA class III** (%): not reported **NYHA class IV** (%): not reported **Hypertension** (%): 59.8 **Diabetes** (%): 28.1 Atrial fibrillation (%): 21.1 **Hospitalisation for HF**: not reported **Coronary heart disease** (%): 30.7 **Stroke**: not reported **Diuretic** (%): 86.7 **Digoxin** (%): 26.6 **Beta-blocker** (%): 76.6 **ACEI** (%): 88.3 **ARB** (%): study drug **MRA** (%): 32.8
Interventions	**Intervention**: candesartan cilexetil, "1 candesartan cilexetil was administered at an initial dose of 4 mg o.d. (one tablet) and, if tolerated, it was up titrated to 8 mg (one tablet o.d.) after 2 weeks of treatment, to 16 mg (one tablet o.d.) after 4 weeks of treatment, and to 32 mg (two tablets of 16 mg o.d.) after 6 weeks of treatment"

CandHeart *(Continued)*

	Comparator: no treatment **Concomitant medication**: ongoing standard therapy
Outcomes	**Planned**: both trial register entries were post-hoc, unclear what was planned **Reported**: primary: 3-month (12-week) changes of BNP from baseline, "The secondary objectives of the study after a 48-week treatment period were to assess:1) change of BNP at 48 weeks from baseline values; 2) changes from baseline of aldosterone. Other exploratory analyses included (1) changes from baseline of LVEF, LVIDD, E wave peak velocity/A wave peak velocity (E/A), deceleration time of E wave (E-DT), atrial dimensions; (2) changes from baseline of BP and heart rate (HR); (3) persistence of active treatment and discontinuation rate; (4) quality of life by Kansas City Cardiomyopathy Questionnaire (KCCQ)."
Notes	Only subgroup of participants with LVEF > 40% of interest to this review. The above data are for this subgroup only. No outcome data reported for this review. Emailed trialists. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"centrally randomized"
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Thirty percent of all echocardiographic exams performed during the study were randomly selected and read at the core laboratory by an experienced cardiologist unaware of study group and visit."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	unable to assess
Selective reporting (reporting bias)	Unclear risk	unclear as post-hoc trial registration and published protocol not identified
Other bias	Unclear risk	The study was funded by Takeda Italia Farmaceutici and endorsed by the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). "The study was stopped before reaching the target number of patients since an interim analysis by the DSMB showed that an unacceptable number of patients (n=1500 per group) would have been needed to show the observed difference in 3-month change of BNP with the predefined power of 0.80, when data on 371 patients were available"

CHARM-Preserved

Methods	**Study design**: parallel RCT

CHARM-Preserved *(Continued)*

	Centres: 618, 26 countries (Australia, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, Italy, Luxembourg, Malaysia, Netherlands, Norway, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, UK/Ireland, USA) **Start of enrolment**: March 1999 **End of enrolment**: July 2000 **Median follow-up**: 36.6 months **Run-in period**: no
Participants	**Inclusion criteria**: "Eligible patients were aged 18 years or older, had New York Heart Association functional class II–IV of at least 4 weeks' duration, had a history of hospital admission for a cardiac reason, and had LVEF higher than 40%." **Exclusion criteria**: Important exclusion criteria for any of the studies include current serum-creatinine > 265mmol/L (> 3 mg/dL); current serum-potassium > 5.5 mmol/L (> 5.5 mEq/L) or a history of marked ACE inhibitor-induced hyperkalemia resulting in either a serum potassium greater than or equal to 6.0 mmol/L (>6.0 mEq/L) or a life-threatening adverse event; known bilateral renal artery stenosis; current symptomatic hypotension; persistent systolic or diastolic hypertension; stroke, acute myocardial infarction, or open heart surgery within the last 4 weeks; previous heart transplant or heart transplant expected to be performed within the next 6 months; presence of any noncardiac disease (eg, cancer) that is likely to significantly shorten life expectancy to less than 2 years. **Randomised** (N): 3023 (1514 intervention, 1509 control) **Withdrawn** (N): for reasons other than death (270 intervention, 204 control) **Lost to follow-up** (N): (2 intervention, 1 control) **Analysed** (N): 3020 (1512 intervention, 1508 control) **Age** (years, mean, SD): intervention: 67.2, 11.1; control: 67.1, 11.1 **Sex** (% men): intervention: 60.8; control: 59.0 **Ethnicity** (%): intervention: European 90.8 , control: European 92.3 **Systolic blood pressure** (mmHg, mean, SD): intervention: 136.0, 18.6; control: 136.3, 18.3 **Heart rate** (beats/min, mean, SD): intervention: 71.2, 12.4; control: 71.4, 12.5 **BMI** (mean, SD): intervention: 29.3, 5.9; control: 29.0, 5.6 **Serum creatinine** (mg/dL): not reported **B-type natriuretic peptide** (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 54.0, 9.4; control: 54.1, 9.4 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 61.5; control: 60.0 **NYHA class III** (%): intervention: 36.7; control: 38.7 **NYHA class IV** (%): intervention: 1.8; control: 1.3 **Hypertension** (%): intervention: 65.0; control: 63.6 **Diabetes** (%): intervention: 28.7; control: 28.0 Atrial fibrillation (%): intervention: 29.0; control: 29.3

CHARM-Preserved *(Continued)*

	Hospitalisation for heart failure (%): intervention: 69.6; control: 68.8 **Coronary heart disease** (%): intervention: 45.0; control: 43.7 **Stroke** (%): intervention: 9.2; control: 8.5 **Diuretic** (%); intervention: diuretic: 75.2, spironolactone 11.3; control: diuretic 74.3, spironolactone 12.0 **Digoxin** (%): intervention: 28.5; control: 27.2 **Beta-blocker** (%): intervention: 55.9; control: 55.5 **ACEI** (%): intervention: 19.6; control: 18.6 **ARB** (%): study drug **MRA** (%): intervention: 11.3; control: 12.0
Interventions	**Intervention**: candesartan. "which could be started at 4 or 8 mg once daily, the assignment code being held by an independent centre and the data safety monitoring board. The treatment dose was doubled every 2 weeks, as tolerated, according to a forced titration protocol, with recommended monitoring of blood pressure, serum creatinine, and potassium. The target dose was 32 mg once daily from 6 weeks onwards." **Comparator**: "matching placebo" **Concomitant medication**: "physicians were free to prescribe all treatments other than angiotensin-receptor blockers." "Initially, angiotensin converting-enzyme inhibitors were not allowed as concomitant treatment, but after publication of the Heart Outcomes Prevention Evaluation trial results, (The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145–53.) their use was optional in appropriate patients." "By the end of the study, 298 (20%) in the candesartan and 340 (23%) in the placebo group were receiving angiotensin-converting-enzyme inhibitors, 712 (47%) and 748 (50%) were receiving blockers, and 136 (9%) and 201 (13%) were receiving spironolactone. Non-study angiotensin-receptor blockers were used in 3% of patients in each of the two groups."
Outcomes	**Planned**: Planned: "The primary outcome was cardiovascular death or unplanned admission to hospital for the management of worsening CHF. Prespecified secondary outcomes were: cardiovascular death, admission to hospital for CHF, or non-fatal myocardial infarction; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, or non-fatal stroke; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation; death (any cause) or admission to hospital for CHF; and development of new diabetes." **Reported**: as planned
Notes	The CHARM program consisted of 3 strands, one of which was CHARM-Preserved. Contacted investigators for end scores of MLHF QoL by treatment arms. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"We randomly assigned patient"
Allocation concealment (selection bias)	Low risk	"the assignment code being held by an independent centre and the data safety monitoring board"

CHARM-Preserved *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"We randomly assigned patients, in a double-blind way", "matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A committee unaware of treatment assignment and which component of the CHARM programme was being undertaken adjudicated the cause of death, first myocardial infarctions, and first hospital admissions for heart failure." "All final data analyses were done by the sponsor and verified independently by the statistical centre at the London school of Hygiene and Tropical Medicine, London, UK"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"two patients who mistakenly received randomisation numbers but had no other data recorded and never received study medication" "Two candesartan patients and one placebo patient were lost to follow-up" 207/204 withdrew due to AE "Anaysis was done by intention to treat."
Selective reporting (reporting bias)	Low risk	outcomes reported as planned
Other bias	Low risk	"MA Pfeffer, K Swedberg, CB Granger, JJV McMurray, and S Yusuf have served as consultants to or received research grants from AstraZeneca and other major cardiovascular pharmaceutical companies. J Östergren has served as a consultant and received research grants from AstraZeneca. P Held, E L Michelson, and B Olofsson are employees of AstraZeneca." "This study was supported by AstraZeneca R&D, Mölndal, Sweden"

ELANDD

Methods	**Study design**: multicenter, double-blind, placebo controlled, randomised, parallel group trial **Centres**: 12 in 8 European countries **Start of enrolment**: not reported **End of enrolment**: not reported **Follow-up**: 6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "To be included into the study, patients had to fulfil the following criteria: willing and able to sign the informed consent form and comply with the requirements of the study, aged ≥ 40 years, have a documented history of HF and persistent symptoms during effort [New York Heart association (NYHA) class II–III], an LVEF ≥ 45%, and LV end-diastolic internal diameter < 3.2 cm/m^2 or LV end-diastolic volume index < 102 mL/m^2 by echocardiography, radionuclide ventriculography, or nuclear magnetic imaging, or any abnormality of LV diastolic function documented by echocardiography, according to the guidelines of the European Study Group on Diastolic Heart Failure. This last inclusion criterion was revised in April 2007 following the online publication of the new consensus statement on the diagnosis of HFPEF by the European Society of Cardiology. Accordingly, an E/E ratio > 15 at tissue Doppler echocardiography was required as an inclusion criterion. Patients with an E/E‘ ratio between 8 and 15 could be included when additional abnormalities of diastolic function were found. These included an E/A ratio < 0.5 and/or a deceleration half-time > 280 ms in patients older than 50 years, and/

ELANDD *(Continued)*

or a duration of reverse pulmonary vein atrial systole flow–mitral valve atrial wave flow > 30 ms, and/or a left atrial volume index > 40 mL/m^2 , and/or an increased LV mass index"

Exclusion criteria: "Major exclusion • Patients unable to perform 6-mi walking test • Planned invasive cardiac procedures or cardiac surgery during the time of the study • Recent (< 3 months) acute coronary syndrome or stroke • Exercise-induced myocardial ischaemia as main cause of exercise limitation as shown by symptoms (angina) or by previous exams (exercise test, stress echocardiography or myocardial scintigraphy) • Concomitant diseases (COPD, peripheral vasculopathy, orthopaedic disease) as main cause of exercise limitation • Major contraindications to beta-blocker therapy (sinus bradycardia, \50/min; atrio-ventricular block, bronchial asthma sensitive to beta-agonists administration) • Ongoing treatment with beta-blockers, diltiazem or verapamil • Systolic blood pressure \100 mm Hg • Pregnancy, breast feeding or childbearing potential during the study • History of alcohol or other illicit drug abuse • Expected poor compliance to drug therapy • Participation in any other clinical trial with an investigational product or scheduled to receive any such product during the study or in the 4 weeks following the study • Suffering from any other medical condition that may exclude the patient for safety reasons or interfere with the objective of the study."

Randomised (N): 116 (57 intervention, 59 control)

Withdrawn (N): for reasons other than death 22 (14 intervention (9 lack of tolerance, 1 protocol violation, 3 consent withdrawal, 1 other), 8 control (consent withdrawal 1, protocol violation 5, 2 other))

Lost to follow-up (N): 1 (1 intervention, 0 control)

Analysed (N): 93 (42 intervention, 51 control)

Age (years, mean, SD): intervention: 66.5, 9.8; control: 65.3, 11.3

Sex (% men): intervention: 35; control: 36

Ethnicity (%): not reported

Systolic blood pressure (mmHg, mean, SD): intervention: 128, 17 (Table 3 of Conraads), 134, 21 (Table 2); control: 129, 23 (Table 3) 133, 18 (Table 2)

Heart rate (beats/min, mean, SD): intervention: 76, 15 (Table 3) 73, 14 (Table 2); control: 78, 13 (Table 3), 73, 11 (Table 2)

BMI (mean, SD): intervention: 30.3, 4.5; control: 30.2, 4.9

Serum creatinine (mg/dL, mean, SD): intervention: 88.5, 33.1; control: 85.8, 25.1

B-type natriuretic peptide (pg/mL): not reported

NT pro B-type natriuretic peptide (pg/mL, median, range): intervention: 147 (9-3577); control: 126 (15-2055)

LVEF (%, mean, SD): intervention: 61.9, 7.8; control: 63.2, 9.2

NYHA class I (%): 0

NYHA class II (%): intervention: 77; control: 78

NYHA class III (%): intervention: 21; control: 22

NYHA class IV (%): 0

Hypertension (%): intervention: 86; control: 86.4

Diabetes (%): intervention: 21; control: 20

Atrial fibrillation (%): not reported

Hospitalisation for heart failure: not reported

Coronary heart disease (%): intervention: 17; control: 20

ELANDD *(Continued)*

	Stroke (%): not reported **Diuretic** (%); intervention: 49; control: 54 **Digoxin** (%): not reported **Beta-blocker** (%): study drug **ACEI** (%): intervention: 75; control: 80 **ARB** (%): not reported **MRA** (%): not reported
Interventions	**Intervention**: nebivolol. "Nebivolol was started at 2.5 mg/day and gradually up-titrated to 10 mg/day over a period of 5 weeks. Down-titration to lower doses was allowed if the higher dose was not tolerated. Treatment at maintenance doses was continued for an additional 21 weeks (6 months of treatment in total)." **Comparator**: placebo **Concomitant medication**: "Ongoing treatment with other drugs was maintained throughout the study."
Outcomes	**Planned**: " The primary endpoint of the study is the change from baseline in the distance walked during the 6-min walking test (6MWT) after 6 months of treatment with nebivolol versus placebo. Additional secondary endpoints are the changes from baseline after 6 months, with nebivolol versus placebo, in the following measurements: • Symptoms, assessed using a five-level scale (extremely worsened, moderately worsened, unchanged, moderately improved, extremely improved); • New York Heart Association (NYHA) functional class; • Minnesota living with heart failure questionnaire [21]; • Maximal exercise duration, peak oxygen consumption, [VO2] and slope of the minute ventilation [VE] to carbon dioxide [VCO2] relation, at cardiopulmonary exercise testing. • Changes in parameters related to LV diastolic function, including peak E velocity at the Doppler recording of transmitral inflow tracing, peak E0 velocity of the mitral valve annulus measured at the level of the septal and lateral wall, respectively, by tissue Doppler recording, and the E/E' ratio. Lastly, the effects of treatment on major outcomes (death, hospitalization and unexpected visit to the outpatient clinic or heart failure unit) as well as adverse events are assessed." **Reported**: as planned
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated 1:1 randomization"
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported

ELANDD *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	reasons provided for withdrawal
Selective reporting (reporting bias)	Low risk	reported as planned
Other bias	Low risk	The trial is funded by a grant from Menarini. "We thank Joachim Klinger Director of Data Management and Statistics, Harrison Clinical Research Deutschland, and Lieven Huysse, who worked at Menarini at the time of the study, for management and statistical support."

Hong Kong DHF

Methods	**Study design**: three-arm, parallel RCT **Centres**: multicentre, no details **Start of enrolment**: not reported **End of enrolment**: not reported **Mean follow-up**: 1 year **Run-in period**: none
Participants	**Inclusion criteria**: "The inclusion criteria were age .18 years, clinical history of heart failure within 2 months prior to screening including a chest x ray demonstrating pulmonary congestion, NYHA functional class II – IV, left ventricular ejection fraction .45% by 2D-echocardiography or a radionuclide technique, and therapy with diuretics with stable dose .14 days prior to recruitment." **Exclusion criteria**: "NYHA functional class I, myocardial infarction within 3 months, unstable angina within 1 month, significant valvular heart disease, uncontrolled hypertension, serious cardiac arrhythmias, concurrent therapy with calcium channel antagonist, b-blockers (a-methyl dopa was used for treating hypertension if required), positive inotropic agents (except digoxin for control of atrial fibrillation) and other angiotensin converting enzyme inhibitors or receptor blockers." **Randomised** (N): 151 (intervention R: 45, intervention I: 56, control: 50) **Withdrawn** (N): for reasons other than death: intervention R: 6 (4 persistent irritating cough, 1 uncontrolled blood pressure, 1 refused to continue), intervention I: 1 due to onset of fast atrial fibrillation, control: 3 (1 uncontrolled high blood pressure, 1 defaulted, 1 refused to continue) **Lost to follow-up** (N): 0 **Analysed** (N): 151 (intervention R: 45, intervention I: 56, control: 50) **Age** (years, mean, SD): intervention R: 74, 6.1; intervention I: 75, 8.5; control: 73, 8.4 **Sex** (% men): intervention R: 40; intervention I: 34; control: 42 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SD): intervention R: 143, 22; intervention I: 145, 19; control: 145, 23 **Heart rate** (beats/min, mean, SD): intervention R: 79, 13; intervention I: 77, 9; control: 76, 14 **BMI** (mean, SD): intervention R: 26.8, 3.9; intervention I: 27.2, 4.1; control: 26.8, 4.2 **Serum creatinine:** not reported

Hong Kong DHF *(Continued)*

B-type natriuretic peptide (pg/mL, mean, SEM): intervention R: 488, 701; intervention I: 568, 757; control: 566, 944

NT pro B-type natriuretic peptide: not reported

LVEF (%, median, IQR): intervention R: 65, 1; intervention I: 66, 1; control: 69, 2

NYHA class I (%): 0

NYHA class II (%): intervention R: 66.7; intervention I: 67.9; control: 72

NYHA class III (%): intervention R: 33.3; intervention I: 30.4; control: 28

NYHA class IV (%): 0

Hypertension (%): intervention R: 73; intervention I: 71; control: 76

Diabetes (%): intervention R: 22; intervention I: 18; control: 20

Atrial fibrillation (%): intervention R: 16; intervention I: 21; control: 10

Hospitalisation for HF: 100% as it was an inclusion criteria

Coronary heart disease (%): intervention R: 18; intervention I: 11; control: 18

Stroke (%): not reported

Diuretic (%): intervention R: Hydrocholorthiazide 8.9 furosemide 80 , dyazide 2.2; intervention I: Hydrocholorthiazide 10.7, furosemide 80.4 , dyazide 10.7; control: Hydrocholorthiazide 6, furosemide 68 , dyazide 12

Digoxin (%): not reported

Beta-blocker (%): 0

ACEI (%): study drug (R)

ARB (%): study drug (I)

MRA (%): not reported

Interventions	**Intervention R**: "Ramipril was started at 2.5 mg daily and similarly titrated to 10 mg daily" **Intervention I:** "The initial dose of irbesartan was 18.75 mg daily which was titrated at 4 and 8 weeks to 75 mg daily." **Comparator**: usual care, "continue with diuretics alone" **Concomitant medication**: "Exclusion criteria were: ...concurrent therapy with calcium channel antagonist, b-blockers (a-methyl dopa was used for treating hypertension if required), positive inotropic agents (except digoxin for control of atrial fibrillation) and other angiotensin converting enzyme inhibitors or receptor blockers."
Outcomes	**Planned**: planned as per clinical trial registry entry: primary: 1. Number of hospital admissions for heart failure or mortality 2. Quality of life assessed by the Minnesota Quality of life Questionnaire 3. In ambulatory patients the exercise duration assessed by 6 min corridor walk test. Secondary: The incidence of side-effects, effect on levels of natriuretic peptides, effect on doppler-echocardiographic derived measurements of left ventricular diastolic function. **Reported**: cardiovascular mortality, hospitalisation for heart failure, all-cause mortality, quality of life, 6MWT, blood pressure, NT-proBNP, peak early diastolic mitral annular velocities, peak systolic velocity, LV mass
Notes	retrospective clinical trial registration

Hong Kong DHF *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated using computer-generated random numbers in blocks of 10"
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All outcomes were reviewed blind to treatment allocation." "with blinded end point design"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	unable to assess
Selective reporting (reporting bias)	Unclear risk	retrospective clinical trial registration, no published protocol identified
Other bias	Unclear risk	"None of the authors received any lecture, advisory board, or consultancy fees relating to this study from the sponsors." "This study was initially supported by a small grant from the manufacturers of Irbesartan, who also donated the irbesartan medication (Sanofi-Synthelabo). Design, conduct, retention of data, analysis and writing were all entirely independent and carried out by the authors only. Data were kept at the Chinese University of Hong Kong and are available for public scrutiny."

I-PRESERVE

Methods	**Study design**: parallel RCT **Centres**: 293 centres in 25 countries (Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Mexico, The Netherlands, Norway, Poland, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, UK, USA) **Start of enrolment**: June 2002 **End of enrolment**: April 2005 **Mean follow-up**: mean follow-up time was 49.5 months, and the trial included 16,798 patient-years of follow-up **Run-in period**: "Eligible patients were treated with single-blind placebo for 1 to 2 weeks before randomization"
Participants	**Inclusion criteria**: "All patients were at least 60 years of age and had heart failure symptoms and a left ventricular ejection fraction of at least 45%. In addition, we required patients to have been hospitalized for heart failure during the previous 6 months and have current New York Heart Association (NYHA) class II, III, or IV symptoms with corroborative evidence; if they had not been hospitalized, they were required to have ongoing class III or IV symptoms with corroborative evidence. Such evidence could in-

I-PRESERVE *(Continued)*

clude findings of pulmonary congestion on radiography, left ventricular hypertrophy or left atrial enlargement on echocardiography, or left ventricular hypertrophy or left bundle-branch block on electrocardiography. Treatment with an angiotensin-converting–enzyme (ACE) inhibitor was permitted only when such therapy was considered essential for an indication other than uncomplicated hypertension."

Exclusion criteria: "Exclusion criteria included previous intolerance to an angiotensin-receptor blocker; an alternative probable cause of the patient's symptoms (e.g. significant pulmonary disease); any previous left ventricular ejection fraction below 40%; a history of acute coronary syndrome, coronary revascularization, or stroke within the previous 3 months; substantial valvular abnormalities; hypertrophic or restrictive cardiomyopathy; pericardial disease; cor pulmonale or other cause of isolated right heart failure; a systolic blood pressure of less than 100 mm Hg or more than 160 mm Hg or a diastolic blood pressure of more than 95 mm Hg despite antihypertensive therapy; other systemic disease limiting life expectancy to less than 3 years; substantial laboratory abnormalities (such as a hemoglobin level of less than 11 g per deciliter, a creatinine level of more than 2.5 mg per deciliter [221 µmol per liter], or liver-function abnormalities); or characteristics that might interfere with compliance with the study protocol"

Randomised (N): 4128 (2067 intervention, 2061 control)

Withdrawn (N): for reasons other than death 1368 (702 intervention, 684 control)

Lost to follow-up (N): 73 (29 intervention, 44 control)

Analysed (N): 4128 (2067 intervention, 2061 control)

Age (years, mean, SD): intervention: 72, 7; control: 72, 7

Sex (% men): intervention: 41; control: 39

Ethnicity (%): intervention: white 94, control: white 93

Systolic blood pressure (mmHg, mean, SD): intervention: 137, 15; control: 136, 15

Heart rate (beats/min, mean, SD): intervention: 72, 11; control: 71, 10

BMI (mean, SD): intervention: 29.7, 5.2; control: 29.6, 5.3

Serum creatinine (mg/dL, mean, SD): intervention: 1.0, 0.32; control: 1.0, 0.34

B-type natriuretic peptide (pg/mL): not reported

NT pro B-type natriuretic peptide (pg/mL, median, IQR): intervention: 360, 139–987; control: 320, 131–946

LVEF (%, mean, SD): intervention: 59, 9; control: 60, 9

NYHA class I (%): 0

NYHA class II (%): intervention: 21; control: 22

NYHA class III (%): intervention: 77; control: 76

NYHA class IV (%): intervention: 3; control: 3

Hypertension (%): intervention: 89; control: 88

Diabetes (%): intervention: 28; control: 27

Atrial fibrillation (%): intervention: 29; control: 29

Hospitalisation for heart failure in the last six months (%): intervention: 44; control: 44

Myocardial infarction (%): intervention: 24; control: 23

Stroke or TIA (%): intervention: 10; control: 10

I-PRESERVE *(Continued)*

	Diuretic (%): intervention: loop: 52, thiazide: 38, spironolactone 15; control: loop: 52, thiazide: 38, spironolactone 15 **Digoxin** (%): intervention: 14; control: 13 **Beta-blocker** (%): intervention: 59; control: 58 **ACEI** (%): intervention: 26; control: 25 **ARB** (%): study drug **MRA** (%): intervention: 15; control: 15
Interventions	**Intervention**: irbesartan. "Patients were started on 75 mg of irbesartan or placebo once daily. The dose was doubled to 150 mg after 1 to 2 weeks and was doubled again to 300 mg after an additional 1 to 2 weeks, according to a forced-titration protocol as tolerated." "At the end of the titration phase, 84% of the patients in the irbesartan group and 88% of those in the placebo group had reached the 300-mg dose (mean doses, 275 mg and 284 mg, respectively)." **Comparator**: "matching placebo" **Concomitant medication**: "During the study, the proportion of patients receiving an ACE inhibitor rose from 25% in the two groups at baseline to 39% in the irbesartan group and 40% in the placebo group, the use of spironolactone rose from 15% in the two groups at baseline to 28% in the irbesartan group and 29% in the placebo group, and the use of beta-blockers rose from 59% in the irbesartan group and 58% in the placebo group to 73% in the two groups."
Outcomes	**Planned**: "The primary end point is defined as time from randomization to the first occurrence of the composite outcome of death (all cause) or cardiovascular hospitalization. [...] The endpoint additionally includes myocardial infarction or stroke occurring during any hospitalization at any point during the study. Secondary endpoints include the effect of irbesartan as compared with placebo in reducing the risk of: cardiovascular death, all-cause mortality, combined vascular endpoint: cardiovascular death, nonfatal myocardial infarction (MI) or nonfatal stroke; or combined HF endpoint: HF mortality or hospitalizations; [...] quality of life as measured by the Minnesota Living with Heart Failure questionnaire, change in New York Heart Associatioin (NYHA) functional class, change in global assessment of symptoms, N-terminal B-type natriuretic peptide levels in blood." (Carson 2005) **Reported**: all planned outcomes reported
Notes	Emailed trialists to enquire about differing data in different publications and to ask for subgroup data. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using an automated, central randomization system"
Allocation concealment (selection bias)	Low risk	"The randomization schedule was implemented with the use of an interactive voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All investigators and committee members who were involved in the conduct of the study (except for members of the data and safety monitoring board) were unaware of study-group assignments." "double-blind" (Carson 2005) "matching placebo"

I-PRESERVE *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"blinded review of event rates in 2004" but blinding of event adjudication not specified overall
Incomplete outcome data (attrition bias) All outcomes	Low risk	"At the end of the study, vital-status data were not available for 29 patients (1%) in the irbesartan group and 44 patients (2%) in the placebo group. If contact could not be made at end of study, data for these patients were censored from the analysis at the date they were last known to be alive." "Data from all patients who underwent randomization were analyzed according to the intention-to-treat principle."
Selective reporting (reporting bias)	Low risk	all planned outcomes reported (comparison between published protocol (Carson 2005) and main results paper (Massie 2008)
Other bias	Low risk	"Dr. Massie reports receiving grant support from Bristol-Myers Squibb, Sanofi-Aventis, and Merck, consulting fees from Bristol- Myers Squibb, Sanofi-Aventis, Merck, Duke Clinical Research Institute, Momentum Research, Novartis, GlaxoSmithKline, Scios–Johnson & Johnson, Corthera, and Niles Therapeutics, and lecture fees from Merck; Dr. Carson, receiving consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, and Merck and lecture fees from AstraZeneca and Novartis; Dr. McMurray, receiving support from Bristol-Myers Squibb (to Glasgow University) for his work on this trial; Dr. Komajda, receiving consulting fees from Bristol-Myers Squibb and Servier and lecture fees from Servier, Sanofi-Aventis, and AstraZeneca; Dr. McKelvie, receiving consulting fees from Bristol-Myers Squibb and Sanofi-Aventis and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Pfizer, Merck, and AstraZeneca; Dr. Zile, receiving consulting fees from Bristol-Myers Squibb and Sanofi-Aventis; Ms. Anderson, being employed by the Statistical Data Analysis Center at the University of Wisconsin–Madison, which conducted statistical analysis for this trial, supported by Bristol-Myers Squibb and Sanofi-Aventis; Drs. Donovan and Ptaszynska, being employees of and having an equity interest in Bristol-Myers Squibb; and Dr. Staiger, being an employee of and having an equity interest in Sanofi-Aventis." **study sponsors**: Bristol-Myers Squibb and Sanofi-Aventis. "The sponsors or a contract research organization collected the trial data, which were then analyzed at the Statistical Data Analysis Center at the University of Wisconsin, Madison, independently of the sponsors."

J-DHF

Methods	**Study design**: parallel RCT **Centres**: "multicenter" but no further details **Start of enrolment**: May 2004 **End of enrolment**: March 2009 **Mean follow-up**: 3.2 years **Run-in period**: no
Participants	**Inclusion criteria**: "All patients were at least 20 years of age, and had an LVEF of > 40% when diagnosed as having heart failure. Clinical diagnosis of heart failure was based on a slight modification of the Framingham criteria as previously described within the 12 months before study entry. There were no changes in baseline therapy and symptoms of heart failure within a month before study entry in any patients."

J-DHF *(Continued)*

Exclusion criteria: Current symptomatic hypotension, • Hypertension that has not been controlled to the satisfaction of the investigator by drugs other than β-blocker • Hemodynamically significant (in the investigators opinion) LV outflow tract obstruction (from either aortic stenosis or ventricular hypertrophy) or mitral valve stenosis • Important aortic or mitral regurgitation in the investigator's opinion • Heart rate < 50 beats/min • Second- or third-degree heart block without permanent pacemaker in situ • Acute coronary syndrome • Arrhythmogenic right ventricular cardiomyopathy • Primary pulmonary hypertension or pulmonary hypertension not from LV dysfunction • Serious cerebrovascular disease • Acute myocardial infarction within the last 3 months • Patients who require intravenous inotropes • Cerebrovascular accident within the last 6 months • Percutaneous coronary intervention or open heart surgery within the last 3 months • On the waiting list for percutaneous coronary intervention or open heart surgery • Serum creatinine > 3.0 mg/dL or creatinine clearance ≤ 30 mL/min • Known bilateral renal artery stenosis • Serum potassium > 5.5 mEq/L • Serious liver disease • Prescription of β-blocker within the last month or a history of a life-threatening adverse event induced by β-blocker • Any change in cardiovascular drug therapy within a month before randomization • History of chronic obstructive pulmonary disease or restrictive lung disease • Diabetes mellitus that has not been controlled to the satisfaction of the investigator • History of any life-threatening noncardiac disease (eg, cancer) within 5 years • Other diseases likely to cause death or serious disability within 1 year • Patients unable to walk without personal aid • Arteriosclerosis obliterans with Fontaine Grade II or more. • Severe anemia (hemoglobin ≤ 6.0 g/dL) • Uncontrolled thyroid dysfunction

Randomised (N): 245 (120 intervention, 125 control)

Withdrawn (N): for reasons other than death (6 intervention, 0 control)

Lost to follow-up (N): (5 intervention, 3 control)

Analysed (N): (120 intervention, 125 control)

Age (years, mean, SD): intervention: 73, 10; control: 71, 11

Sex (% men): intervention: 57.5; control: 58.4

Ethnicity (%): not reported

Systolic blood pressure (mmHg, mean, SD): intervention: 134, 21; control: 133, 21

Heart rate (beats/min, mean, SD): intervention: 72, 11; control: 74, 13

BMI (mean, SD): intervention: 24.2, 4.4; control: 24.1, 4.1

Serum creatinine (mg/dL, mean, SD): intervention: 0.98, 0.37; control: 1.01, 0.45

B-type natriuretic peptide (pg/mL, mean, SD): intervention: 219.2, 294.9; control: 234.9, 281.6

NT pro B-type natriuretic peptide (pg/mL): not reported

LVEF (%, mean, SD): intervention: 62, 10; control: 63, 11

NYHA class I (%): intervention: 18.3; control: 18.4

NYHA class II (%): intervention: 69.2; control: 75.2

NYHA class III (%): intervention: 10.8; control: 4.8

NYHA class IV (%): intervention: 1.7; control: 1.6

Hypertension (%): intervention: 80.0; control: 80.8

Diabetes (%): intervention: 27.5; control: 33.6

Atrial fibrillation (%): intervention: 50.8; control: 45.6

Hospitalisation for heart failure (%): intervention: 60.0; control: 60.0

Ischaemic heart disease (%): intervention: 28.3; control: 24.0

J-DHF *(Continued)*

	Stroke (%): intervention: 11.7; control: 12.8 **Diuretic** (%); intervention: 63.3; control: 56.8 **Digoxin** (%): intervention: 19.2; control: 21.6 **Beta-blocker** (%): study drug **ACEI** (%): intervention: 24.2; control: 22.4 **ARB** (%): intervention: 50.8; control: 56.0 **MRA** (%): intervention: 20.8; control: 25.6
Interventions	**Intervention**: carvedilol. "In the carvedilol arm, carvedilol was up-titrated from 1.25 mg twice daily to the target dose of 10 mg twice daily within 8 weeks based on tolerability. Patients were maintained at the target dose or the maximum tolerated dose for the remainder of the study." **Comparator**: usual care **Concomitant medication**: "In both arms, patients were treated with standard cardiovascular therapy excluding beta-blockers."
Outcomes	**Planned**: "The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive heart failure. The secondary outcomes are listed as follows: all-cause mortality; worsening of the symptoms (defined by either a decrease by 1 Mets in the SAS questionnaire score or an increase by 1 class in the New York Heart Association functional class for at least 3 months compared with the baseline); an increase in brain natriuretic peptide by 30% of the value at the randomization in patients with brain natriuretic peptide 200 pg/mL at the randomization; unplanned admission to hospital for congestive heart failure; or a need for modification of the treatment for heart failure (changes in oral medicine for at least 1 month or addition of intravenous inotropes for at least 4 hours)." (Hori 2005) **Reported**: as planned
Notes	Emailed investigators on 13 November 2017 to ask about data on cardiovascular mortality and all-cause mortality as different numbers are provided in Table 2 of Yamamoto 2013 (primary reference). No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomized to the arm " but no details
Allocation concealment (selection bias)	Unclear risk	no information
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Deaths and hospitalizations were adjudicated by a blinded independent Endpoint Committee, using prespecified criteria." "Outcomes were assessed by the Endpoint Committee (see Appendix) where all the committee members were blinded to the allocated group."

J-DHF *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"The primary outcome was a composite of cardiovascular death and un- planned hospitalization for heart failure using a time-to-first-event ana- lysis and the intention-to-treat principle." unspecified for secondary outcomes lost to follow-up low/similar in both groups (4.2% intervention, 2.4% control)
Selective reporting (reporting bias)	Low risk	outcomes reported as planned in published protocol (Hori 2005)
Other bias	Low risk	authors CoI: "none declared" funding: "The Ministry of Health, Labor andWelfare, Japan; the Japan Heart Foundation."

Karapysh 2015

Methods	**Study design**: RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported **Follow-up**: 6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "patients with chronic heart failure (CHF) with preserved ejection fraction (EF)." "with stable coronary arterial disease (CAD) and mild CHF (no higher IIfunctional class (NYHA)) with preserved systolic function of the LV (EF > 45%)" **Exclusion criteria**: not reported **Randomised** (N): 79 **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, mean, SD): 54.5, 10.5 **Sex** (% men): 61 **Ethnicity** (%): intervention: white , control: white **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported

Karapysh 2015 *(Continued)*

	LVEF not reported **NYHA class**: not reported **Diabetes** not reported Atrial fibrillation not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** not reported **Stroke** (%): not reported **Diuretic** (%); not reported **Digoxin** (%): not reported **Beta-blocker** (%): not reported **ACEI** (%): not reported **ARB** (%): not reported **MRA** (%): not reported
Interventions	**Intervention**: spironolactone. "SPRL group was treated with the standard therapy (ACE inhibitors or angiotensin receptor blockers II, beta-blockers,statins, antiplatelet agents) plus SPRL (25 mg/day, titrated to 50 mg/day if tolerated)" **Comparator**: standard therapy **Concomitant medication**: standard therapy (ACEI, ARB, beta-blocker, statins, antiplatelet agents)
Outcomes	**Planned**: unclear **Reported**: "V posterior wall thickness (LVPWT), intraventricular septal thickness (IVST), relative wall thickness (RWT) and LV mass index (LVMI)"
Notes	Intended to contact trialists to obtain missing details and to enquire whether outcomes of interest to this review were measured. This was not possible as we could not find contact details for trialists. No relevant outcome data for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"were randomly divided" but no further detail
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported

Karapysh 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	could not be assessed
Selective reporting (reporting bias)	Unclear risk	could not be assessed
Other bias	High risk	reported only as conference abstract

Kasama 2005

Methods	**Study design**: individual, parallel RCT **Centres**: 1, Japan **Start of enrolment**: January 2002 **End of enrolment**: September 2003 **Follow-up**: 6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "first episode of nonischemic heart failure and preserved LVEF. We confirmed that all patients had symptoms and signs of congestive heart failure in this study."..."they were in New York Heart Association (NYHA) functional class II or III at the time of enrollment, and all had an LVEF > 40%. " **Exclusion criteria**: "Patients were excluded if they had a history of myocardial infarction, coronary artery disease, congenital heart disease, primary hepatic failure, or active cancer." **Randomised** (N): 50 (intervention: 25, control: 25) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, mean, SD): intervention: 66, 10; control: 67, 8 **Sex** (% men): intervention: 68; control: 64 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SD): intervention: 132, 18; control: 130, 20 **Heart rate** (beats/min, mean, SD): intervention: 72, 12; control: 74, 14 **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): intervention: 202, 125; control: 204, 127 **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 54, 7; control: 55, 7 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 64; control: 68

Kasama 2005 *(Continued)*

	NYHA class III (%): intervention: 36; control: 32 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 64; control: 60 **Diabetes** (%): not reported Atrial fibrillation (%): not reported **Hospitalisation for heart failure** (%): 100 **Coronary heart disease** (%): intervention: 0; control: 0 **Stroke** (%): not reported **Diuretic** (%); intervention: 92; control: 88 **Digoxin** (%): not reported **Beta-blocker** (%): intervention: 12; control: 12 **ACEI** (%): intervention: 92; control: 96 **ARB** (%): study drug **MRA** (%): intervention: 16; control: 20
Interventions	**Intervention**: candesartan. "the initial daily dose of candesartan was 2 to 4 mg, which was increased to a maintenance dose of 8 to 12 mg/day (mean 10 2 mg/day)." **Comparator**: placebo **Concomitant medication**: "in addition to baseline therapy"
Outcomes	**Planned**: unclear as unaware of published protocol or pre-registration with a clinical trial registry **Reported**: hemodynamics, I-MIBG, echocardiographic findings, NYHA functional class, BNP
Notes	No outcomes reported for relevance to this review. Emailed trialist to ask for outcome data relevant to this review. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly classified" but no further details
Allocation concealment (selection bias)	Unclear risk	no information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blinded" but no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"assessment was performed in a blinded fashion by two independent observers with no knowledge of the clinical status or medical therapy of the patients."
Incomplete outcome data (attrition bias)	High risk	ITT used for all outcomes, but loss to follow-up and withdrawals not reported

Kasama 2005 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	unable to assess as we are not aware of a published protocol or a pre-registration in a clinical trial registry
Other bias	Unclear risk	funding source not reported

Kitzman 2010

Methods	**Study design**: individual parallel RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported **Follow-up**: 12 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "As previously described, isolated HFPEF was defined as history, symptoms, and signs of HF; a preserved LVEF (50%); and no evidence of significant coronary, valvular, or pulmonary disease or other medical condition that could mimic HF symptoms, such as anemia or thyroid dysfunction." **Exclusion criteria**: "Coronary disease was excluded by history, medical records, ECG, and rest and exercise echocardiogram." "Patients were excluded if they had ever been prescribed an ACEI or ARB." **Randomised** (N): 71 (35 intervention, 36 control) **Withdrawn** (N): for reasons other than death 12 (10 intervention (3 patient request, 1 pancreatitis, 1 elective rotator cuff surgery, 1 alopecia, 1 worsening cough, 1 hypotension, 1 ankle fracture, exacerbation of knee arthritis, 1 leg and hip pain and fatigue), 2 control (1 elective knee replacement surgery, no details for second participants) **Lost to follow-up** (N): not reported **Analysed** (N): 59 completed study (25 intervention, 34 control) **Age** (years, mean, SD): intervention: 69, 8; control: 70, 7 **Sex** (% men): intervention: 20; control: 11 **Ethnicity** (%): intervention: black 9, control: black 6 **Systolic blood pressure** (mmHg, mean, SD): intervention: 143, 17; control: 144, 18 **Heart rate** (beats/min, mean, SD): intervention: 129, 20; control: 133, 16 **BMI** (mean, SD): intervention: 30, 5; control: 30, 5 **Serum creatinine** (mg/dL, mean, SD): intervention: 1.1, 0.2; control: 1.1, 0.2 **B-type natriuretic peptide** (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 65, 8; control: 65, 7 **NYHA class I** (%): 0:

Kitzman 2010 *(Continued)*

	NYHA class II (%): intervention: 83; control: 75 **NYHA class III** (%): intervention: 17; control: 25 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 71; control: 75 **Diabetes** (%): intervention: 9; control: 17 Atrial fibrillation not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): 0 **Stroke** not reported **Diuretic** (%); intervention: 49; control: 58 **Digoxin** (%): 0 **Beta-blocker** (%): intervention: 29; control: 39 **ACEI** (%): study drug **ARB** not reported **MRA** not reported
Interventions	**Intervention**: enalapril. "The study drug was initiated at 2.5 mg BID and titrated up to 10 mg BID as tolerated by the patient within the first 4 weeks of the study." **Comparator**: placebo **Concomitant medication**: not reported
Outcomes	**Planned**: unclear as clinical trial registration was post hoc **Reported**: exercise capacity, aortic distensibility and LV structure and function, carotid artery stiffness, LV diastolic filling, QoL
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All investigators, staff, and patients were fully blinded to treatment group assignment throughout the entire study period."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All investigators, staff, and patients were fully blinded to treatment group assignment throughout the entire study period."

Kitzman 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	not reported
Other bias	Low risk	"Dr Kitzman has served as consultant for and received grant support from Synvista ($10 000), Bristol-Meyers Squibb ($10 000), Novartis ($10 000), Boston Scientific ($10 000), Relypsa ($10 000), Forest Laboratories, and Medtronic. Dr Little has served as consultant for CorAssist Cardiovascular Ltd, Celladon, Boston Scientific, Medtronic ($10 000), Bio-Control Medical, CVRx ($10 000), Amylin Pharmaceuticals, Gilead, and BristolMeyers Squibb ($10 000). Drs Hundley, Brubaker, and Morgan; Mr Moore; and Ms Steward report no conflicts."

Kurrelmeyer 2014

Methods	**Study design**: parallel RCT **Centres**: 1 hospital, Houston, Texas **Start of enrolment**: 2004 **End of enrolment**: 2008 **Follow-up**: 6 months **Run-in period**: "patients were treated with 25 mg open-label spironolactone for 1 week before randomization to ensure drug tolerability, defined as serum potassium < 5 mEq/L and absence of other major side effects."
Participants	**Inclusion criteria**: "≥ 18 years old with a previous diagnosis of HFpEF. HFpEF was defined as current New York Heart Association (NYHA) functional class II or III HF symptoms or signs, left ventricular ejection fraction (LVEF) ≥ 50% according to echocardiography, diastolic dysfunction with elevated LV filling pressure according to Dopplerechocardiograph" "the subjects had to have a blood pressure of ≤ 150/95 mm Hg for 4 weeks before enrollment and the ability to walk ≥ 50 m at the time of enrollment. Treatment with an ACEI, or ARB if ACEI intolerant, was required for ≥ 4 weeks before enrollment. " **Exclusion criteria**: "Exclusion criteria included current treatment with spironolactone or epleronone, previous intolerance to spironolactone, creatinine > 2.5 mg/dL, serum potassium > 5.0mEq/L, significant valvular heart disease, pericardial disease, severe chronic lung disease with cor pulmonale, unstable angina or myocardial infarction ≤ 4 weeks before enrollment, severe peripheral vascular disease with claudication that limited walking distance, presence of other severe comorbid conditions with a life expectancy < 6 months, and pregnant or lactating women." **Randomised** (N): 48 (24 intervention, 24 control) **Withdrawn** (N): for reasons other than death (3 intervention (hyperkalaemia),0 control) **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, mean, SEM): intervention: 66.3, 2.2; control: 76.4, 1.6 **Sex** (% men): 0 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SEM): intervention: 137.0, 4.1; control: 133.1, 2.8

Kurrelmeyer 2014 *(Continued)*

	Heart rate (beats/min, mean, SEM): intervention: 64.2, 2.3; control: 61.1, 1.2 **BMI** (mean, SEM): intervention: 29.4, 2.2; control: 26.3, 1.2 **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SEM): intervention: 62.5, 1.2; control: 62.9, 1.2 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 33; control: 42 **NYHA class III** (%): intervention: 67; control: 58 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 87.5; control: 79.2 **Diabetes** (%): intervention: 50; control: 25 Atrial fibrillation (%): intervention: 25; control: 25 **Hospitalisation for heart failure** (%): intervention: 58.3; control: 54.2 **Coronary heart disease** (%): intervention: 37.5; control: 33.3 **Stroke** (%): not reported **Diuretic** (%): intervention: 83.3; control: 75 **Digoxin** (%): intervention: 12.5; control: 8.3 **Beta-blocker** (%): intervention: 62.5; control: 62.5 **ACEI** (%): intervention: 70.8; control: 66.7 **ARB** (%): intervention: 29.2; control: 37.5 **MRA** (%): study drug
Interventions	**Intervention**: Spironolactone, 25mg once daily **Comparator**: placebo **Concomitant medication**: not reported
Outcomes	**Planned**: no known published protocol or pre-enrolment clinical trial registry record **Reported**: 6 min walk distance, clinical composite score, doppler echocardiography, biomarkers, Kansas City Cardiomyopathy Questionnaire clinical summary score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated", no further details

Kurrelmeyer 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	"subjects were randomly allocated with the use of pharmacy-controlled concealed randomization methods.", no further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	double-blind, placebo controlled, no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	no able to assess due to lack of pre-registration in clinical trial registry and published protocol
Other bias	High risk	clinical trial registry entry after start of enrolment, was originally marked as an observational study (2005-2013) and changed to a randomised trial status in 2013. reported as a RCT in 2014 publication. funded by Women's Fund; Houston, Texas

Mak 2009

Methods	**Study design**: RCT **Centres**: 1 **Start of enrolment**: not reported **End of enrolment**: not reported **Follow-up**: 12 months **Run-in period**: not reported
Participants	**Inclusion criteria**: heart failure with preserved systolic function, "prior New York Heart Association (NYHA) functional class IV HF admission or symptoms consistent with HF, B-type natriuretic peptide (BNP) >100 pg/ml, left ventricular ejection fraction >45%, and evidence of diastolic dysfunction on Doppler-echocardiographic study." **Exclusion criteria**: "Patients were excluded if they were clinically unstable as defined by any change in diuretic dose a month before enrollment or were already receiving eplerenone or spironolactone therapy. Other exclusion criteria were evidence of significant inflammatory disease, hepatic disease, or metabolic bone disease that may alter parameters of collagen metabolism, serum creatinine >200 mol/l, prior documented left ventricular ejection fraction <45%, hemodynamically significant valvular disease, corpulmonale, hypertrophic, restrictive, or constrictive cardiomyopathy, atrial fibrillation or flutter with resting ventricular rate >120 beats/min, severe anemia, clinically significant pulmonary disease as evidenced by hospitalizations, or use of oral corticosteroids for pulmonary decompensation within 12 months or patients who require home oxygen therapy." **Randomised** (N): 44 (24 intervention, 20 control) **Withdrawn** (N): for reasons other than death 0 **Lost to follow-up** (N): 2 (0 intervention, 2 control)

Mak 2009 *(Continued)*

	Analysed (N): 40 (23 intervention, 17 control)
	Age (years, mean, SD): intervention: 80, 7.7; control: 79, 7.9
	Sex (% men): intervention: 38; control: 55
	Ethnicity (%): Caucasian: 100
	Systolic blood pressure (mmHg, mean, SD): intervention: 140, 20; control: 146, 20
	Heart rate (beats/min, mean, SD): intervention: 69, 13; control: 66, 13
	BMI (mean, SD): intervention: 31.3, 6.9; control: 31.8, 5.7
	Serum creatinine: not reported
	B-type natriuretic peptide (pg/mL, median, IQR): intervention: 219 (157-317); control: 192 (132-330)
	NT pro B-type natriuretic peptide: not reported
	LVEF (%, mean, SD): intervention: 63, 9.0; control: 64, 9.6
	NYHA class I (%): not reported
	NYHA class II (%): 87%
	NYHA class III (%): not reported
	NYHA class IV (%): not reported
	Hypertension (%): intervention: 92; control: 90
	Diabetes (%): intervention: 21; control: 35
	Atrial fibrillation (%): intervention: 58; control: 60
	Hospitalisation for heart failure: not reported
	Coronary heart disease (%): not reported
	Stroke (%): not reported
	Diuretic (%); intervention: 88; control: 90
	Digoxin (%): intervention: 38; control: 30
	Beta-blocker (%): intervention: 62; control: 75
	ACEI (%): intervention: 67; control: 60
	ARB (%): intervention: 29; control: 40
	MRA (%): study drug
Interventions	**Intervention**: eplerenone. "we evaluated patients with a dose of 25 mg daily for 6 months followed by a dose increment to 50 mg until the 12-month time point"
	Comparator: usual heart failure treatment
	Concomitant medication: not reported
Outcomes	**Planned**: unable to assess
	Reported: serum levels of markers of collagen turnover, inflammatory markers, doppler-echocardiographic indexes, clinical and biochemical measurements, withdrawals, quality of life

Mak 2009 *(Continued)*

Notes	Emailed investigators to ask whether ITT or PP analysis was used. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated" but no further detail
Allocation concealment (selection bias)	Unclear risk	nor reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"all parameters were assessed by persons blinded to treatment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	unable to assess
Selective reporting (reporting bias)	Unclear risk	unable to assess as unaware of published protocol or pre-trial registration
Other bias	Low risk	Dr. Mak received grant support from the Irish Heart Foundation (The Noel Hickey Bursary) sponsored by Pfizer. Drs. Ledwidge and McDonald have received honoraria from Pfizer.

Mittal 2017

Methods	**Study design**: RCT **Centres**: 1, Cardiology Outpatient Department and HTN clinic of Postgraduate Institute of Medical Education and Research, India **Start of enrolment**: 15 November 2009 (from clinical trial registry) **End of enrolment**: not reported for pilot study, full study ongoing **Follow-up**: 12 weeks **Run-in period**: 2 weeks placebo run in (beta-blocker withdrawn but co-existing therapies were continued)
Participants	**Inclusion criteria**: "18 years and above, had New York Heart Association (NYHA) functional Class II–III of at least 4 weeks' duration, LVEF ≥ 50% in a nondilated LV (LV enddiastolic volume < 97 ml/m measured by echocardiography), echocardiographic evidence of LV diastolic dysfunction, and were willing to give written informed consent." **Exclusion criteria**: "They were excluded if: (1) Clinically unstable as defined by any change in diuretic dose in the month before enrollment, (2) significant valvular heart disease, pericardial disease, hypertrophic or restrictive cardiomyopathy, (3) unstable angina or MI within past 4 weeks, (4) any previous LVEF below 40%, (5) any contraindication to metoprolol use, (6) patients already on beta blockers which cannot be withdrawn, (7) current participation (including prior 30 days) in any other therapeutic

Mittal 2017 *(Continued)*

	trial, and (8) any condition that, in the opinion of investigator, may prevent the participant from adhering to the trial protocol." **Randomised** (N): 40 (20 intervention, 20 control) **Withdrawn** (N): for reasons other than death 0 **Lost to follow-up** (N): 6 (3 intervention, 3 control) **Analysed** (N): 40 (20 intervention, 20 control) **Age** (years, mean, SD): intervention: 55.2, 7.1; control: 57.2, 9.8 **Sex** (% men): intervention: 45; control: 50 **Ethnicity** (%): not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** (pg/mL, median (IQR)): intervention: 238.2 (107.7-2230.2); control: 227.6 (58.3-3645) **LVEF** (%, mean, SD): intervention: 62.9, 6.2; control: 62.1, 6.57 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 55; control: 65 **NYHA class III** (%): intervention: 45; control: 35 **NYHA class IV** (%): 0 **Hypertension** (%): not reported **Diabetes** (%): not reported Atrial fibrillation (%): not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): not reported **Stroke** (%): not reported **Diuretic** (%); intervention: 35; control: 40 **Digoxin** (%): not reported **Beta-blocker** (%): intervention: 40; control: 45 **ACEI** (%): intervention: 15; control: 60 **ARB** (%): intervention: 15; control: 15 **MRA** (%): not reported
Interventions	**Intervention**: metoprolol succinate, 25 mg. "A dose upward titration protocol with monitoring of blood pressure and heart rate (target blood pressure and heart rate as 120/80 mm Hg and 60 beats/min, respectively) was implemented for dose increments up to a maximum dose of 100 mg once daily. For pa-

Mittal 2017 *(Continued)*

	tients not tolerating increased titration of drug, temporary reduction in dosage was done and decision on further escalation made on individual basis by the treating cardiologist." **Comparator**: placebo **Concomitant medication**: "During the study, calcium channel blockers were added in three patients (one in placebo and two in metoprolol group) due to high blood pressure records." coexisting therapies were continued
Outcomes	**Planned**: unable to assess **Reported**: primary: NYHA class. Secondary: exercise capacity, diastolic dysfunction, change in LV wall thickness, LV mass, NT-proBNP, PICP, QoL (SF-36), adverse events, withdrawals
Notes	published results after our search date, identified via search for clinical trial registry number: CTRI/2010/091/000438 which was retrieved by search of the WHO ICTRP register Emailed investigators to ask when completion of full trial is anticipated. Response confirmed that full trial was not conducted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"block randomised" but no further details
Allocation concealment (selection bias)	Low risk	"Randomization and allocation sequence generation were done by investigators not directly involved in the evaluation of outcomes" From clinical trial registry: "sequentially numbered, sealed, opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" From clinical trial registry entry: "participant and outcome assessor blinded" Unclear whether personnel was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To avoid interobserver variability, all the echocardiographic parameters were evaluated by a single cardiologist who was blinded to study medication and the order of assessment." From clinical trial registry entry: "participant and outcome assessor blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	pilot study - full study ongoing same numbers lost to follow-up in both arms ITT and per-protocol analysis used
Selective reporting (reporting bias)	Unclear risk	unable to assess due to lack of published protocol and uncertainty over trial registration date
Other bias	Low risk	"The study was supported by Postgraduate Institute of Medical Education and Research, Chandigarh, India." "There are no conflicts of interest" Results from pilot study only so far.

Mottram 2004

Methods	**Study design**: individual, double-blind, placebo-controlled, RCT **Centres**: 1, Australia **Start of enrolment**: February 2002 **End of enrolment**: October 2002 **Follow-up**: 6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "To be eligible, patients had to have hypertension requiring antihypertensive medication and report exertional dyspnea (New York Heart Association class II) but no history of angina or myocardial infarction." **Exclusion criteria**: "Patients taking angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, or spironolactone were excluded, as were patients with renal impairment (creatinine 0.20 mmol/dL) or hyperkalemia at baseline." "we excluded patients with evidence of pulmonary disease, ischemic heart disease, abnormal regional or global resting LV systolic function (ejection fraction < 50%), or significant (>mild) valvular dysfunction." **Randomised** (N): 30 (not reported by treatment arm, assumed 15 in each) **Withdrawn** (N): not reported **Lost to follow-up** (N): 1 (intervention: 1 (migrated overseas); control: 0) **Analysed** (N): not reported **Age** (years, mean, SD): intervention: 61, 6; control: 62, 5 **Sex** (% men): intervention: 40; control: 34 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg): intervention: 199, 18; control: 198, 26 **Heart rate** (beats/min): intervention: 139, 24; control: 153, 13 **BMI**: intervention: 29.8, 4.7; control: 31.2, 4.6 **Serum creatinine** (mg/dL): intervention: 0.07, 0.01; control: 0.07, 0.01 **B-type natriuretic peptide** (pg/mL) intervention: 29.3, 26.8; control: 29.7, 27.8 **NT pro B-type natriuretic peptide** not reported **LVEF**: intervention: 68, 5; control: 67, 4 **NYHA class** not reported **Hypertension** (%): not reported **Diabetes** (%): intervention: 7; control: 0 Atrial fibrillation (%): not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): not reported **Stroke** (%): not reported

Mottram 2004 *(Continued)*

	Diuretic (%); intervention: 40; control: 27 **Digoxin** (%): not reported **Beta-blocker** (%): intervention: 40; control: 20 **ACEI** (%): not reported **ARB** (%): not reported **MRA** (%): study drug
Interventions	**Intervention**: spironolactone, 25mg/d **Comparator**: placebo **Concomitant medication**: not reported
Outcomes	**Planned:** unable to assess as we are not aware of a published protocol or pre-registered clinical trial registry entry **Reported: m**ean 24hr ambulatory blood pressure, posterior wall thickness, left atrial area, SR, peak systolic strain, and CVIB
Notes	no outcome data of interest to this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomised, but no details
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	double blind, matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators remained blinded to the treatment until after analysis of results."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Unclear risk	"This work was supported in part by a grant and scholarship from the National Heart Foundation of Australia, Melbourne, Australia, in association with a Centers of Clinical Research Excellence Award, National Health and Medical Research Council, Canberra, Australia. The authors are grateful to the Princess Alexandra Hospital Pharmacy for supervision of randomization and dispensing of active and placebo tablets."

Orea-Tejeda 2007

Methods	**Study design**: RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported **Mean follow-up**: 13.8 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "Patients with diastolic heart failure attending to Heart Failure Clinic were considered eligible, independently of etiology, if they had history of arterial hypertension (and/or were on antihypertensive treatment), but no history of angina, myocardial infarction or myocardial revascularization (PTCA and / or aortocoronary bypass grafting) during the 3 months previous to recruitment and they referred fatigue, dyspnea on exercise and/or orthopnea." "Diastolic dysfunction was considered when the ejection fraction was over 45%, and shortening fraction = 28%, without severe segmental dyskynesia of the left ventricle, left atrial enlargement, or increased thickness or posterior wall, interventricular septum, and left ventricular mass index." **Exclusion criteria**: not reported **Randomised** (N): 28 (14 intervention, 14 control) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, mean, SD): intervention: 63.7, 21.6; control: 64.8, 11.9 **Sex** (% men): intervention: 28.6; control: 71.4 **Ethnicity** (%): not reported **Blood pressure** (mmHg): intervention: 112, 12; control: 114, 8 **Heart rate** (beats/min): intervention: 86, 4; control: 82, 6 **BMI** (mean, SD): intervention: 27.5, 9.4; control: 26.9, 4.7 **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 48.79, 4.65; control: 51.57, 11.71 **NYHA class I** (%): intervention: 42.9; control: 75.0 **NYHA class II** (%): intervention: 0; control: 16.7 **NYHA class III** (%): intervention: 57.1; control: 8.3 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 85.7; control: 92.9 **Diabetes** (%): intervention: 28.6; control: 64.3 Atrial fibrillation (%): not reported

Orea-Tejeda 2007 *(Continued)*

	Hospitalisation for heart failure: not reported **Ischaemic heart disease** (%): intervention: 42.9; control: 57.1 **Stroke** (%): not reported **Diuretic** (%): intervention: thiazide: 76.9, loop: 5.1; control: thiazide: 62.3, loop: 13 **Digoxin** (%): not reported **Beta-blocker** (%): intervention: 79.5; control: 79.7 **ACEI** (%): intervention: 38.5; control: 29 **ARB** (%): intervention: 69.2; control: 73.9 **MRA** (%): study drug
Interventions	**Intervention**: spironolactone, mean dose of 37.5 mg/d (25-50 mg once a day) **Comparator**: no treatment **Concomitant medication**: "In our study, patients with diastolic heart failure were all treated with ACE inhibitors/ARA and Beta blockers."
Outcomes	**Planned:** We are not aware of a published protocol or pre-registered clinical trial register entry **Reported:** echocardiographic parameters, adverse events
Notes	no outcome data of interest to this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The echocardiogram was made by a Cardiologist blinded to the clinical evaluation and treatment received."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Unclear risk	no funding reported

Parthasarathy 2009

Methods	**Study design**: RCT **Centres**: 10 (5 in Germany, 5 in UK) **Start of enrolment**: December 2002 (from clinical trial registry) **End of enrolment**: March 2007 (from clinical trial registry) **Mean follow-up**: 13.8 weeks **Run-in period**: not reported
Participants	**Inclusion criteria**: "Patients were ≥ 21 years of age and had the following characteristics: symptoms of breathlessness on exertion (based on patient questioning) with normal lung function at rest, an extrapolated maximum oxygen consumption (EMOC) and/or peak oxygen consumption <85% of the age-corrected normal value on cardiopulmonary exercise testing, preserved systolic function (ejection fraction ≥ 40%) with evidence of diastolic dysfunction on echocardiography (≥ 1 of the following: abnormal flow propagation velocity, prolongation of isovolumic relaxation time, E/A ratio reversal, and abnormal E deceleration time), and ability to exercise for ≥ 3 min on a treadmill." **Exclusion criteria**: "Uncontrolled hypertension (sitting systolic blood pressure >160 mmHg or sitting diastolic blood pressure > 100 mmHg) Presence of clinically significant asthma or chronic obstructive pulmonary disease Abnormal lung function (forced expiratory volume in 1 s [FEV1]/ forced vital capacity [FVC] ratio < 75%) Treatment with ≥ 2 bronchodilators Exercise limiting symptomatic angina Haemodynamically significant cardiac valvular disease Documented evidence of systolic heart failure (ejection fraction <40%, fractional shortening <25%) Uncontrolled atrial fibrillation (> 100 b.p.m. at rest) History of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass within the previous 3 months Use of ARBs within the previous 1 month" **Randomised** (N): 152 (70 intervention, 82 control) **Withdrawn** (N): for reasons other than death 5 (4 intervention (N = 2 adverse events, N = 1 protocol violation, N = 1 withdrew consent), 1 control (N = 1 protocol violation)) **Lost to follow-up** (N): 0 **Analysed** (N): 152 (70 intervention, 82 control), except QoL: 67 intervention, 82 placebo **Age** (years, mean, SD): intervention: 61.0, 11.5; control: 63.1, 10.3 **Sex** (% men): intervention: 50; control: 50 **Ethnicity** (%): intervention: Caucasian: 95.6, Other: 4.4 , control: Caucasian: 93.9, other: 6.1 **Systolic blood pressure** not reported **Heart rate** not reported **BMI** (mean, SD): intervention: 31.0, 4.7; control: 29.3, 5.3 **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): intervention: 93.2, 80.2; control: 120.3, 119.5 **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 70.48, 11.43; control: 71.52, 12.08 **NYHA class** not reported **Hypertension** (%): intervention: 92.2; control: 89.0 **Diabetes** (%): intervention: 22.1; control: 14.6 Atrial fibrillation (%): intervention: 16.2; control: 9.8

Parthasarathy 2009 *(Continued)*

	Hospitalisation for heart failure: not reported **Coronary heart disease** (%): not reported **Stroke** (%): not reported **Diuretic** (%): not reported **Digoxin** (%): not reported **Beta-blocker** (%): intervention: 33.8; control: 34.1 **ACEI** (%): intervention: 41.2; control: 37.8 **ARB** (%): study drug **MRA** (%): not reported
Interventions	**Intervention**: valsartan. 80 mg once daily. "Study medication was force-titrated between days 5 and 14 (Visit 3) to valsartan 160 mg daily or matching placebo, and between days 10 and 28 (Visit 4) to valsartan 320 mg daily or matching placebo. Up-titration occurred provided the current dose was adequately tolerated. Down-titration occurred for any of the following: evidence of persistent symptomatic hypotension, systolic blood pressure <100 mmHg or decrease of >40 mm Hg from baseline, creatinine increase of >50% from baseline, or if the investigators judged the given dose level as potentially harmful to the patient. A safety evaluation was performed between days 15 and 42 (Visit 5). After the dose-titration period, patients received their maximum tolerated dose through to the end of the study at week 14 (+7 days) (Visit 6)." **Comparator**: matching placebo **Concomitant medication**: "Use of other ARBs as concomitant medication was prohibited, but other background medications (e.g. diuretics, calcium channel blockers) were allowed and continued throughout the study. Angiotensin-converting enzyme inhibitors and beta-blockers were permitted, although therapy was to be maintained at the same level throughout the study and no new treatment with one of these drugs was permitted during the trial."
Outcomes	**Planned**: unclear **Reported**: exercise time, neurohormone levels, echocardiographic parameters, QoL, adverse events
Notes	Response to email enquiring for further details received on 2 December 2017: confirmed that no outcome data are available for heart failure hospitalisation and hyperkalaemia and provided number of centres.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Eligible patients were allocated to either the active treatment group or the placebo group according to a stratified randomization process in order to minimize the differences between study groups. Stratification was based on exercise test time at Visit 2 divided into sections of: 3–6 min, .6 min to 9 min, and .9 min, each stratum being randomized in blocks of 4." No details on how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias)	Low risk	"double-blind" but not specified

Parthasarathy 2009 *(Continued)*

All outcomes		"To maintain blinding, valsartan and placebo capsules were identical in appearance."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT, higher withdrawals in intervention group (5.7%) compared to control (1.2%)
Selective reporting (reporting bias)	Unclear risk	unable to assess, unaware of published protocol and clinical trial register entry (Sept 2005) after planned study start (Dec 2002)
Other bias	Low risk	"H.K.P. and B.P. have no conflicts of interest; C.D.A., M.W., and P.B. remain in the employ of Novartis Pharma and have no other conflicts of interest; A.D.S. received one honorarium (£1000) from Novartis for intellectual input to the rationale and the design of the study; T.M.MacD: competing interests statement Nov 2008: my department has had research grants from GSK, Aventis, Novartis, AstraZeneca, BMS, Bohringer Ingelheim, Pfizer, and Novartis, I am or have been the principal investigator on trials paid for by Pfizer and Novartis, I have been paid Consulting fees by Pfizer, Novartis, Kaiser Permanante, Takeda, Recordati, Quintiles, and Speedel." "The study was funded by Novartis."

PEP-CHF

Methods	**Study design**: RCT **Centres**: 53 centres (Bulgaria (3), Czech Republic (5), Hungary (10), Ireland (1), Poland (26), Russia (1), Slovakia (2), and the UK (5)) **Start of enrolment**: 2000 **End of enrolment**: 2003 **Mean follow-up**: mean follow-up 26.2 months (range, excluding deaths 12.0-54.2) **Run-in period**: "A 24-h open label run in phase, during which patients will receive a single 2-mg dose of perindopril"
Participants	**Inclusion criteria**: "Patients had to be aged ≥70 years and treated with diuretics for a clinical diagnosis of CHF due to LV diastolic dysfunction as defined below and to have had a cardiovascular hospitalization within the previous 6 months. Patients had to be able to walk without the aid of another person in order to exclude very frail patients who might not respond to any treatment.""Patients had to be aged 70 years and treated with diuretics for a clinical diagnosis of CHF due to LV diastolic dysfunction as defined below and to have had a cardiovascular hospitalization within the previous 6 months. Patients had to be able to walk without the aid of another person in order to exclude very frail patients who might not respond to any treatment." "As there are no widely agreed criteria for the diagnosis of diastolic heart failure, at least three out of nine clinical and at least two out of four additional echocardiographic criteria were required. Clinical criteria were: exertional breathlessness; orthopnoea or paroxysmal nocturnal dyspnoea; ankle swelling; improved breathlessness with diuretic therapy; increased jugular venous pressure; prior episode of clinical pulmonary oedema; prior MI; cardiothoracic ratio > 0.55; and previous radiological pulmonary oedema. Echocardiographic criteria were: an LV wall motion index of 1.4–1.6 inclusive, roughly equivalent to an LVEF fraction between 40 and 50%, since abnormal diastolic dysfunction is often associated with some impairment of systolic function; a left atrial diameter > 25 mm/m^2 body surface area or > 40 mm because chronic elevation of LV filling pressure should lead to atrial dilatation; an interventricular septum or posterior LV wall ≥ 12 mm in thickness suggesting

PEP-CHF *(Continued)*

hypertrophy, a common cause of impaired diastolic function or, finally, evidence of impaired LV filling by at least one of the criteria recommended by the European Society of Cardiology Study Group on Diastolic Heart Failure. These included an E/A ratio < 0.5 or deceleration time of > 280 ms from the mitral inflow pattern or an isovolumic relaxation time of > 105 ms. These criteria effectively exclude patients with atrial fibrillation (AF) and therefore, in a protocol modification early in the course of the study, this arrhythmia was counted as equivalent to evidence of impaired LV filling by Doppler."

Exclusion criteria: "Patients with a wall motion index of < 1.4, roughly equivalent to an LVEF of 40%, were excluded." "Important exclusion criteria were haemodynamically significant valve disease, stroke within the previous month, sitting systolic arterial pressure < 100 mmHg, serum creatinine > 200 mmol/L or potassium > 5.4mmol/L, history of ACE-inhibitor intolerance or use of an ACE-inhibitor or angiotensin receptor blocker within the previous week, potassium-sparing diuretics (other than low-dose spironolactone), or potassium supplements."

Randomised (N): 850 (424 intervention, 426 control)

Withdrawn (N): due to serious adverse events 13 (9 intervention, 4 control)

Lost to follow-up (N): 4 (4 intervention, 0 control)

Analysed (N): 846 (420 intervention, 426 control)

Age (years, median, IQR): intervention: 75, 72–79; control:75, 72-79

Sex (% men): intervention: 46; control: 43

Ethnicity (%): not reported

Systolic blood pressure (mmHg, median, IQR): intervention: 138, 128–150; control: 140, 129–150

Heart rate (beats/min, median, IQR): intervention: 74, 66 to 81; control: 73, 66 to 82

BMI (median, IQR): intervention: 27.5, 25.1 to 30.0; control: 27.6, 25.3 to 30.7

Serum creatinine (mg/dL, median, IQR, converted from umol/L using http://www.endmemo.com/medical/unitconvert/Creatinine.php): intervention: 1.07, 0.92-1.24; control: 1.10, 0.95-1.26

B-type natriuretic peptide (pg/mL): not reported

NT pro B-type natriuretic peptide (pg/mL): intervention: 335, 160–1014 (for subgroup n =191); control: 453, 206–1045 (for subgroup n = 184)

LVEF (%, median, IQR): intervention: 65, 56– 66; control: 64, 56– 66

NYHA class I/II (%): intervention: 77; control: 74

NYHA class III/IV (%): intervention: 23; control: 26

Hypertension (%): intervention: 79; control: 79

Diabetes (%): intervention: 21; control: 20

Atrial fibrillation (%): intervention: 19; control: 22

Hospitalisation for heart failure: not reported

Coronary heart disease (%): intervention: 27; control: 26

Stroke not reported

Diuretic (%); intervention: loop: 47, thiazide 54, low dose spironolactone 9; control: loop: 44, thiazide 55, low dose spironolactone 11

Digoxin (%): intervention: 11; control: 13

Beta-blocker (%): intervention: 55; control: 54

PEP-CHF *(Continued)*

	ACEI: study drug **ARB** not reported **MRA** (%): intervention: 9; control: 11
Interventions	**Intervention**: perindopril. "Patients were reviewed weekly for the first 5 weeks to ensure that treatment was tolerated and to check serum potassium and creatinine. The dose of perindopril was increased to 4 mg once daily at the second follow-up visit if no clinical contraindication, such as hypotension or worsening renal function existed. Study medication was reduced or discontinued if serum creatinine rose to > 250 mmol/L or by > 50 mmol/L from baseline or potassium rose to > 5.5mmol/L. Patients were reviewed at 8, 12, and every 12 weeks thereafter until 1 year follow-up, then according to the investigator's judgment until the end of the study." **Comparator**: placebo **Concomitant medication**: not reported
Outcomes	**Planned**: "The primary end-point of this study will be the time to first occurrence of the combined end-point of total mortality and unplanned heart failure related hospitalisation." "Secondary 1. Death all causes 2. Death or worsening symptoms and/or signs of CHF requiring hospitalisation or an increase in diuretic treatment for CHF of >40 mg/day of frusemide compared to baseline or equivalent. This will be a time to first event analysis. 3. Cardiovascular mortality. 4. Number of days alive and out of hospital. 5. Number of days alive and not in hospital for cardiovascular reasons including CHF 6. QoL questionnaire change from baseline to 1 year. 7. CHF symptom score change from baseline to 1 year. 8. NYHA heart failure score change from baseline to 1 year." (Cleland 1999) **Reported**: primary outcome, all-cause mortality, cardiovascular mortality, HF hospitalisation, days in hospital for cardiovascular reasons, days in hospital for any reason, NYHA class, 6-min walk distance, plasma concentrations of NTproBNP, cardiovascular death or unplanned HF related hospitalisation, stroke, acute coronary syndrome, blood pressure, serum potassium and creatinine **Planned but not reported**: QoL
Notes	Protocol (Cleland 1999) mentions subgroup analyses by age and sex but not found in published papers. Emailed investigators. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"patients were randomly assigned from a computer-generated list in blocks of four within treatment centres"
Allocation concealment (selection bias)	Low risk	"through a centrally administered process, concealed from the study investigators."

PEP-CHF *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study medication was provided in externally indistinguishable tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Potential classifying events were independently classified by MT and JGFC, blind to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/850 lost to follow up
Selective reporting (reporting bias)	Low risk	Primary outcomes reported, but not all secondary outcomes reported as planned (eg QoL)
Other bias	Low risk	"Servier funded the trial and provided site monitors for source data verification. The sponsor had access to the database and participated in the analysis under the supervision of an independent statistician (NF). The Steering Committee wrote the manuscript. Servier representatives commented on it prior to submission."

RAAM-PEF

Methods	**Study design**: individual, placebo-controlled, double-blind RCT **Centres**: 1 medical centre, USA **Start of study**: August 2004 **End of Study**: October 2007 **Follow-up**: 24 weeks **Run-in period**: "2-week open label period of eplerenone 25 mg daily to establish tolerability"
Participants	**Inclusion criteria**: "All patients were defined as having HFpEF based on the presence of all the following criteria: 1) Clinical HF for ≥ 2 months before the screening visit with New York Heart Association (NYHA) functional Class II or III HF symptoms at enrollment; 2) left ventricular ejection fraction ≥ 50% (by echocardiography, radionuclide ventriculography, or contrast angiography) within 2 months of screening; and 3) B-type natriuretic peptide (BNP) levels ≥ 100 pg/mL within 2 months of screening. Other inclusion criteria included age ≥ 18 years, systolic blood pressure ≤150, and diastolic blood pressure ≤ 95 mm Hg for 4 weeks before and at enrollment, ability to walk ≥ 50 m, current use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), if tolerated, for at least 4 weeks before enrollment. Patients were expected to be euvolemic on clinical examination or all attempts were made to achieve euvolemia with change in diuretic doses prior to enrollment into the study." **Exclusion criteria**: "Exclusion criteria included the need for eplerenone or spironolactone for treatment of other comorbid illnesses (eg, ascites); hepatic impairment; serum creatinine > 2.5 mg/dL or serum potassium > 5.0 mEq/L; prior intolerance to eplerenone or spironolactone; significant valvular heart disease, pericardial disease or severe chronic lung disease; patients with technically inadequate echocardiographic windows; patients with severe mitral annular calcification; unstable angina or acute myocardial infarction within 4 weeks before enrollment; severe peripheral vascular disease with claudication or other physical conditions limiting the distance walked; pregnant or lactating females; history of active alcohol or substance abuse or history of repeated noncompliance; history of cancer within 3 years (other than resected cutaneous basal or squamous cell carcinoma); and participation in any other drug trial within 30 days before enrollment." **Randomised** (N): 46 (23 intervention, 23 control)

RAAM-PEF *(Continued)*

	Withdrawn (N): 0
	Lost to follow-up (N): 2 (2 intervention (relocation))
	Analysed (N): 44 (21 intervention, 23 control)
	Age (years, mean, SD): intervention: 72.2, 9.8; control: 68.7, 9.1
	Sex (% men): intervention: 95.2; control: 91.3
	Ethnicity (%): not reported
	Systolic blood pressure (mmHg, mean, SD): intervention: 129.7, 12.4; control: 130.6, 10.7
	Heart rate (beats/min, mean, SD): intervention: 65.0, 9.3; control: 63.0, 12.1
	BMI (mean, SD): intervention: 30.1, 6.1; control: 34.6, 5.8
	Serum creatinine (mg/dL, mean, SD): intervention: 1.62, 0.50; control: 1.43, 0.51
	B-type natriuretic peptide (pg/mL): intervention: 254.9, 163.0; control: 283.5, 211.6
	NT pro B-type natriuretic peptide (pg/mL): not reported
	LVEF (%, median, IQR): intervention: 62.1, 5.0; control: 62.5, 7.5
	NYHA class I (%): 0
	NYHA class II (%): intervention: 66.7; control: 52.2
	NYHA class III (%): intervention: 33.3; control: 47.8
	NYHA class IV (%): 0
	Hypertension (%): 100
	Diabetes (%): intervention: 61.9; control: 60.9
	Atrial fibrillation (%): intervention: 14.3; control: 13.0
	Hospitalisation for heart failure (%): intervention: 42.9; control: 60.9
	Coronary heart disease (%): intervention: 66.7; control: 47.8
	Stroke (%): nor reported
	Diuretic (%); intervention: 95.2; control: 100
	Digoxin (%): not reported
	Beta-blocker (%): intervention: 76.2; control: 82.6
	ACEI or ARB (%): intervention: 95.2; control: 100
	MRA (%): study drug
Interventions	**Intervention**: eplerenone. "After randomization, patients received study drug at a dose of 25 mg daily for 2 weeks followed by 50 mg daily for 22 weeks, if tolerated" "Study drug dose was adjusted according to the following algorithm. If the serum K+ was ≥ 5.0 mEq/L but < 5.5 mEq/L, the dose of eplerenone was not increased. If the level was ≥ 5.5 but < 6.0 mEq/L, the dose of eplerenone was reduced to half. If the serum potassium was ≥ 6.0 mEq/L eplerenone was stopped, at least transiently. If an underlying condition that was correctable was identified, the medication could be restarted at the lowest dose once the serum K+ was < 5.0 mEq/L. If no correctable cause was identified for the serum potassium ≥ 6.0 mEq/L, eplerenone was discontinued permanently and serum K+ was followed with adjustments in other medications as indicated. Oral potassium supplements were allowed if the serum potassium was < 4.0 mEq/L after the study drug was started."

RAAM-PEF *(Continued)*

	Comparator: matching placebo **Concomitant medication**: "Potassium supplements were stopped when eplerenone was initiated."
Outcomes	**Planned**: in clinical trial register: all of the below, except NYHA class, hospitalisation and mortality **Reported**: primary: 6MWD. Secondary: echocardiographic measures of diastolic dysfunction, biomarkers including markers of collagen turnover and B-type natriuretic peptide, HF-related quality of life measured by the Kansas City Cardiomyopathy Questionnaire, NYHA class, hospitalisation, mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" but no details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"all end points were evaluated blinded to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT not used, analysis based on participants that completed study, minimal loss to follow-up (reasons reported)
Selective reporting (reporting bias)	Unclear risk	although there is a clinical trial registry record, it's unclear whether this was a pre- or post-registration
Other bias	Low risk	"Supported by a VA Clinical Research Service grant # CLIN-010-03S (to Dr. Deswal)." "The study was sponsored by the Department of Veterans Affairs (VA). The study drug was provided by Pfizer Pharmaceuticals, but they did not provide any other funding for the study and did not have any role in the conduct and analysis of this study" originally registered as assessing spironolactone, then changed to epleronone

Sahoo 2016

Methods	**Study design**: RCT **Centres**: 1, India **Start of enrolment**: not reported **End of enrolment**: not reported

Sahoo 2016 *(Continued)*

	Mean follow-up: 3-6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "Patients with moderate or severe MR on color flow Doppler, LVEF ≥ 55%, and LV end-systolic dimension < 40 mm were included" **Exclusion criteria**: "Patients with NYHA class IV symptoms, known coronary artery disease, significant other valvular disease, serum creatinine > 2.5 mg/dL, and hypertension were excluded" **Randomised** (N): 100 (48 intervention, 52 control) **Withdrawn** not reported **Lost to follow-up** not reported **Analysed** (N): at 3 months: 100 (48 intervention, 52 control); at 6 months: 75 (39 intervention, 36 control) **Age** (years, mean, SD): intervention: 30.24, 12.76; control: 29.6, 15.58 **Sex** (% men): intervention: 35.6; control: 22.7 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SD): intervention: 125, 10.1; control: 124.4, 7.4 **Heart rate** (beats/min, mean, SD): intervention: 90.1, 11.78; control: 88.5, 18.12 **BMI**: intervention: 21.04, 4.74; control: 19.04, 4.7 **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): intervention: 194, 178.5; control: 166, 165.7 **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 62.5, 6.5; control: 61.4, 6.9 **NYHA class**: "most patients were in NYHA class II (77%) while 23% were in NYHA class III" **Hypertension** (%): intervention: 61.1; control: 62.3 **Diabetes** (%): intervention: 26.9; control: 25.3 Atrial fibrillation (%): intervention: 33.8; control: 35.5 **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): intervention: 68.9; control: 67.6 **Stroke** (%): intervention: 0.1; control: 0 **Diuretic** (%): 92 **Digoxin** (%): 33 **Beta-blocker** (%): study drug **ACEI** (%): 58 **ARB** (%): not reported **MRA** (%): not reported

Sahoo 2016 *(Continued)*

Interventions	**Intervention**: metoprolol succinate. "initiated at 12.5–25 mg/day and titrated as tolerated at 2-week intervals to a maximum of 100 mg/day. Prior to each escalation, care was taken to ensure that resting heart rate was > 60 bpm and systolic BP > 100 mm Hg" **Comparator**: placebo **Concomitant medication**: "in addition to ongoing therapy"
Outcomes	**Planned**: unclear as we did not identify a published protocol or clinical trial registry entry **Reported**: withdrawals due to adverse events, echocardiographic outcomes, blood pressure, MR grade, NYHA class
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"by a computerized random number generating protocol"
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Detailed echocardiography […] was performed by two operators who were blinded to the treatment protocol."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	unclear loss-to-follow up of 25 participants at 6 months as no reasons given
Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Unclear risk	"The authors declare no conflict of interest" no funding source reported

SENIORS

Methods	**Study design**: RCT **Centres**: multi-centre, international (Czech Republic, Hungary, Italy, Ukraine, UK, France, Germany, Romania, Spain, Switzerland, The Netherlands) **Start of enrolment**: September 2000 **End of enrolment**: December 2002 **Mean follow-up**: 21 months

SENIORS *(Continued)*

	Run-in period: no
Participants	**Inclusion criteria**: "To be eligible, patients had to be age ≥ 70 years, provide written informed consent, and have a clinical history of chronic HF with at least 1 of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive HF or documented LVEF ≤ 35% within the previous 6 months. " **Exclusion criteria**: "The main exclusion criteria were new drug therapy for heart failure in the 6 weeks prior to randomization, any change in cardiovascular drug therapy in the 2 weeks prior to randomization, heart failure due primarily to uncorrected valvular heart disease, contraindication or previous intolerance to beta-blockers (e.g. heart rate < 60 beats/min or systolic blood pressure < 90 mmHg), current use of beta-blockers, significant hepatic or renal dysfunction, cerebrovascular accidents within the previous 3 months, and being on a waiting list for percutaneous coronary intervention or cardiac surgery or other major medical conditions that may have reduced survival during the period of the study." **Randomised** (N): 2128 (1067 intervention, 1061 control); subgroup of interest: 643 (nebivolol N = 320, placebo N = 323) **Withdrawn** not reported **Lost to follow-up** (N): 37 (16 intervention, 21 control) **Analysed** (N): 2128 (1067 intervention, 1061 control) **Age** (years, mean, SD): intervention: 76.1, 4.8; control: 76.1, 4.6 **Sex** (% men): intervention: 61.6; control: 64.7 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, mean, SD): intervention: 138.6, 20.1; control: 139.5, 21.1 **Heart rate** (beats/min, mean, SD): intervention: 79.2, 13.6; control: 78.9, 13.7 **BMI**: not reported **Serum creatinine** (mg/dL, mean, SD)*: intervention: 1.2, 0.4; control: 1.2, 0.4 **B-type natriuretic peptide** (pg/mL): not reported **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 36, 13; control: 36, 12 **NYHA class I** (%): intervention: 3.0; control: 2.7 **NYHA class II** (%): intervention: 56.5; control: 56.3 **NYHA class III** (%): intervention: 38.7; control: 38.7 **NYHA class IV** (%): intervention: 1.8; control: 2.3 **Hypertension** (%): intervention: 61.1; control: 62.3 **Diabetes** (%): intervention: 26.9; control: 25.3 Atrial fibrillation (%): intervention: 33.8; control: 35.5 **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): intervention: 68.9; control: 67.6 **Stroke** (%): intervention: 0.1; control: 0 **Diuretic** (%); intervention: 85.8; control: 85.5

SENIORS *(Continued)*

	Digoxin (%): not reported **Beta-blocker** (%): study drug **ACEI** (%): intervention: 81.7; control: 82.6 **ARB** (%): intervention: 6.2; control: 7.1 **MRA** (%): intervention: 28.8; control: 26.4
Interventions	**Intervention**: nebivolol "Nebivolol or placebo tablets were provided in identical packaging and tablet appearance. The initial dose was 1.25 mg once daily, and, if tolerated, this was increased to 2.5 and 5 mg, respectively, every 1–2 weeks, reaching a target of 10 mg once daily over a maximum of 16 weeks." **Comparator**: placebo **Concomitant medication**: exclusion criteria: current use of beta blockers
Outcomes	**Planned**: planned in protocol (Shibata 2002): primary: all cause mortality and cardiovascular hospital admissions (time to first event). Secondary: all cause mortality, composite of all cause mortality or all cause hospital admissions, cardiovascular hospital admissions, cardiovascular mortality, functional capacity by NYHA class, functional capacity by 6 min walk test **Reported**: reported: compliance to treatment, haemodynamics, death or cardiovascular hospital admission, all cause mortality, cardiovascular hospital admissions, total mortality, cardiovascular mortality, all cause hospitalisation
Notes	subgroup of interest, partial outcome data reported baseline data for all participants, outcome data for subgroup only (nebivolol N = 320, placebo N = 323) emailed trialists to ask for details on HF hospitalisation for LVEF > 40%, withdrawal due to AE, hyperkalaemia. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization to nebivolol or placebo on a 1:1 basis was carried out by telephone call to a central office (Clinical Data Care, Lund, Sweden)."
Allocation concealment (selection bias)	Low risk	"Patients were allocated a treatment number which corresponded to the appropriate study treatment packs."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used
Selective reporting (reporting bias)	Low risk	primary outcomes reported as planned

SENIORS *(Continued)*

Other bias	Low risk	"Dr. van Veldhuisen has received lecture fees from Menarini and was a member of the steering committee of the SENIORS trial. Dr. Cohen-Solal has received lecture and consultancy fees from Menarini, and was a member of the steering committee for the SENIORS trial and received lecture fees. Dr. Böhm has received speaker fees from Menarini. Dr. Anker has received speaking honoraria from Menarini Ricerche SpA, Roche, Merck, and Tanabe. Dr. Babalis's department has received a grant from Menarini. Dr. Coats has received honoraria from Menarini. Dr. Poole-Wilson has received honoraria from Menarini for speaking about the SENIORS trial. Dr. Flather has received research grant funding to his institution from Menarini and speaker fees from Menarini for lectures at scientific meetings and symposia. The original SENIORS trial was supported by Menarini Ricerche SpA, Italy. Funding for additional statistical analyses for the present study to the Clinical Trials and Evaluation Unit in London were obtained. All members of the Steering Committee of the SENIORS trial have received honoraria for speaking on aspects of heart failure and beta-blockers at meetings funded by companies in the pharmaceutical industry." "SENIORS is sponsored by Menarini Ricerche SpA."

Shu 2005

Methods	**Study design**: two-arm, individual, RCT **Centres**: not reported **Start of enrolment**: August 2000 **End of enrolment**: March 2002 **Follow-up**: 6-12 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "Patients were included in the study if they had (1) a history of uncorrected rheumatic heart valvular disease or New York Heart Association (NYHA) functional class III or IV disease, necessitating hospitalization; (2) a cardiothoracic ratio of less than 65%; (3) AF with a resting ventricular rate of 70 beats/ minute or more for at least three months, as depicted on the electrocardiogram (ECG); and (4) an echocardiogram showing a significant mitral stenosis or aortic lesions and mitral valve regurgitation." **Exclusion criteria**: "Patients were excluded from the study if they had uncorrected congenital heart disease, sustained ventricular tachycardia, severe liver and kidney dysfunction, chronic obstructive pulmonary disease, bronchial asthma, obstructive or restrictive cardiomyopathy or myocarditis, myocardial infarction, or unstable angina within the previous three months. Patients were also ineligible for enrollment if they required intensive care or concurrent intravenous therapy or if they were using calcium-channel blockers, class I or III antiarrhythmic drugs, monoamine oxidase (MAO)–inhibitors or beta2-agonists." **Randomised** (N): 88 (not reported by treatment arm) **Withdrawn** (N): 20 (did not complete the study) intervention: 11 (5 due to suspected adverse drug effects); control: 9 **Lost to follow-up** (N): 14 (excluded from the evaluation at follow-up - 7 had insufficient quality of echocardiography or difficulties with telephone-connection) **Analysed** (N): 67 (intervention: 33; control: 34) **Age** (years, mean, SD): intervention: 40.6, 6.8; control: 43.5, 7.4

Shu 2005 *(Continued)*

	Sex (% male): intervention: 36; control: 35 **Ethnicity** not reported **Systolic blood pressure** (mmHg, mean, SD): intervention: 115, 12; control: 121, 14 **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** not reported **LVEF** not reported **NYHA class** not reported **Hypertension** not reported **Diabetes** not reported Atrial fibrillation not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** not reported **Stroke** not reported **Diuretic** not reported **Digoxin** not reported **Beta-blocker** not reported **ACEI** not reported **ARB** not reported **MRA** not reported
Interventions	**Intervention**: Bisoprolol, "All patients in the treatment group received bisoprolol at the initial dose of 1.25 mg/day. The recommended maximal dose was 10 mg/day. The dose schedule for titration of the selective beta1 blocker was gradually increased over three to five days, by two to three weeks, to as high as 10 mg/day, with adjustments of diuretics and ACE-inhibitors, as clinically indicated." **Comparator**: "control" (unspecified) **Concomitant medication**: "At the discretion of the treating physicians, all patients were given concomitant therapy consisting of one of the following: • diuretics, as required, to control fluid retention • digoxin, extracted from Digitalis lanata • ACE-inhibitors (or ARBs when ACE-inhibitors were not tolerated) unless there were specific contraindications • nitrates, depending on the presence of valvular lesions and on blood pressure readings"
Outcomes	**Planned:** we did not identify a published protocol or pre-registered clinical trial register record
Notes	
Risk of bias	

Shu 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"On the basis of admission sequence, patients were randomly assigned to a treatment group or a control group"
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	unclear reporting of withdrawals/loss-to-follow up
Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Unclear risk	no funding source reported

SNEGOVIK

Methods	**Study design**: two-arm, individual, RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported **Follow-up**: 3 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "in ambulatory patients (pts) with arterial hypertension and CHF and preserved systolic left ventricular (LV) function" "According including/exclusion criteria pts have had seated systolic BP(SBP)≤160mmHg and diastolic BP(DBP) ≤ 95mmHg at randomization." "with stable symptomatic CHF (NYHA class II-III) as a result of arterial hypertension (AH) with preserved LV ejection fraction (EF) ≥ 50%" **Exclusion criteria**: not reported **Randomised** (N): 726 (416 intervention, 310 control) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** not reported **Sex** not reported

SNEGOVIK *(Continued)*

	Ethnicity not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** not reported **LVEF** not reported **NYHA class** not reported **Hypertension** not reported **Diabetes** not reported Atrial fibrillation not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** not reported **Stroke** not reported **Diuretic** not reported **Digoxin** not reported **Beta-blocker** not reported **ACEI** not reported **ARB** not reported **MRA** not reported
Interventions	**Intervention**: quinapril **Comparator**: "conventional treatment, recommended for CHF [congestive heart failure] and AH [arterial hypertension] treatment" **Concomitant medication**: not reported
Outcomes	**Planned**: unclear **Reported**: NYHA, 6MWD, clinical status, QoL (MLHFQ), 2D echocardiography, blood pressure
Notes	Unable to find contact details to ask investigators for end scores for QoL, full publication of results and mortality data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"were randomly assigned" but no detail

SNEGOVIK *(Continued)*

Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	not reported
Other bias	High risk	published conference abstract only

STRUCTURE

Methods	**Study design**: two-arm, individual, RCT **Centres**: Poland, "of each centre" suggests multicentre trial, no details **Start of enrolment**: Novemer 2011 **End of enrolment**: February 2015 **Mean follow-up**: 6 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "Patients who presented with signs or symptoms of HF (dyspnea, fatigue, and exercise intolerance) consistent with New York Heart Association functional class II or III, with preserved LV ejection fraction (> 50%), and with evidence of diastolic dysfunction, were considered suitable for screening." **Exclusion criteria**: "Exclusion criteria were: Atrial fibrillation or flutter Resting heart rate > 90 beats/min Ischemic heart disease (defined by a positive coronary angiogram or inducible ischemia during exercise testing) Moderate or worse valvular heart disease Primary myocardial diseases Established or suspected pulmonary diseases (spirometry results < 80% of age- and sex-specific reference values) Hemoglobin ≤ 11 g/dl Adrenocortical, hepatic, rheumatic, neoplastic, skeletal, thyroid, and renal diseases (including renal insufficiency with serum creatinine > 1.5 mg/dl [132 mmol/l]) Hyperkalemia > 5.0 mmol/l Known intolerance or treatment with an MRA within the last 3 months Concomitant therapy with a potassium-sparing agent Current lithium use Pregnancy" **Randomised** (N): 150 (75 intervention, 75 control) **Withdrawn** (N): for reasons other than death 12 (7 intervention, 5 control) **Lost to follow-up** (N): 7 (4 intervention, 3 control) **Analysed** (N): 131 (64 intervention, 67 control) **Age** (years, mean, SD): intervention: 66.3, 7.7; control: 67.6, 9.1

STRUCTURE *(Continued)*

	Sex (% men): intervention: 12; control: 19
	Ethnicity (%): not reported
	Systolic blood pressure (mmHg, mean, SD): intervention: 131, 15; control: 130, 18
	Heart rate (beats/min, mean, SD): intervention: 72, 10; control: 73, 10
	BMI (mean, SD): intervention: 30.7, 4.5; control: 29.7, 4.6
	Serum creatinine (mg/dL, mean, SD): intervention: 0.99, 0.20; control: 1.03, 0.24
	B-type natriuretic peptide (pg/mL, median, IQR): intervention: 40 (26-63); control: 54 (27-99)
	NT pro B-type natriuretic peptide (pg/mL): not reported
	LVEF (%, median, IQR): intervention: 72.6 (70.4–74.8); control: 71.4 (69.2–73.5)
	NYHA class I (%): 0
	NYHA class II (%): intervention: 78; control: 79
	NYHA class III (%): intervention: 22; control: 21
	NYHA class IV (%): 0
	Hypertension (%): intervention: 92; control: 91
	Diabetes (%): intervention: 39; control: 40
	Atrial fibrillation (%): not reported
	Hospitalisation for heart failure (%): intervention: 17; control: 21
	Coronary heart disease (%): significant CAD excluded
	Stroke (%): not reported
	Diuretic (%); intervention: thiazides 54, loop 13; control: thiazides 46, loop 18
	Digoxin (%): not reported
	Beta-blocker (%): intervention: 78; control: 72
	ACEI/ARB (%): intervention: 97; control: 95
	MRA (%): study drug
Interventions	**Intervention**: spironolactone, 25mg/day
	Comparator: matching placebo (120 mg/day of microcellulose)
	Concomitant medication: "Enrollees continued to receive other prescribed treatments throughout the study period."
Outcomes	**Planned**: unclear
	Reported: "Coprimary outcomes were change at 6 months in exercise capacity (assessed by peak VO2) and exertional E/e' (reflecting LVFP). The secondary outcomes included change at follow-up in exercise blood pressure (BP) response and post-treatment global longitudinal myocardial deformation (GLS) measured by 2-dimensional strain."
Notes	Emailed investigator to ask for additional outcome data relevant to this review. No response.
Risk of bias	

STRUCTURE *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The study coordinator, who was not involved in study procedures, was responsible for drug randomization and dispensing"
Allocation concealment (selection bias)	Low risk	"sequentially-numbered, opaque, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and investigators performing the assessments and data analysis were blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"core laboratory in Hobart, Australia, for independent adjudication of the primary endpoint"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT not used, withdrawals reported with reasons, lost to follow-up reported, similar numbers for treatment arms
Selective reporting (reporting bias)	Unclear risk	unclear, clinical trial registration was post-hoc
Other bias	Low risk	"The authors have reported that they have no relationships relevant to the contents of this paper to disclose" "This study was funded by grants ST-678 from Wroclaw Medical University and 13-024 from the Royal Hobart Hospital Foundation."

SUPPORT

Methods	**Study design**: parallel, individual RCT **Centres**: 17, Japan **Start of enrolment**: October 2006 **End of enrolment**: March 2010 **Median follow-up**: 4.4 years **Run-in period**: not reported
Participants	**Inclusion criteria**: The inclusion criteria of the present study were designed to enroll symptomatic CHF patients with hypertension aged 20 to 79 years who were treated with ACEI or beta-blocker or both. Inclusion criteria: NYHA Classes II to IV CHF, History of hypertension or treated with anti-hypertensive medications, Aged 20 or older and, 80 years at the entry, Stable with angiotensin-converting enzyme inhibitors and/or b-blockers, Not treated with angiotensin II receptor blockers **Exclusion criteria**: The exclusion criteria were designed to exclude patients with substantive confounding medical conditions or an inability to meaningfully participate in the SUPPORT trial. Exclusion criteria: Patients who have renal dysfunction (serum creatinine ≥3.0 mg/dL), or those who are under chronic haemodialysis, Drug hypersensitivity to olmesartan, Severe liver dysfunction, History of angioedema, History of malignant tumour or life-threatening illness of poor prognosis, Pregnant or possibly pregnant patients, Cardiovascular surgery within 6 months prior to the date of the entry, Acute myocardial infarction within 6 months prior to the date of the entry, Percutaneous coronary intervention with or without stent implantation within 6 months prior to the date of the entry.

SUPPORT *(Continued)*

Randomised (N): 1146 (1 patient excluded prior to this for protocol violation) (578 intervention, 568 control)

Withdrawn (N): for reasons other than death 9 (1 protocol violation, 8 no LVEF data)

Lost to follow-up (N): not reported

Analysed (N): Total 1138 (HFpEF 709, HFrEF 429) (HFpEF 363 intervention, HFpEF 346 control)

Age (years, mean, SD): intervention: 66.5, 10.1; control: 65.9, 9.7

Sex (% men): intervention: 70.2; control: 71.1

Ethnicity (%): not reported

Systolic blood pressure (mmHg, mean, SD): intervention: 131.5, 17.1; control: 130.1, 17.1

Heart rate (beats/min, mean, SD): intervention: 70.6, 13.2; control: 71.4, 14.9

BMI (mean, SD): intervention: 24.4, 4.2; control: 24.8, 4.2

Serum creatinine (mg/dL, mean, SD): intervention: 0.9, 0.3; control: 0.9, 0.3

B-type natriuretic peptide (pg/mL, median, IQR): intervention: 71.1 (30.2, 148.0); control: 58.7 (27.5, 139.0)

NT pro B-type natriuretic peptide (pg/mL): not reported

LVEF (%, mean, SD): intervention: 63.8, 8.8; control: 63.1, 8.6

NYHA class I (%): 0

NYHA class II (%): intervention: 94.2; control: 93.4

NYHA class III (%): intervention: 5.5; control: 6.4

NYHA class IV (%): 0

Hypertension (%): 100

Diabetes (%): intervention: 46.6; control: 53.9

Atrial fibrillation (%): not reported

Hospitalisation for heart failure (%): intervention: 52.2; control: 44.1

Coronary heart disease (%): intervention: 48.8; control: 45.1

Stroke (%): not reported

Diuretic (%); intervention: 45.7; control: 48.0

Digoxin (%): not reported

Beta-blocker (%): intervention: 63.4; control: 65.4

ACEI (%): intervention: 79.9; control: 79.0

ARB (%): study drug

MRA (%): intervention: 18.5; control: 22.0

Interventions	**Intervention**: olmesartan. "Olmesartan was initiated at a dose of 5–10 mg/day, and then up titrated to 40 mg/ day, if tolerable, in the olmesartan group, while no ARB use was allowed in the control group"
	Comparator: no treatment

SUPPORT *(Continued)*

	Concomitant medication: treated with ACEI and/or beta-blocker in inclusion criteria, not treated with ARB
Outcomes	**Planned**: Clinical trial registry entry at point of enrolment: primary outcomes all-cause death, nonfatal acute myocardial infarction, nonfatal stroke, hospital admission due to congestive heart failure **Reported**: Primary Endpoint: A composite of the following outcomes: all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, hospital admission due to worsening heart failure Secondary Endpoints: cardiovascular death, death due to heart failure, sudden death, acute myocardial infarction, stroke, hospital admission from any cardiovascular reasons, fatal arrhythmia or appropriate ICD discharge, new-onset diabetes, development of renal dysfunction (equal to or more than twofold increase of serum creatinine level), new-onset atrial fibrillation, a need to modify treatment procedures for heart failure, a decrease in left ventricular ejection fraction (equal to or more than 20% decrease), an increase in B-type natriuretic peptide levels (> 2-fold increase if the baseline level was > 50 pg/mL and an increase of > 100 pg/mL if the baseline level was < 50 pg/mL), changes in serum markers for metabolic syndrome (high sensitive C-reactive protein, adiponectin, microRNAs)
Notes	Emailed investigators to ask for outcome date for participants with LVEF > 40%. No response. Published (and presented above) are baseline characteristics and results for HFpEF as defined by investigators (LVEF ≥ 50%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	blinded endpoint study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	withdrawals reported with reasons, not detailed by treatment arm ITT used, but after exclusion of some randomised patients
Selective reporting (reporting bias)	Low risk	primary outcomes reported as planned
Other bias	Low risk	"The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by the unrestricted research grants from Daiichi Sankyo Co, Ltd (Tokyo, Japan), Bayer Yakuhin, Ltd (Osaka, Japan), Kyowa Hakko Kirin Co, Ltd (Tokyo, Japan), Kowa Pharmaceutical Co, Ltd (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co, Ltd (Osaka, Japan), and Nippon Boehringer Ingelheim Co, Ltd (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin, Ltd (Osaka, Japan), Daiichi Sankyo Co, Ltd (Tokyo, Japan) and Novartis Pharma K.K. (Tokyo, Japan)."

SUPPORT *(Continued)*

	"This study was supported in part by the grants-in-aid from the Ministry of Health, Labour, and Welfare and those from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. Funding to pay the Open Access publication charges for this article was provided by the author."

SWEDIC

Methods	**Study design**: two-arm, individual, parallel RCT **Centres**: 12, Sweden **Start of enrolment**: not reported **End of enrolment**: not reported **Mean follow-up**: not reported **Run-in period**: not reported
Participants	**Inclusion criteria**: "patients with symptoms and/or signs of HF, normal or almost normal systolic function and abnormal DF who did not have a contraindication to receiving therapy with a beta- adrenoceptor blocking agent were included into the study." "Major inclusion criteria were a wall motion index (WMI) ≤ 1.2, i.e akinesia of one segment or less or hypokinesia of 2 segments or less, using a 16 segment model with at least 10 segments visible, corresponding to an LVEF > 45%, and evidence of abnormal DF using at least one of the following criteria to assess diastolic dysfunction" **Exclusion criteria**: "Major exclusion criteria were restrictive or hypertrophic cardiomyopathies, significant uncorrected obstructive or regurgitant valvular diseases, unstable angina, active myocarditis, uncontrolled symptomatic ventricular arrhythmias, history of sick sinus syndrome, second or third degree AV-block, heart rate less than 60 bpm, systolic blood pressure -85 mmHg, uncontrolled hypertension, atrial fibrillation, evidence of obstructive pulmonary disease, unstable diabetes, treatment with beta-2-agonists, MAO-inhibitors, calcium channel blockers or beta-receptor blockers" **Randomised** (N): 113 **Withdrawn** (N): for reasons other than death: "16 patients had echocardiographic data of insufficient quality and were excluded from the evaluation." **Lost to follow-up** (N): 2 (reasons not reported) **Analysed** (N): 97 (47 intervention, 50 control) **Age** (years, median, IQR): intervention: 67 (48 to 81); control: 66 (48 to 84) **Sex** (% men): intervention: 59.6; control: 54.0 **Ethnicity** (%): not reported **Systolic blood pressure** (mmHg, median, IQR): intervention: 155 (122 to 180); control: 150 (110 to 200) **Heart rate** (beats/min, median, IQR): intervention: 74 (60 to 95); control: 73 (60 to 101) **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL): intervention: 67.7, 76.1; control: 67.7, 67.7 **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** not reported **NYHA class I** (%): intervention: 40; control: 26

SWEDIC *(Continued)*

	NYHA class II (%): intervention: 53; control: 53 **NYHA class III** (%): intervention: 7; control: 21 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 70.2; control: 62 **Diabetes** (%): intervention: 12.8; control: 16.0 Atrial fibrillation (%): 0 **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): intervention: 17; control: 6 **Stroke** (%): not reported **Diuretic** (%); not reported **Digoxin** (%): not reported **Beta-blocker** (%): study drug **ACEI** (%): not reported **ARB** (%): not reported **MRA** (%): not reported
Interventions	**Intervention**: carvedilol. "carvedilol or placebo twice daily in addition to their conventional treatment" "All patients were uptitrated to the maximum tolerated dose or to the target dose (25 mg b.i.d., or 50 mg b.i.d. in patients weighing 85 kg) of carvedilol or matching placebo. After completion of uptitration they were to continue on double blind medication for a 6 month maintenance period. At study end patients were withdrawn from blinded study medication in a stepwise manner over a 1–3 week period. Optimal therapy for the patient's condition was then reinstated at the investigator's discretion" "Overall, carvedilol was well tolerated, with 81% of patients receiving the maximum dose at the end of the uptitration phase (25 mg b.i.d. or 50 mg b.i.d.) and 82% at the end of the study" **Comparator**: placebo **Concomitant medication**: "as an addition to conventional treatment"
Outcomes	**Planned**: not able to assess as we are unaware of a published protocol or pre-registration in a clinical trial register **Reported**: primary: diastolic dysfunction. Secondary: Secondary endpoints were the effects of carvedilol as compared to placebo on combined all cause mortality and cardiovascular hospitalisations, combined all-cause mortality and heart failure hospitalisation, progression of heart failure, individual cardiovascular endpoints and outcome and individual diastolic variables. Additional exploratory analyses on LV dimensions atrial size and WMI were also prespecified."
Notes	Emailed investigators for details for RoB assessment, reasons for 2 participants not completing study, start/end of enrolment, duration of follow-up. No response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported

SWEDIC *(Continued)*

Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	double-blind but no details, matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"All assessments as to whether the LV diastolic dysfunction had improved, was unchanged, or had worsened were made by two echocardiographers from the core laboratory, who were blinded to the order of the assessment and to the study medication received by the patient." only partial outcome assessment and for outcomes not relevant to this review
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	unable to assess - withdrawals not reported by treatment arm ITT used
Selective reporting (reporting bias)	Unclear risk	unable to assess due to lack of published protocol or pre-registration in a clinical trial register
Other bias	Low risk	"The study was investigator-initiated and was partly funded by F. Hoffmann-La Roche Ltd."

Takeda 2004

Methods	**Study design**: parallel RCT **Centres**: 1, Japan **Start of enrolment**: April 2000 **End of enrolment**: March 2001 **Mean follow-up**: 12 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "All patients met Framingham criteria for diagnosis of heart failure. LVEF, as assessed by echocardiography using Simpson's method, was ≥ 45% in each subject at the screening examination." **Exclusion criteria**: "Patients with primary significant valvular disease, cor pulmonale, thyroid dysfunction, diabetes mellitus with hemoglobin A1C > 8%, alcohol abuse, other systemic diseases, obvious contraindication to carvedilol, or using angiotensin II receptor antagonists or adrenergic blockers were excluded from the initial entry." **Randomised** (N): 40 (19 intervention, 21 control) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, median, IQR): intervention: 69.1, 64.4-73.7; control: 73.1, 69.7–76.4 **Sex** (% men): intervention: 68; control: 38

Takeda 2004 *(Continued)*

	Ethnicity (%): not reported **Systolic blood pressure** (mmHg, median, IQR): intervention: 129.6, 124.5–134.6; control: 138.0, 130.7–145.3 **Heart rate** (beats/min, median, IQR): intervention: 70.6, 64.3–77.0; control: 68.9, 63.8–74.0 **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** (pg/mL, median, IQR): intervention: 172, 135–209; control: 150, 114–186 **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, median, IQR): intervention: 55.8, 51.4–60.3; control: 57.5, 53.4–61.5 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 63.3; control: 71 **NYHA class III** (%): intervention: 37; control: 29 **NYHA class IV** (%): 0 **Hypertension** not reported **Diabetes** not reported Atrial fibrillation (%): intervention: 21; control: 38 **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): intervention: 58; control: 48 **Stroke** not reported **Diuretic** not reported **Digoxin** not reported **Beta-blocker** study drug **ACEI** (%): intervention: 79; control: 86 **ARB** not reported **MRA** not reported
Interventions	**Intervention**: carvedilol. "initial daily dosage of 1.25 mg in addition to conventional therapy, and the dose was doubled every week until reaching >= 5 mg/day. The decision to increase carvedilol to > 5 mg/day was made by the attending cardiologists on the basis of subjective symptoms, physical findings, and chest roentgenography; the cardiologists were guided to increase carvedilol to 20 mg/day if the patient tolerated it." **Comparator**: conventional treatment **Concomitant medication**: not reported
Outcomes	**Planned:** we are not aware of a published protocol or a pre-registered clinical trial registry entry **Reported:** BNP, NYHA, exercise capacity, heart failure hospitalisations, deaths
Notes	

Takeda 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Unclear risk	funding not reported

TOPCAT

Methods	**Study design**: parallel RCT **Centres**: "233 sites in 6 countries (1151 participants in the United States, 326 in Canada, 167 in Brazil, 123 in Argentina, 1066 in Russia, and 612 in Georgia)" **Start of enrolment**: August 2006 **End of enrolment**: January 2012 **Mean follow-up**: 3.3 years **Run-in period**: no
Participants	**Inclusion criteria**: "≥ 50 years old, "had at least one sign and at least one symptom of heart failure on a prespecified list of clinically defined signs and symptoms, a left ventricular ejection fraction of 45% or more as measured at the local site by means of echocardiography or radionuclide ventriculography, controlled systolic blood pressure (defined as a target systolic blood pressure of < 140 mm Hg or ≤ 160 mm Hg if the patient was taking three or more medications to control blood pressure), and a serum potassium level of less than 5.0 mmol per liter. In addition, eligible patients had a history of hospitalization within the previous 12 months, with management of heart failure a major component of the care provided (not adjudicated by the clinical-events adjudication committee), or an elevated natriuretic peptide level within 60 days before randomization (a brain natriuretic peptide [BNP] level ≥ 100 pg per milliliter or an N-terminal pro-BNP [NTproBNP] level ≥360 pg per milliliter)." **Exclusion criteria**: "severe systemic illness with a life expectancy of less than 3 years, severe renal dysfunction (an estimated glomerular filtration rate [GFR] of <30 ml per minute per 1.73 m^2 of body-surface area or a serum creatinine level that was ≥ 2.5 mg per deciliter [221 µmol per liter]), and specific coexisting conditions, medications, or acute events."

TOPCAT *(Continued)*

	Randomised (N): 3445 (1722 intervention, 1723 control)
	Withdrawn (N): 311 for reasons other than death (160 intervention, 151 control)
	Lost to follow-up (N): 132 (67 intervention, 65 control)
	Analysed (N): 3445 (1722 intervention, 1723 control)
	Age (years, median, IQR): intervention: 68.7, 61.0 to 76.4; control: 68.7, 60.7 to 75.5
	Sex (% men): intervention: 48.4; control: 48.5
	Ethnicity (%): intervention: white 88.6, control: white 89.2
	Systolic blood pressure (mmHg, median, IQR): intervention: 130 ,120-139; control: 130, 120-140
	Heart rate (beats/min, median, IQR): intervention: 68, 62-76; control: 68, 62-76
	BMI (median, IQR): intervention: 31, 27-36; control: 31, 27-36
	Serum creatinine (mg/dL, median, IQR): intervention: 1.0, 0.9-1.2; control: 1.1, 0.9-1.2
	B-type natriuretic peptide (pg/mL): only in subgroup
	NT pro B-type natriuretic peptide (pg/mL): only in subgroup
	LVEF (%, median, IQR): intervention: 56, 51-61; control: 56, 51-62
	NYHA class I (%): intervention: 3.3; control: 3.1
	NYHA class II (%): intervention: 63.3; control: 64.1
	NYHA class III (%): intervention: 33.0; control: 32.1
	NYHA class IV (%): intervention: 0.4; control: 0.5
	Hypertension (%): intervention: 91; control: 92
	Diabetes (%): intervention: 33; control: 32
	Atrial fibrillation (%): intervention: 35; control: 35
	Hospitalisation for heart failure: not reported
	Coronary heart disease (%): intervention: 26; control: 26
	Stroke (%): intervention: 7; control: 8
	Diuretic (%); intervention: 81; control: 82
	Digoxin not reported
	Beta-blocker (%): intervention: 78; control: 77
	ACEI or ARB (%): intervention: 84; control: 84
	MRA (%): 0
Interventions	**Intervention**: spironolactone
	"Study drugs were initially administered at a dose of 15 mg once daily, which was increased to a maximum of 45 mg daily during the first 4 months after randomization. Subsequent dose adjustments were made as required."
	Comparator: matching placebo

TOPCAT *(Continued)*

	Concomitant medication: "Study patients continued to receive other treatments for heart failure and coexisting illnesses throughout the trial."
Outcomes	**Planned**: From NCT record 21 April 2006: primary outcomes: cardiovascular mortality, aborted cardiac arrest, composite of hospitalisation for the management of heart failure (ie hospitalisation for non-fatal myocardial infarction or non-fatal stroke). Secondary outcomes: all-cause mortality, composite of cardiovascular mortality or cardiovascular related hospitalization (i.e. hospitalization for non-fatal myocardial infarction, non-fatal stroke, or the management of heart failure), hospitalization for the management of heart failure incidence rate, sudden death or aborted cardiac arrest **Reported**: "composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure; myocardial infarction; stroke; hospitalisation from any cause; hyperkalemia (potassium level, ≥ 5.5 mmol per liter); hypokalemia (potassium level, < 3.5 mmol per liter); an elevated serum creatinine level (≥ 2 times the baseline value and above the upper limit of the normal range); serum creatinine level of 3.0 mg per deciliter (265 µmol per liter) or higher; serious adverse events"
Notes	Kao 2017 mentions subgroup analysis by sex for all-cause mortality and hospitalisations but no usable data. NCT record reports on QoL but no usable data. Hamo 2015 reports baseline QoL data but not by intervention arm. Solomon 2016 reports data for four LVEF groups for HF hospitalisation, CV death, death (table 2) - 40-49%, 50-54.99%, 55-59.99%, 60% and over. Data for all-cause mortality, lost to follow up, hyperkalemia differ between Pitt 2014 and NCT results. Emailed investigators to ask for end scores for QoL KCCQ, clarification on withdrawals due to adverse events and subgroup data for primary outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible participants were randomly assigned to receive either spironolactone or placebo in a 1:1 ratio with the use of permuted blocks." "the randomization software will return a Treatment Allocation Code corresponding to either spironolactone or placebo"
Allocation concealment (selection bias)	Low risk	"The nurse coordinator will utilize a master list of Treatment Allocation Codes to determine which labelled study drug packet to provide to the subject."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects and treating physicians will be blinded to whether subjects are receiving spironolactone or placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data were collected and managed electronically by the New England Research Institutes Clinical Trial Coordinating Center, which also coordinated site monitoring and analyzed the trial results (with independent verification at Brigham and Women's Hospital)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All randomly assigned participants were included in all analyses according to the intention-to-treat principle."
Selective reporting (reporting bias)	Low risk	reported as planned

TOPCAT *(Continued)*

Other bias	Low risk	"sponsored by National Heart, Lung and Blood Institute, National Institutes of Health"

Upadhya 2017

Methods	**Study design**: parallel, individual, RCT **Centres**: not reported **Start of enrolment**: not reported **End of enrolment**: not reported **Follow-up**: 9 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "HFpEF was defined as history, symptoms, and signs of HF, a preserved LVEF of 50% or greater and no evidence of other medical condition that could mimic HF symptoms" **Exclusion criteria**: "Coronary disease was excluded according to history, medical record, electrocardiogram, and rest and exercise echocardiogram" "Exclusions included aldosterone antagonist use within the previous 3 months, a known contraindication, concomitant therapy with a potassium-sparing diuretic or potassium supplementation, baseline serum potassium level greater than 5.0 mEq/L, or serum creatinine level of 2.5 mg/dL or greater." **Randomised** (N): 80 (42 intervention, 38 control) **Withdrawn** (N): for reasons other than death 9 (5 intervention (adverse event N = 1, patient choice N = 4), 4 control (patient choice N = 3, death N = 1)) **Lost to follow-up** (N): not reported **Analysed** (N): 71 (37 intervention, 34 control) **Age** (years, mean, SD): intervention: 70.0, 1.1; control: 72.0, 1.2 **Sex** (% men): intervention: 19; control: 21 **Ethnicity** (%): African American: intervention: 21 , control: 37 **Systolic blood pressure** (mmHg, mean, SD): intervention: 139, 2.7; control: 143, 3.2 **Heart rate** not reported **BMI** (mean, SD): intervention: 31.5, 0.8; control: 32.4, 1.2 **Serum creatinine** not reported **B-type natriuretic peptide** (unit not reported): intervention: 55, 46; control: 61, 50 **NT pro B-type natriuretic peptide** (pg/mL): not reported **LVEF** (%, mean, SD): intervention: 62.6, 1.1; control: 62.0, 1.1 **NYHA class I** (%): 0 **NYHA class II** (%): intervention: 29; control: 26 **NYHA class III** (%): intervention: 64; control: 63 **NYHA class IV** (%): 0

Upadhya 2017 *(Continued)*

	Hypertension (%): intervention: 83; control: 92 **Diabetes** (%): intervention: 17; control: 29 Atrial fibrillation (%): not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): 0 **Stroke** (%): not reported **Diuretic** (%); intervention: 74; control: 71 **Digoxin** (%): intervention: 2; control: 0 **Beta-blocker** (%): intervention: 31; control: 32 **ACEI** (%): not reported **ARB** (%): not reported **MRA** (%): study drug
Interventions	**Intervention**: spironolactone. "The starting dose of spironolactone was 12.5 mg/d in individuals with baseline creatinine of 2.0 mg/dL or greater or potassium greater than 4.5 mEq/L; in all other participants, the starting dose was 25 mg/d. In participants who initiated therapy with the 12.5-mg/d dose, the dose was increased to 25 mg/d once creatinine fell below 2.5 mg/dL and potassium fell below 5.0 mEq/L and maintained at that dosage as long as those levels were maintained. Spironolactone was discontinued if 1-week creatinine was 2.5 mg/ dL or higher or potassium was 5.0 mEq/L or higher. " "The mean daily dose of spironolactone was 24.3 2.9 mg/d." **Comparator**: matching placebo **Concomitant medication**: not reported
Outcomes	**Planned**: July 2005, NCT record: primary outcomes: exercise intolerance, quality of life **Reported**: exercise performance, aortic distensibility and LV structure and function, carotid artery stiffness, pulse wave velocity, LV diastolic filling, QoL
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The research pharmacy prepared and distributed placebo and active drug using a secure methodology. All investigators, staff, and participants were fully blinded to treatment group assignment throughout the study period"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The research pharmacy prepared and distributed placebo and active drug using a secure methodology. All investigators, staff, and participants were fully blinded to treatment group assignment throughout the study period"

Upadhya 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	unable to assess
Selective reporting (reporting bias)	Unclear risk	posthoc clinical trial registration
Other bias	High risk	"This study was funded by the National Institutes of Health (NIH; R01AG18915), the Claude D. Pepper Older Americans Independence Center, Wake Forest University (P30AG21332), the Clinical and Translational Science Institute, Wake Forest School of Medicine (NIH UL1TR001420), and the Kermit G. Phillips Chair in Cardiovascular Medicine of Wake Forest School of Medicine" Published as conference abstract only.

Wang 2010

Methods	**Study design**: parallel, individual, RCT **Centres**: 1, Taiwan **Start of enrolment**: not reported **End of enrolment**: not reported **Follow-up**: at least 3 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "hypertensive pts who had DHF, defined as the presence of HF signs/symptoms, diastolic dysfunction (mitral annular early diastolic velocity (E') < 8 cm/s), and left ventricular (LV) ejection fraction (EF) > 50%" **Exclusion criteria**: not reported **Randomised** (N): 36 (19 intervention, 17 control) **Withdrawn** (N): not reported **Lost to follow-up** (N): not reported **Analysed** (N): not reported **Age** (years, mean, SD): not reported **Sex** (% men): not reported **Ethnicity** (%): not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** not reported **LVEF** (%, mean, SD): intervention: 67, 7; control: 66, 7

Wang 2010 *(Continued)*

	NYHA class not reported **Hypertension** not reported **Diabetes** not reported Atrial fibrillation not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** not reported **Stroke** not reported **Diuretic** not reported **Digoxin** not reported **Beta-blocker** not reported **ACEI** not reported **ARB** not reported **MRA** study drug
Interventions	**Intervention**: spironolactone. 50 mg/d **Comparator**: no treatment control **Concomitant medication**: not reported
Outcomes	**Planned:** we are not aware of a published protocol or pre-registered clinical trial registry entry **Reported:** echo-parameters, systolic myocardial velocities
Notes	does not contribute outcome data to this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported

Wang 2010 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Unclear risk	funding not reported

Yuksek 2012

Methods	**Study design**: parallel, individual, RCT **Centres**: 1, Turkey **Start of enrolment**: May 2008 **End of enrolment**: March 2009 **Mean follow-up**: 11 months **Run-in period**: not reported
Participants	**Inclusion criteria**: "HF symptoms. They were ≥ 50 years old, had EF ≥ 50% and echocardiographic diastolic dysfunction." **Exclusion criteria**: not reported **Randomised** (N): 108 (54 intervention, 54 control) **Withdrawn** (N): for reasons other than death 17 (not reported by arm) **Lost to follow-up** (N): 3 (not reported by arm) **Analysed** (N): not reported **Age** not reported **Sex** not reported **Ethnicity** not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** not reported **LVEF** not reported **NYHA class** not reported **Hypertension** not reported **Diabetes** not reported Atrial fibrillation not reported **Hospitalisation for heart failure**: not reported **Coronary heart disease** not reported

Yuksek 2012 *(Continued)*

	Stroke not reported **Diuretic** not reported **Digoxin** not reported **Beta-blocker** not reported **ACEI** study drug **ARB** not reported **MRA** not reported
Interventions	**Intervention**: perindopril, 10 mg/d **Comparator**: "standard DHF treatment" **Concomitant medication**: not reported
Outcomes	**Planned:** we are not aware of a published protocol or a pre-registration in a clinical trial register **Reported:** T-proBNP values and echocardiography
Notes	no outcome data of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomised, but no details
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not reported
Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Unclear risk	funding not reported

Zi 2003

Methods	**Study design**: parallel, individual, RCT **Centres**: 1, Royal Liverpool and Broadgreen University Hospitals

Zi 2003 *(Continued)*

	Start of enrolment: 1997 **End of enrolment**: 1999 **Follow-up**: 6 months **Run-in period**: mentioned but no details
Participants	**Inclusion criteria**: "aged 65 years or older, with heart failure" "They all had left ventricular ejection fraction (LVEF) on echocardiography or radionuclide ventriculography equal or greater than 40%. Where a left ventricular ejection fraction could not be measured systolic function had to be preserved or only mildly impaired by direct visualisation of the echocardiograms" **Exclusion criteria**: "Patients with haemodynamically significant valvular disease, pulmonary hypertension, right ventricular systolic dysfunction, uncontrolled atrial fibrillation or flutter, unstable angina pectoris, hypotension, myocardial infarction within one month, renal failure (serum creatinine >150 mmol/L), renal-artery stenosis, severe liver or pulmonary disease were excluded. patients treated with tetracyclines, lithium, benzodiazepines, major tranquillisers, anti-depressants (with the exception of selective serotonin re-uptake inhibitors) or major psychoactive drugs were also excluded." **Randomised** (N): 74 (36 intervention, 38 control) **Withdrawn** (N): for reasons other than death 4 (0 intervention, 4 control (worsening heart failure)) **Lost to follow-up** (N): not reported **Analysed** (N): 74 (36 intervention, 38 control) **Age** (years, mean, SD): intervention: 77, 7; control: 78, 7 **Sex** (% men): intervention: 38.9; control: 31.6 **Ethnicity** (%): not reported **Systolic blood pressure** not reported **Heart rate** not reported **BMI** not reported **Serum creatinine** not reported **B-type natriuretic peptide** not reported **NT pro B-type natriuretic peptide** not reported **LVEF** not reported **NYHA class I** (%): intervention: 5.5; control: 0 **NYHA class II** (%): intervention: 77.8; control: 73.7 **NYHA class III** (%): intervention: 16.7; control: 26.3 **NYHA class IV** (%): 0 **Hypertension** (%): intervention: 27.8; control: 31.6 **Diabetes** (%): intervention: 11.1; control: 18.4 **Atrial fibrillation** (%): intervention: 38.9; control: 31.6 **Hospitalisation for heart failure**: not reported **Coronary heart disease** (%): intervention: 55.6; control: 57.9 **Stroke** (%): not reported

Zi 2003 *(Continued)*

	Diuretic (%); intervention: 94.4; control: 97.1 **Digoxin** (%): intervention: 38.9; control: 26.3 **Beta-blocker** (%): intervention: 19.4; control: 7.9 **ACEI** (%): study drug **ARB** (%): not reported **MRA** (%): not reported
Interventions	**Intervention**: quinapril. "Both drugs were titrated at two-week intervals from 5 mg to 40 mg daily or equivalent within the first six weeks." **Comparator**: placebo **Concomitant medication**: "All patients continued concomitant treatment with diuretics, nitrates, digitalis glycosides, calcium channel blockers, and beta-blockers as appropriate without change of dose except for diuretics. Therapy with ACE inhibitors for heart failure was withdrawn at least two weeks prior to the run-in period."
Outcomes	**Planned:** we are not aware of a published protocol or pre-registered clinical trial registry entry **Reported:** 6-minutes walking distance, hypotension, worsening heart failure, changes of electrolytes, adverse events, quality of life, deaths, heart failure hospitalisation, hyperkalaemia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomised, but no further detail
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	double-blind, matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	withdrawals due to worsening heart failure reported
Selective reporting (reporting bias)	Unclear risk	unable to assess
Other bias	Low risk	"This study was supported by the grants from Parke Davis & Co. Ltd., UK."

quotes are from the primary reference unless otherwise stated
* mmol/L converted to mg/dL using online converter
ACEI: angiotensin converting enzyme inhibitor

ARB: angiotensin receptor blocker
BMI: body mass index
CVD: cardiovascular disease
EF: ejection fraction
IQR: interquartile range
ITT: intention-to-treat
LV: left ventricular
LVEF: left ventricular ejection fraction
MRA: mineralocorticoid receptor antagonist
N: number of people
NCT: clinicaltrials.gov identifier
QoL: quality of life
RCT: randomised controlled trial
SD: standard deviation
TNF-a: tumour necrosis factor-alpha

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12610001087044	Trial registry entry suggested two parts of a trial of which only the second was of interest to this review. Contact with trialists confirmed that the part of interest was registered and reported on separately (ACTRN: 12614000088640, STRUCTURE study).
Adgey 1992	Wrong patient population
Ammon 2001	Wrong study design
Andersson 1996	Wrong patient population
Andersson 1999	Wrong patient population
Andersson 2000	Wrong patient population
Anonymous 1996	Wrong patient population
Anonymous 1999	Wrong intervention
Anonymous 2000	Wrong patient population
Anonymous 2001	Wrong study design
Anonymous 2002	Wrong study design
Anonymous 2003	Wrong comparator
Anonymous 2003a	Wrong study design
Anonymous 2003b	Wrong study design
Anonymous 2003c	Wrong patient population
Anonymous 2005	Wrong patient population
Anonymous 2008	Wrong study design
Anonymous 2008a	Wrong study design

Study	Reason for exclusion
Anonymous 2013	Wrong study design
ANZ HF carvedilol	Subgroup of participants of interest (LVEF = 40-44%). We did not receive a response from the trialists to our enquiry for details on the subgroup of interest.
Aoyama 2007	Wrong study design
Apostolovic 2013	Wrong comparator
Apostolovic 2014a	Wrong comparator
Apostolovic 2014b	Wrong comparator
Arena 2007	Wrong study design
Armstrong 1999	Wrong study design
Aronow 1991	Wrong study design
Aronow 2001	Wrong study design
Axelsson 2015	Wrong patient population
Balaban 2007	Turkish paper. Translated methods and data extraction. Unclear if participants had heart failure. We did not receive a response from the investigator when we asked for clarification.
Bao 2005	Wrong population
Barr 1995	Wrong patient population
Barrios 2009	Wrong patient population
Barry 2003	Wrong study design
Bartels 1999	Wrong patient population
Baruch 1999	Ineligible participants. Emailed trialists to clarify inclusion criteria. Response received: "Our study was confined to individuals with a reduced ejection fraction and the data therefore would not be applicable to your quest."
Baruch 2004	Wrong patient population
Bauersachs 2004	Wrong study design
Baumhakel 2008	Wrong study design
Bellenger 2004	Wrong patient population
Berry 2001	Wrong study design
Bettencourt 1999	Wrong study design
Beygui 2016	Wrong patient population
Blagodar 2003	Wrong patient population

Study	Reason for exclusion
Blomer 1990	Wrong study design
Borghi 2011	Wrong comparator
Borgi 1990	Wrong patient population
Borlaug 2014	Wrong study design
Bornkessel 1992	Wrong patient population
Bounhoure 1991	EF not reported. Could not identify current contact details.
Braunwald 2004	Wrong patient population
Brilla 1989	Wrong study design
Brilla 1991	EF unclear, unclear whether allocation was random, unable to identify current contact details.
Bristow 1994	Wrong patient population
Bristow 1996	Wrong patient population
Bussmann 1987	EF unclear. We did not receive a response to our enquiry for details.
Butler 2017	Wrong patient population
Cafaro 2010	Wrong study design
Cardoso 1999	Wrong study design
Castagno 2010	Wrong patient population
Choi 2001	Wrong patient population
Cicoira 2002	subgroup of participants of interest; we did not receive a response from the trialist to our enquiry for details.
Cleland 1984	unclear EF. contacted trialists. no response
Cleland 1999	Wrong patient population
Cleland 2001	Wrong patient population
Cleland 2003	Wrong patient population
Cleland 2004	Wrong study design
Cleland 2006	Wrong study design
Cleland 2007	Wrong study design
Cleland 2010	Wrong study design
Cleland 2011	Wrong study design

Study	Reason for exclusion
Cleland 2013	Wrong study design
Cohen-Solal 2005	Wrong patient population
Cohn 1993	Wrong study design
Cohn 1996a	Wrong study design
Cohn 1996b	Wrong study design
Cohn 2007	Wrong study design
Coletta 2008	Wrong study design
Coletta 2009	Wrong study design
Comin-Colet 2002	Wrong study design
CONSENSUS	EF unclear. We did not receive a response from the trialists to our enquiry for details.
CONSENSUS II	Mean EF suggests a subgroup of eligible participants. We did not receive a response from the trialists to our enquiry.
Conti 2005	Wrong study design
Corder 1993	EF unclear. Unable to identify current contact details.
Crouse 2011	Wrong study design
Dahlstrom 2007	Wrong study design
Davie 2001	Wrong study design
De Melo 2011	Wrong comparator
de Teresa 1995	Wrong study design
DeBock 1994	EF unclear. Unable to find current contact details for trialists.
Dekleva 2012	Wrong comparator
Demers 2001	Wrong patient population
Desai 2013	Wrong study design
Deswal 2010	EF unclear. We did not receive a response from trialists to our query on the clarification of inclusion criteria.
Ding 2008	Wrong comparator
Ditiatkov 1999	Wrong study design
Donal 2008	Wrong study design
Dragana 2015	Wrong comparator

Study	Reason for exclusion
Edner 2013	Wrong study design
Eichhorn 1994	subgroup of participants of interest; did not receive a response from trialists to our enquiry.
Eichhorn 2003	Wrong patient population
Er 2005	Wrong study design
Ertl 1999	Wrong study design
EudraCT 2004-004169-13	Trial registry record states completed but no contact details given an no published results identifiable. Sponsor: South Manchester University Hospital NHS Trust. Emailed sponsor to ask whether results are available. Unclear whether http://www.isrctn.com/ISRCTN77645264 is the same trial. Tried to contact investigator but email was undeliverable.
Fauchier 2009	Wrong study design
Feola 2003	Wrong study design
Flammer 2013	Wrong patient population
Flather 2016	Wrong study design
Flesch 2006	Wrong study design
Follath 1996	Wrong study design
Fonarow 2004	Wrong study design
Fonarow 2007	Wrong patient population
Fowler 1999	Wrong study design
Franciosa 2002	Wrong intervention
Fukunami 1991	Wrong study design
Galinier 2007	Wrong study design
Galloe 2006	Potential eligible subgroup. Did not receive a response from trialists to our enquiry for outcome data for subgroup.
Gardner 2003	Wrong study design
Gardner 2004	Wrong study design
Ghali 2002	Wrong patient population
Gheorghiade 2009	Wrong patient population
Good 1994	Wrong patient population
Goodfield 1999	Wrong patient population

Study	Reason for exclusion
Gottlieb 1996	Wrong patient population
Grajek 2008	Review
Greenberg 1996	Wrong patient population
Gremmler 2000	EF unclear. Unable to identify current contact details.
Groenning 2000	Wrong patient population
Groenning 2001	Wrong study design
Groenning 2002	Wrong patient population
Gruner 2007	Wrong patient population
Guazzi 1998	Wrong patient population
Guazzi 1999	Wrong patient population
Gøtzsche 1992	subgroup with HF and LVEF >40%. We did not receive a response from trialists to our enquiry.
Hanping 1997	Wrong study design
Hara 2000	Wrong comparator
Hauf 1993	Wrong study design
Hole 2004	Wrong patient population
Holland 2010	Limited information in conference abstract. Response to our enquiry for further details received: "the data you've requested was not collected on this group of patients beyond what has been published in that abstract". As we could not confirm whether the participants meet our inclusion criteria, this study was excluded.
Hong 2003	Wrong intervention
Hoppe 2007	Wrong study design
Hori 2004	Wrong patient population
Hung 2010	Wrong study design
IRIS-HF	Response from trialists received when asked for outcome data for subgroup of interest: no data specifically for participants in subgroup of interest (LVEF 40-45%) provided. Confirmed that QoL, mortality and HF hospitalisation were not formal endpoints. Hyperkalaemia was not shown by any participants.
Ito 2012	Wrong study design
Jamieson 1991	Wrong study design
Jellis 2014	HF/EF unclear. No response to our enquiry for details.
Jessup 2003	Wrong study design

Study	Reason for exclusion
Jong 2010	Wrong study design
Kanoupakis 2008	Wrong patient population
Kapel'ko 2011	Wrong study design
Kasama 2007	Wrong comparator
Keren 1992	Wrong patient population
Keren 1994	Wrong patient population
Khalid 2013	Wrong study design
Khand 2015	Wrong patient population
Kikuchi 2016	Wrong patient population
Kimura 2011	Wrong patient population
Kinugawa 2007	Wrong study design
Kjekshus 2007	Wrong study design
Kjøller-Hansen 1998	Wrong patient population
Kleber 1991a	No participants with heart failure with preserved ejection fraction (confirmed by trialist via email on 20 November 2017).
Kleber 1991b	Heart failure was not an inclusion criteria (confirmed by trialist via email on 15 November 2017).
Kongstad-Rasmussen 1998	EF unclear ("ejection fraction measurement was not part of the protocol")
Krum 1996	Wrong patient population
Krum 2015	Wrong patient population
Kulbertus 2003	wrong study design
Kuznar 2003	Wrong patient population
Lang 1995	cross-over trial
Larsen 1996	EF unclear. Contacted trialists. Response: data are no longer available.
Lechat 1993	LVEF unclear, otherwise eligible. Emailed investigator but did not receive a response.
Leonetti 1999	Wrong patient population
Lewis 1988	EF unclear. Unable to find current contact.
Li 2005	Wrong population
Liebson 2004	Wrong patient population

Study	Reason for exclusion
Lindenfeld 2001	Wrong patient population
Lindsay 1999	Wrong study design
Liu 2014	Wrong patient population
Logeart 2006	Wrong study design
Lopez 2000	Wrong study design
Lou 2009	Wrong study design
Luo 2007	Wrong study design
Ma 2005	Wrong population
MacGregor 2009	Wrong patient population
Mak 2008	EF unclear. unable to find current contact details for trialist.
Malnick 2007	Wrong patient population
Maron 2013	LVEF unclear. Contacted trialists. No response.
Mazayev 1998	LVEF unclear, otherwise eligible. Unable to find current contact details for investigators.
McAnulty 2004	Wrong comparator
McCullough 2012	Wrong patient population
McIlwain 1997	Wrong study design
McKelvie 2012	Wrong study design
McMurray 2000	Wrong study design
McMurray 2004	Wrong study design
Melo 2011	Wrong comparator
Melo 2012	Wrong comparator
Messias 2016	Wrong study design
Meuleman 2007	wrong participants
Mitrovic 2005	Wrong study design
Mochizuki 2004	retraction
Morales 2011	Wrong patient population
Murdoch 2001	Wrong patient population
NCT00293150	terminated due to lack of eligible participants

Study	Reason for exclusion
NCT00523757	Trial did not take place as planned (as per information from trialists: "We abandoned this study as we could not adequately recruit. No results to present.")
NCT01691118	Completed but no publication with results identified. Emailed trialists to ask for clarification on comparator (placebo or conventional antihypertensive treatment). No response.
Nodari 2003	Wrong comparator
Nunez 2016	Wrong study design
O'Callaghan 1995	Wrong study design
O'Keefe 2008	Wrong patient population
O'Keeffe 2015	Wrong comparator
O'Meara 2012	Wrong patient population
Ostergren 2004	Wrong study design
Palazzuoli 2005	Wrong patient population
Paolisso 1992	Wrong study design
Paraskevaidis 2006	Wrong patient population
Park 2016	Wrong comparator
Patten 1997	Wrong patient population
Pennell 2000	Wrong patient population
Pierard 2002	Wrong patient population
Pina 2004	Wrong study design
Pitt 2005	Wrong patient population
Pitt 2008	Wrong patient population
Pitt 2011	Wrong intervention
Pourdjabbar 2015	Wrong study design
Premkumar 2016	Wrong patient population
Quaife 1998	Wrong patient population
Ramaswamy 2003	Wrong study design
Remme 2001	Wrong patient population
Remme 2004	Wrong patient population
Remme 2005	Wrong patient population

Study	Reason for exclusion
Rimatori 1990	LVEF unclear, otherwise eligible. Unable to find current contact details for investigators.
Roongsritong 2005	Wrong patient population
Rosa 2011	Wrong intervention
Rosenkranz 2003	Wrong study design
Rossignol 2011	Wrong patient population
Sakai 2011	Wrong intervention
Sanderson 1998	Subgroup of interest LVEF 40-45%. Investigator responded to our enquiry for data: "the mean EF was only 26.9% and I doubt any of the patients were in the group of EF 40% to <45%. [...] I do not have the original data now."
Sanghera 2011	Wrong study design
Santulli 2015	Wrong study design
Sardu 1991	LVEF not specified as an inclusion criteria, mean LVEF at baseline 35.4, 4.7%. Could not find current contact details for investigator.
Schindler 2008	Wrong patient population
Schwab 2009	Wrong study design
Segovia 2008	Wrong study design
Shimamoto 2007	Wrong patient population
Sidorenko 2008	Wrong patient population
Silva 2014	Wrong patient population
Smith 2012	Wrong study design
Spoto 2002	Wrong study design
Stecker 2005	Wrong patient population
Stiefelhagen 2006	Wrong study design
Struthers 2004	Wrong study design
Swedberg 1996	Wrong study design
Swedberg 1999	Wrong study design
Szajnbok 1993	Portuguese paper. Reported outcomes not of interest but subgroup of participants eligible. Emailed investigators to ask about measured outcomes for subgroup of interest. Response: data not available.
Szymanski 2009	Wrong study design

Study	Reason for exclusion
Taheri 2009	subgroup of interest LVEF 40-45%. Contacted investigators. No response.
Takekoshi 2004	Wrong study design
Tala 2011a	Wrong patient population
Tala 2011b	Wrong patient population
Tan 2013	Wrong study design
Tatsumi 2006	Wrong study design
Taylor 2003	Wrong intervention
Teerlink 2003	Wrong patient population
Tereshchenko 2005	Wrong comparator
Thornton 2004	Wrong study design
Thune 2008	Wrong patient population
Tinoco 2004	Wrong study design
Tsutamoto 2000	Wrong study design
Tsutamoto 2001	Subgroup of interest (LVEF 40-45%). Emailed investigators. No response.
Tsutamoto 2005	Wrong study design
Tumasyan 2010	Wrong comparator
Umemoto 2003	Wrong study design
Uusimaa 2001	Wrong comparator
Van den Berg 1993	Wrong study design
Van den Berg 1995	LVEF unclear; response to our enquiry for details: cannot provide data
Vasiuk 2001	Wrong study design
Vincent 2012	Wrong patient population
Vizir 2000	Wrong patient population
Vizzardi 2010	Wrong patient population
Vizzardi 2012	LVEF unclear. Emailed investigators. No response.
Vizzardi 2015a	Wrong study design
Vizzardi 2015b	Wrong patient population

Study	Reason for exclusion
Volpe 1992	Subgroup of interest LVEF 40-45%. We received a response to our enquiry for more details on the subgroup of interest confirming that the study was conducted in "patients with reduced EF".
Volpe 2010	Wrong patient population
Voors 2008	Wrong study design
Waagstein 2003	Wrong patient population
Waldo 1995	Wrong patient population
Waldo 1996	Wrong patient population
Warner 1999	Wrong patient population
Weinberg 2001	Wrong study design
Weintraub 2005	Wrong patient population
Weir 2011	Wrong patient population
Wong 2002	Wrong patient population
Wong 2004	Wrong patient population
Woodley 1991	Wrong patient population
Wright 2014	Wrong patient population
Wu 2002	LVEF unclear, otherwise eligible. Unable to find current contact details for investigators.
Xu 2007	Wrong population
Yamamoto 2005	Wrong study design
Yan 2012	LVEF unclear, otherwise eligible. Unable to find current contact details for investigators.
Yoshihiro 2011	Wrong intervention
Young 2004	Wrong patient population
Zeng 2006	Wrong patient population

Characteristics of studies awaiting assessment *[ordered by study ID]*

Anonymous 2003d

Methods	No abstract
Participants	No abstract
Interventions	Eplerenone

Anonymous 2003d *(Continued)*

Outcomes	No abstract
Notes	Could not yet obtain full text

Botoni 2010

Methods	Individual, two-arm, RCT
Participants	42
Interventions	Placebo versus carvedilol
Outcomes	QoL
Notes	Unclear EF/HF status

Dielievska 2015

Methods	Individual, two-arm, RCT
Participants	80 participants with EHT and COPD of ll-lll grade of bronchial obstruction (GOLD 2-3) with chronic heart failure of the II and III NYHA classes and evidence of diastolic dysfunction
Interventions	Spironolactone versus standard therapy, 3 months
Outcomes	Left ventricular diastolic function, impaired relaxation of left ventricle, adverse events
Notes	Have not yet obtained full text

Gao 2010

Methods	Unclear if RCT
Participants	32 elderly people with chronic heart failure
Interventions	Control group and metoprolol group, 8 weeks
Outcomes	Left ventricular end-diastolic diameter and left ventricular ejection fraction, lymphocyte GRK2 mRNA level
Notes	Chinese language paper (with translator)

Liu 2006

Methods	No abstract
Participants	Elderly hypertensive people with diastolic heart failure

Liu 2006 *(Continued)*

Interventions	Spironolactone
Outcomes	No abstract
Notes	Chinese language paper. Eligibility criteria for trial unclear regarding LVEF. Emailed investigator.

Metra 1999

Methods	No abstract
Participants	No abstract
Interventions	No abstract
Outcomes	No abstract
Notes	Could not yet retrieve full text

Rapezzi 1999

Methods	No abstract
Participants	No abstract
Interventions	No abstract
Outcomes	No abstract
Notes	Could not yet retrieve full text

Zheng 2009

Methods	Two-arm, individual, RCT
Participants	76 older people with diastolic heart failure
Interventions	Carvediol versus routine treatment
Outcomes	Unknown
Notes	Chinese language paper. With translator

EF: ejection fraction
EHT: essential hypertension
HF: heart failure
RCT: randomised controlled trial
LVEF: left ventricular ejection fraction
GRK2: G protein-coupled receptor kinase 2
mRNA: messenger RNA
COPD: chronic obstructive pulmonary disease

NYHA: New York Heart Association functional Classification of heart failure
QoL: quality of life

Characteristics of ongoing studies *[ordered by study ID]*

EudraCT 2013-000867-10

Trial name or title	Effects of Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction (HF-PEF): Cardiac MRI, Echocardiography, Exercise Physiology & Quality of Life Assessment
Methods	**Study design**: RCT, open label, parallel 2-arm trial **Follow-up**: 6 months
Participants	**Planned inclusion:** 60 participants **Inclusion criteria**: Diagnosis of heart failure with preserved ejection fraction (HF-PEF), NYHA II-IV heart failure, Compliance with medical treatment, aged 18 years and over **Exclusion criteria**: Contra-indication to undergoing full cardiac magnetic resonance study, Contra-indication to aldosterone antagonist therapy, Contra-indication to exercise testing, Unable to give informed consent
Interventions	Spironolactone versus placebo
Outcomes	**Primary**: Serial change in ECV, as calculated by T1 map using Cardiac Magnetic Resonance Imaging following treatment with an aldosterone antagonist. **Secondary**: To determine the effect of spironolactone in HF-PEF on: Alternative methods of measuring ECV with CMR, Echocardiographically & CMR derived measures of cardiac relaxation, Establish correlation between change in ECV and measures of cardiac relaxation, Exercise tolerance & quality of life
Starting date	Unclear. Date of Ethics Committee Opinion: 13 November 2013
Contact information	Sven Plein, s.plein@leeds.ac.uk
Notes	Status 'ongoing' in clinical trial registry entry. Emailed trialist to confirm status of trial. Response: "The study is complete and the main manuscript being prepared for submission expected in the next weeks." Emailed trialists to ask for release of results data prior to publication. Response: not possible.

IMPRESS-AF

Trial name or title	Spironolactone in Atrial Fibrillation (IMPRESS-AF)
Methods	**Study design**: parallel RCT
Participants	**Inclusion criteria:** • Permanent atrial fibrillation • Left ventricular ejection fraction >= 55% as established by echocardiography • Able to perform cardio-pulmonary exercise testing using a cycling ergometer and complete quality of life questionnaires in English or in their native language. **Exclusion criteria:**

IMPRESS-AF *(Continued)*

	• Severe systemic illness (life expectancy < 2 years) • Severe chronic obstructive pulmonary disease (e.g. requiring home oxygen or chronic oral steroid therapy) • Severe mitral/aortal valve stenosis/regurgitation • Significant renal dysfunction (serum creatinine 220 µmol/L or above), anuria, active renal insufficiency, rapidly progressing or severe impairment of renal function, confirmed or suspected renal insufficiency in diabetic patients/ diabetic nephropathy • Increase in potassium level to >5mmol/L • Recent coronary artery bypass graft surgery (within 3 months) • Use of aldosterone antagonist within 14 days before randomisation • Use of or potassium sparing diuretic within 14 days before randomisation • Systolic blood pressure > 160 mm Hg • Addison's disease • Hypersensitivity to spironolactone or any of the ingredients in the product • Any participant characteristic that may interfere with adherence to the trial protocol
Interventions	Spironolactone versus placebo
Outcomes	Exercise tolerance, QoL, left ventricular diastolic function, exercise tolerance, all-cause hospitalisations, spontaneous return to sinus rhythm
Starting date	January 2015
Contact information	Eduard Shantsila: e.shantsila@bham.ac.uk
Notes	Contacted trialists to ask about status and anticipated completion date, also queried whether heart failure with preserved ejection fraction was an inclusion criteria. No response.

NCT02901184

Trial name or title	Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction, SPIRRIT-HFPEF
Methods	**Study design**: parallel, open-label, RCT **Anticipated start date:** December 2017 **Anticipated completion date:** June 2022
Participants	**Estimated enrolment:** 3500 **Inclusion criteria:** • Written informed consent • Age ≥50 years • Stable heart failure defined by symptoms and signs of heart failure as judged by local Investigator • Left ventricular ejection fraction (LVEF) ≥40% recorded in last 12 months (stratified to max 2/3rd in either 40-49% or ≥50% group) • NT-proBNP (the N-terminal prohormone of brain natriuretic peptide) >300 ng/L in sinus rhythm or >750 ng/L in atrial fibrillation as an outpatient or prior to hospital discharge **Exclusion criteria:** • Previously enrolled in this study • Known Ejection Fraction < 40% ever

NCT02901184 *(Continued)*

	• Current absolute indication or contraindication for MRA (mineral receptor antagonist) in judgement of Investigator • Any condition other than heart failure with a life expectancy < 3 years • Known chronic liver disease • Probable alternative explanations for symptoms:Known primary cardiomyopathy (hypertrophic, constrictive, restrictive, infiltrative, congenital)Primary hemodynamically significant valve diseaseRight-sided HF not due to left-sided HFSignificant chronic pulmonary disease defined by Investigator or by requirement for home O2 or oral steroids,Hemoglobin < 10 g/dL (100 g/L)BMI (body mass index) > 40Heart rate > 105 bpmAny other condition judged by Investigator to be responsible for symptoms and/or signs • Heart transplant or LVAD (left ventricular assist device) recipient • Systolic blood pressure <90 or >160 • K (potassium) >5.0 mmol/L • eGFR (estimated glomerular filtration rate) by MDRD (Modification of Diet in Renal Disease) < 30 mL/min/1.73m2 or creatinine > 2.5 mg/dL (221 µmol/L) • Current lithium use • Actual or potential for pregnancy • Participation in another clinical trial where treatment for HF is studied • Any condition that in the opinion of the Investigator may interfere with adherence to trial protocol
Interventions	Spironolactone versus standard care
Outcomes	**Primary**: Time to death from any cause [Time Frame: Collected at data base lock, five (5) years after study start] **Secondary**: Time to first hospitalization for heart failure [Time Frame: Collected at data base lock, five (5) years after study start]
Starting date	December 2017
Contact information	Inger Ekman (inger.ekman@ucr.uu.se)
Notes	

NCT03066804

Trial name or title	A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients (PARALLAX)
Methods	**Study design**: parallel RCT, blinding: participant, care provider, investigator, outcomes assessor **Anticipated start date:** 29 September 2017 **Anticipated completion date:** 4 December 2019
Participants	**Estimated enrolment:** 2200 **Inclusion criteria:** • Left ventricular ejection fraction (LVEF) ≥45% by echo within 6 months prior to study entry or during the screening epoch • Symptom(s) of heart failure (HF) requiring treatment with diuretics (including loop, or thiazide diuretics, or mineralocorticoid antagonist [MRAs]) for at least 30 days prior to study entry • NYHA class II-IV • Structural heart disease (left atrial enlargement or left ventricular hypertrophy) documented by echocardiogram.

NCT03066804 *(Continued)*

- NT-proBNP > 220 pg/mL for patients with no atrial fibrillation/atrial flutter or > 600 pg/mL for patients with atrial fibrillation
- KCCQ clinical summary score < 75
- Patients on ACEi or ARB therapy must have a history of HTN

Exclusion criteria:

- Any prior measurement of LVEF < 40%
- Acute coronary syndrome (including myocardial infarction), cardiac surgery, other major CV surgery within 3 months , or urgent percutaneous coronary intervention (PCI) within 3 months or an elective PCI within 30 days prior to study entry
- Any clinical event within the 6 months prior to Visit 1 that could have reduced the LVEF (eg myocardial infarction, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be ≥ 40% and EF ≥ 45% by the time of screening
- Current acute decompensated HF requiring therapy.
- Current use of renin inhibitor(s)
- History of hypersensitivity to LCZ696 or its components
- Patients with a known history of angioedema
- Walking distance primarily limited by non-cardiac comorbid conditions
- Alternative reason for shortness of breath such as: significant pulmonary disease or severe COPD, haemoglobin (Hgb) < 10 g/dL males and < 9.5 g/dL females, or body mass index (BMI) > 40 kg/m^2.
- Systolic blood pressure (SBP) ≥ 180 mmHg at study entry, or SBP >150 mmHg and <180 mmHg at study entry unless the patient is receiving 3 or more antihypertensive drugs, or SBP < 110 mmHg at study entry.
- Patients with HbA1c > 7.5% not treated for diabetes
- Patients with prior major organ transplant or intent to transplant (i.e. on transplant list)
- eGFR < 30 mL/min/1.73 m^2 as measured by MDRD at screening
- Serum potassium > 5.2 mmol/L at study entry
- History or presence of any other disease with a life expectancy of < 3 years
- Pregnant or nursing women or women of child-bearing potential unless they are using highly effective methods of contraception

Other protocol-defined inclusion/exclusion criteria may apply.

Interventions	All patients who fulfill the inclusion/exclusion criteria will be stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata will receive LCZ696 or enalapril. Patients in the ARB strata will receive LCZ696 or valsartan. Patients in the no RASi strata will receive LCZ696 or matching placebo.
Outcomes	**Primary:** Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) after 12 weeks **Secondary:** • Mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) [Time Frame: baseline, week 24] • Percentage of patients with ≥ 5-points deterioration in KCCQ CSS at Week 24 [Time Frame: baseline, week 24] • Percentage of patients with ≥ 5-points improvement in KCCQ CSS at Week 24 [Time Frame: baseline, week 24] • Change from baseline in the 6-minute walk test (6MWT) to week 24 [Time Frame: baseline, week 24] • Change in NYHA functional class from baseline to week 24 [Time Frame: baseline, week 24] • Change from baseline in SF-36 physical component summary (PCS) score to week 24 [Time Frame: baseline, week 24]
Starting date	29 September 29 2017

NCT03066804 *(Continued)*

Contact information	Novartis Pharmaceuticals (novartis.email@novartis.com)
Notes	Comparison of interest: LCZ696 or matching placebo Sponsor: Novartis Pharmaceuticals Other identifiers: CLCZ696D2302, 2016-003410-28 (EudraCT Number)

Zhou 2010

Trial name or title	b-PRESERVE
Methods	**Study design**: "multicentre, prospective, randomized, open-label, blinded endpoint trial"
Participants	"A total of 1200 patients will be randomized to either b-blocker (metoprolol succinate) or control (n = 600 per group)." "The most essential criteria for HFNEF in this trial are: heart failure symptoms, elevated NT-proBNP 1500 pg/mL, and LVEF 50%. In addition, age .40 years and a recent hospitalization for heart failure, but not within 3 months prior to enrolment, are required."
Interventions	"The follow-up period is a minimum of 2 years."
Outcomes	"The primary endpoint is a composite of hospitalization for heart failure and cardiovascular death. The secondary endpoints include cardiovascular death, heart failure mortality or hospitalization, all-cause mortality, change in New York Heart Association class, change in left ventricular ejection fraction, increase in NT-proBNP (by 50% of the value at randomization), b-blocker tolerance, and premature termination of b-blocker therapy due to adverse events"
Starting date	not reported
Contact information	Email: ge.junbo@zs-hospital.sh.cn or jbge@zs-hospital.sh.cn
Notes	Could not find the entry in the Chinese Clinical Trial Register with ID ChiCTR-TNC-00000144. Contacted investigators to clarify status of study. No response.

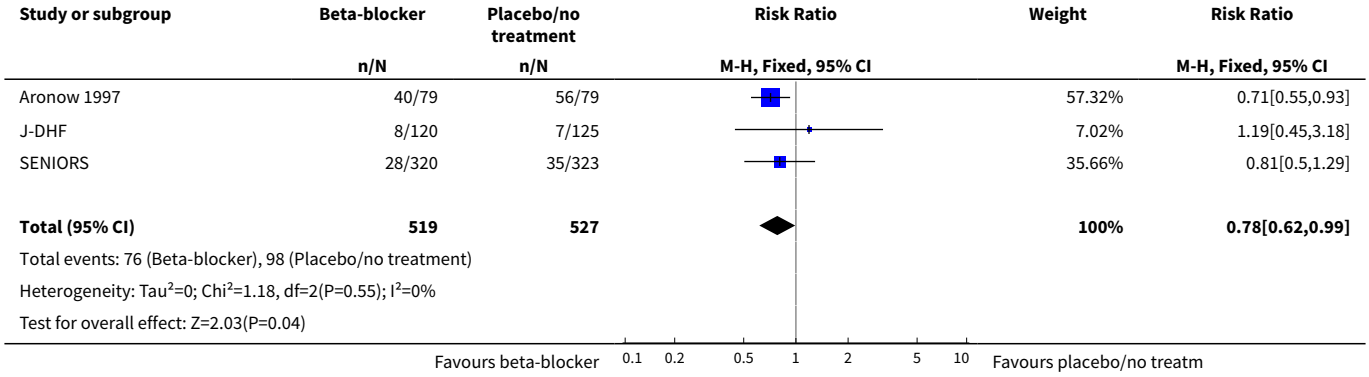
ACEI: angiotensin-converting-enzyme inhibitor
ARB: angiotensin II receptor blockers
CMR: cardiac magnetic resonance
ECV: extra-cellular volume
HTN: hypertension
KCCQ: Kansas City Cardiomyopathy Questionnaire
LVEF: left ventricular ejection fraction
NYHA: New York Heart Association Classification of heart failure
QoL: quality of life
RCT: randomised controlled trial

DATA AND ANALYSES

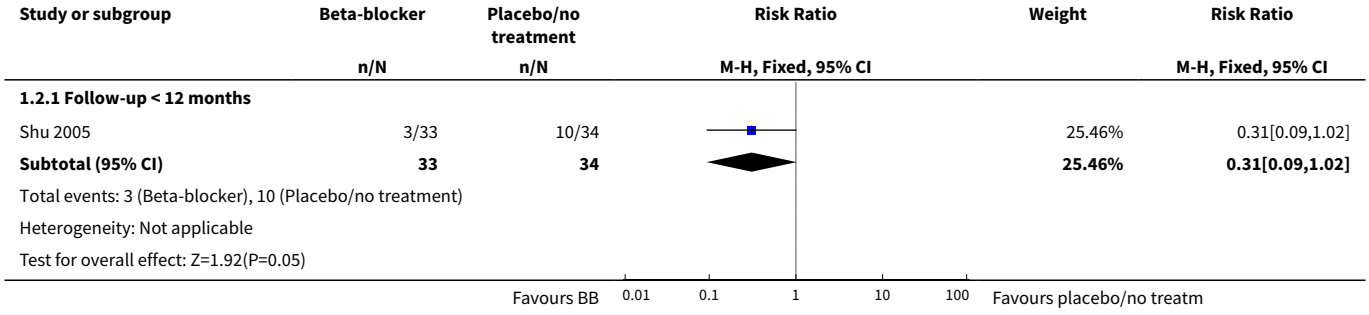
Comparison 1. Beta-blockers versus placebo or no treatment

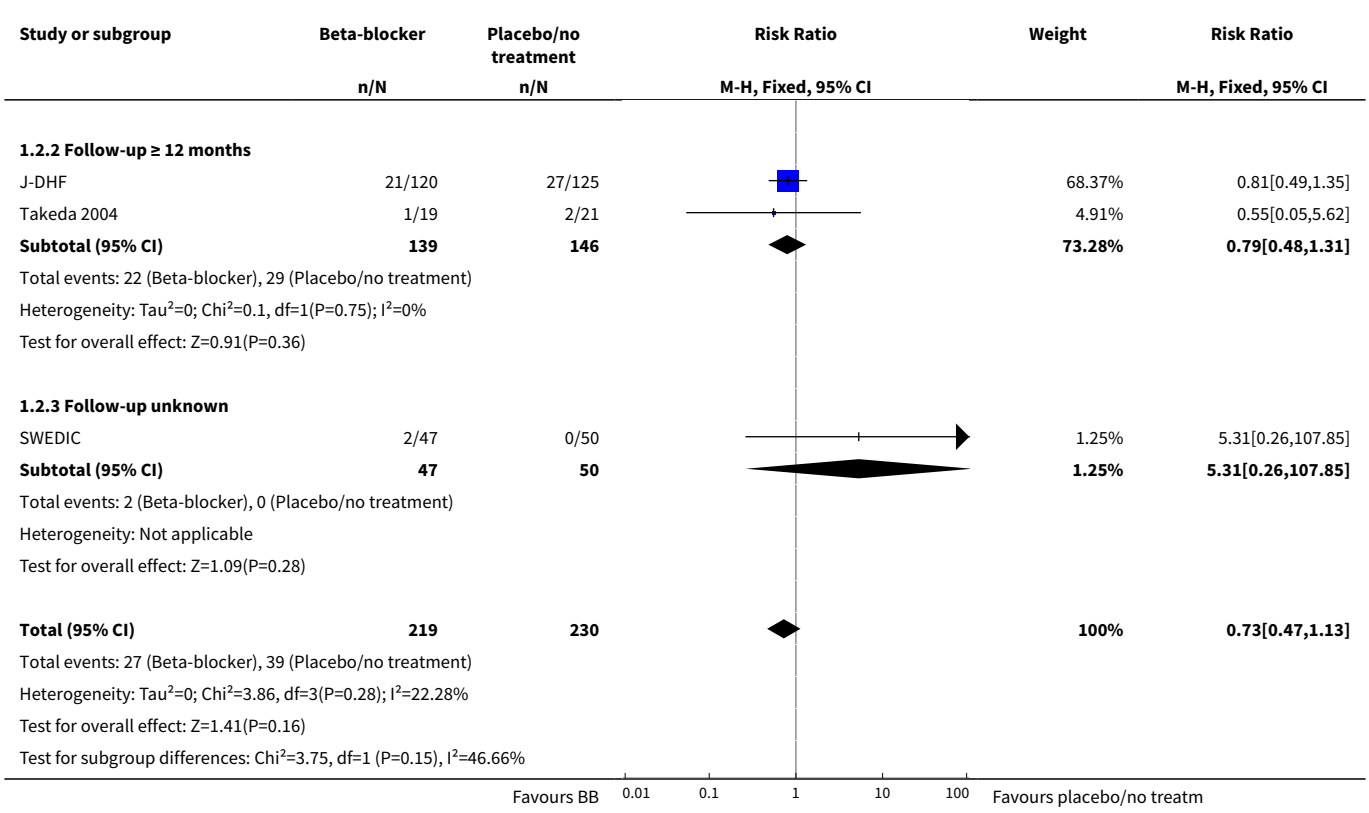
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular mortality (RR)	3	1046	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.62, 0.99]
2 Heart failure hospitalisation (RR)	4	449	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.13]
2.1 Follow-up < 12 months	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.09, 1.02]
2.2 Follow-up ≥ 12 months	2	285	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.31]
2.3 Follow-up unknown	1	97	Risk Ratio (M-H, Fixed, 95% CI)	5.31 [0.26, 107.85]
3 All-cause mortality (RR)	4	1105	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.67, 1.00]
4 Quality of life (Minnesota)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Withdrawal due to adverse event	2	338	Risk Ratio (M-H, Fixed, 95% CI)	18.07 [2.45, 133.04]

Analysis 1.1. Comparison 1 Beta-blockers versus placebo or no treatment, Outcome 1 Cardiovascular mortality (RR).

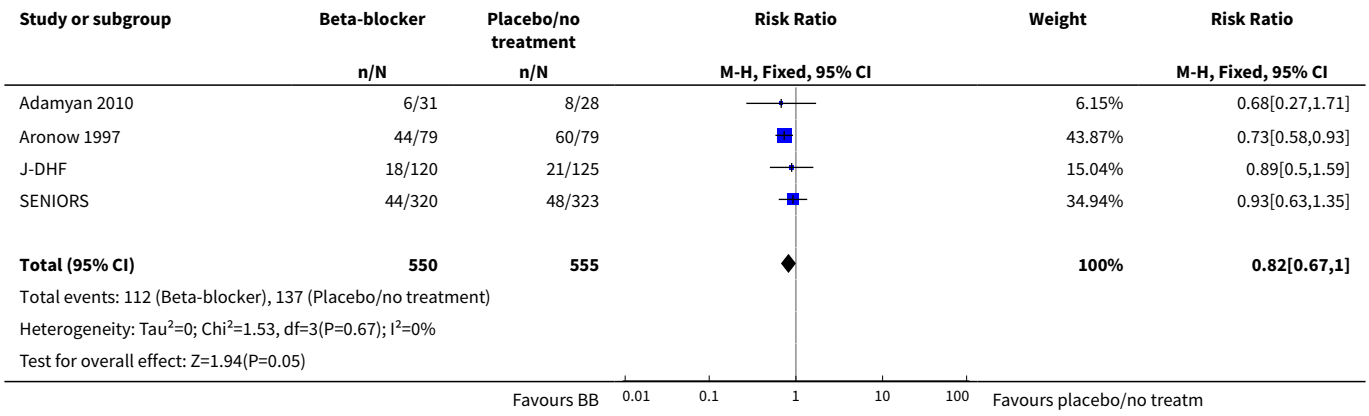


Analysis 1.2. Comparison 1 Beta-blockers versus placebo or no treatment, Outcome 2 Heart failure hospitalisation (RR).

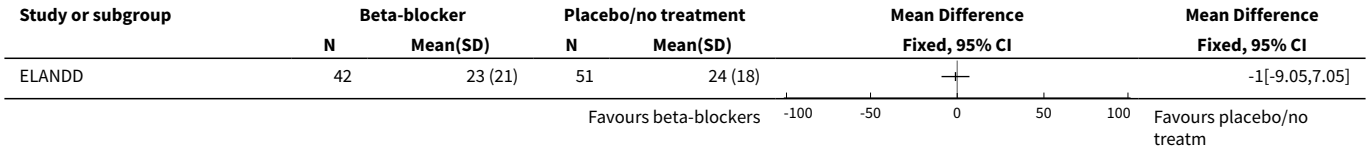




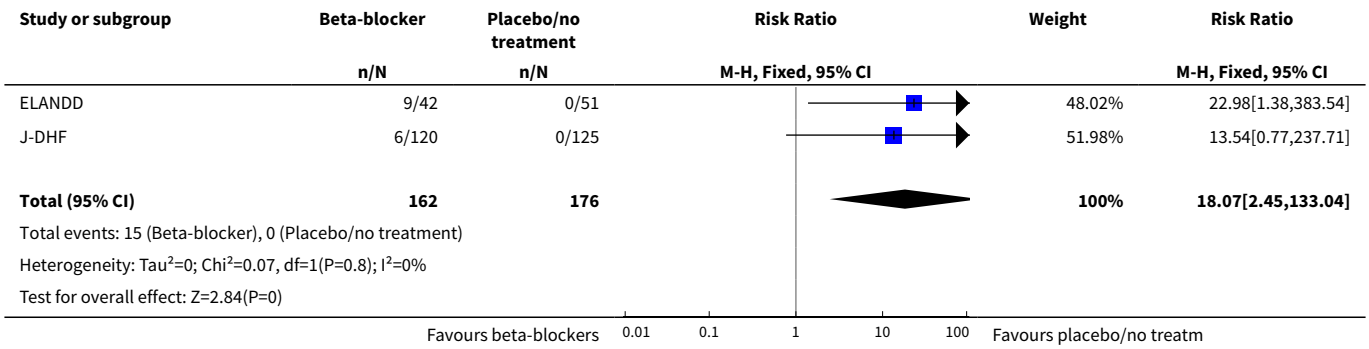
Analysis 1.3. Comparison 1 Beta-blockers versus placebo or no treatment, Outcome 3 All-cause mortality (RR).



Analysis 1.4. Comparison 1 Beta-blockers versus placebo or no treatment, Outcome 4 Quality of life (Minnesota).



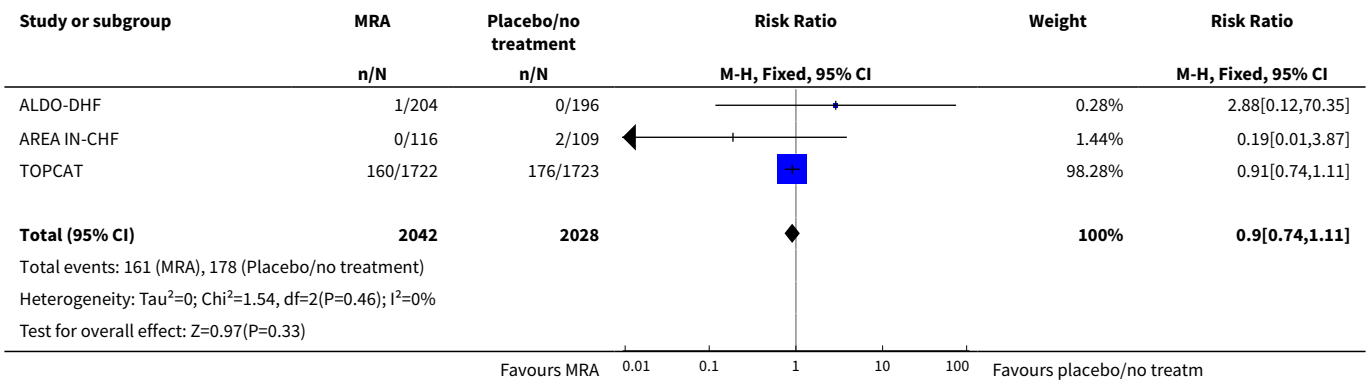
Analysis 1.5. Comparison 1 Beta-blockers versus placebo or no treatment, Outcome 5 Withdrawal due to adverse event.



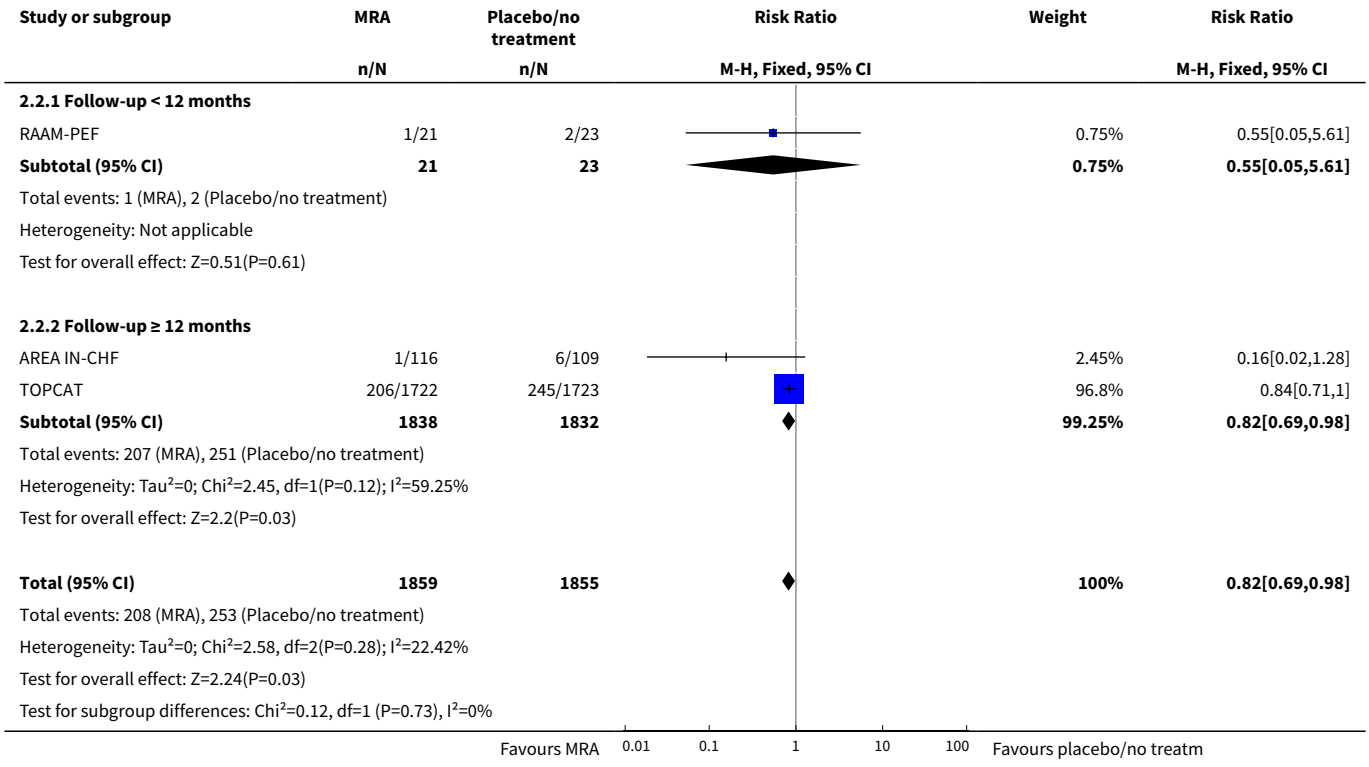
Comparison 2. Mineralocorticoid receptor antagonists versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular mortality (RR)	3	4070	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.11]
2 Heart failure hospitalisation (RR)	3	3714	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
2.1 Follow-up < 12 months	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.05, 5.61]
2.2 Follow-up ≥ 12 months	2	3670	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
3 Heart failure hospitalisation (HR)	2	3670	Hazard Ratio (Fixed, 95% CI)	0.82 [0.69, 0.98]
4 Hyperkalaemia	6	4291	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.77, 2.51]
5 All-cause mortality (RR)	5	4207	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.06]
6 Quality of life	5	603	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.23, 0.34]
7 Quality of life (KCCQ)	2	92	Mean Difference (IV, Random, 95% CI)	-0.78 [-28.02, 26.46]
8 Quality of life (Minnesota)	3	511	Mean Difference (IV, Random, 95% CI)	0.84 [-2.30, 3.98]
9 Withdrawal due to adverse event	4	3986	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.00, 1.21]

Analysis 2.1. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 1 Cardiovascular mortality (RR).

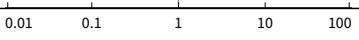


Analysis 2.2. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 2 Heart failure hospitalisation (RR).



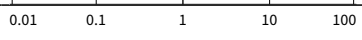
Analysis 2.3. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 3 Heart failure hospitalisation (HR).

Study or subgroup	MRA N	Placebo/no treatment N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
AREA IN-CHF	116	109	-1.9 (1.094)		0.67%	0.15[0.02,1.28]
TOPCAT	1722	1723	-0.2 (0.09)		99.33%	0.83[0.7,0.99]
Total (95% CI)					**100%**	**0.82[0.69,0.98]**
Heterogeneity: Tau²=0; Chi²=2.43, df=1(P=0.12); I²=58.85%						
Test for overall effect: Z=2.2(P=0.03)						



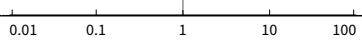
Analysis 2.4. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 4 Hyperkalaemia.

Study or subgroup	MRA n/N	Placebo/no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ALDO-DHF	1/203	1/195		0.63%	0.96[0.06,15.25]
AREA IN-CHF	10/116	2/109		1.27%	4.7[1.05,20.96]
Kurrelmeyer 2014	4/24	1/24		0.62%	4[0.48,33.22]
RAAM-PEF	3/21	1/23		0.59%	3.29[0.37,29.2]
STRUCTURE	2/64	0/67		0.3%	5.23[0.26,106.89]
TOPCAT	322/1722	157/1723		96.6%	2.05[1.72,2.45]
Total (95% CI)	**2150**	**2141**		**100%**	**2.11[1.77,2.51]**
Total events: 342 (MRA), 162 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=2.36, df=5(P=0.8); I²=0%					
Test for overall effect: Z=8.33(P<0.0001)					



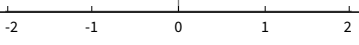
Analysis 2.5. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 5 All-cause mortality (RR).

Study or subgroup	MRA n/N	Placebo/no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ALDO-DHF	1/213	0/209		0.18%	2.94[0.12,71.86]
AREA IN-CHF	0/116	3/109		1.29%	0.13[0.01,2.57]
Mak 2009	1/24	1/20		0.39%	0.83[0.06,12.49]
TOPCAT	252/1722	274/1723		97.59%	0.92[0.79,1.08]
Upadhya 2017	0/37	1/34		0.56%	0.31[0.01,7.29]
Total (95% CI)	**2112**	**2095**		**100%**	**0.91[0.78,1.06]**
Total events: 254 (MRA), 279 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=2.61, df=4(P=0.63); I²=0%					
Test for overall effect: Z=1.18(P=0.24)					



Analysis 2.6. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 6 Quality of life.

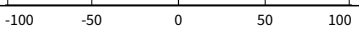
Study or subgroup	MRA N	MRA Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
ALDO-DHF	204	21 (21.7)	196	21 (14.2)		35.57%	0[-0.2,0.2]
Kurrelmeyer 2014	24	-48.5 (26.9)	24	-61.8 (25.5)		15.72%	0.5[-0.08,1.07]
Mak 2009	23	23 (20)	17	20 (13)		14.02%	0.17[-0.46,0.8]
RAAM-PEF	21	-68.7 (22.8)	23	-54.2 (22.8)		14.67%	-0.62[-1.23,-0.02]
Upadhya 2017	37	29 (18)	34	25 (18)		20.03%	0.22[-0.25,0.69]
Total ***	**309**		**294**			**100%**	**0.05[-0.23,0.34]**
Heterogeneity: Tau^2=0.05; Chi^2=7.93, df=4(P=0.09); I^2=49.55%							
Test for overall effect: Z=0.37(P=0.71)							



Favours MRA — Favours placebo/no treatm

Analysis 2.7. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 7 Quality of life (KCCQ).

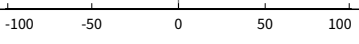
Study or subgroup	MRA N	MRA Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kurrelmeyer 2014	24	-48.5 (26.9)	24	-61.8 (25.5)		49.36%	13.3[-1.54,28.14]
RAAM-PEF	21	-68.7 (22.8)	23	-54.2 (22.8)		50.64%	-14.5[-27.99,-1.01]
Total ***	**45**		**47**			**100%**	**-0.78[-28.02,26.46]**
Heterogeneity: Tau^2=334.1; Chi^2=7.39, df=1(P=0.01); I^2=86.46%							
Test for overall effect: Z=0.06(P=0.96)							



Favours MRA — Favours placebo/no treatm

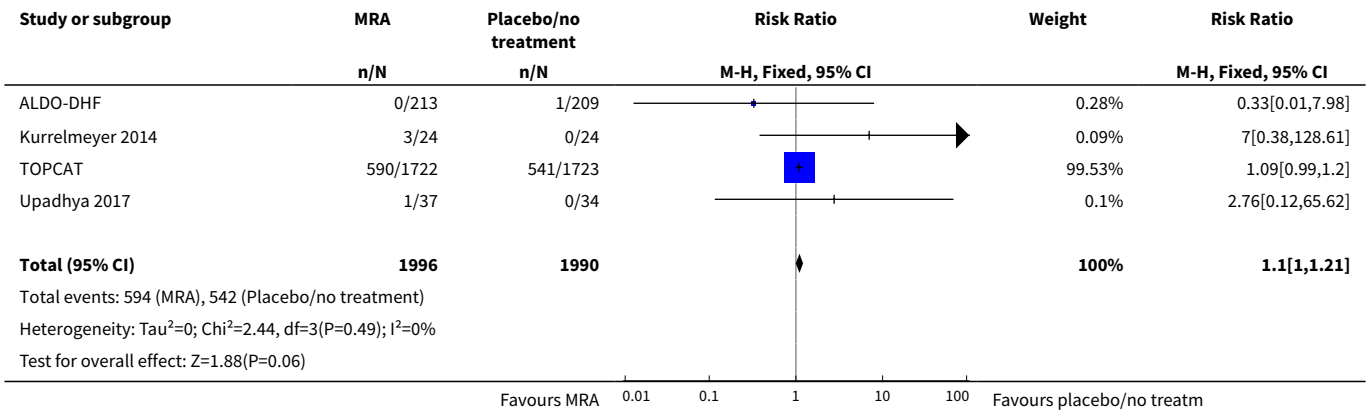
Analysis 2.8. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 8 Quality of life (Minnesota).

Study or subgroup	MRA N	MRA Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
ALDO-DHF	204	21 (21.7)	196	21 (14.2)		76.62%	0[-3.58,3.58]
Mak 2009	23	23 (20)	17	20 (13)		9.37%	3[-7.25,13.25]
Upadhya 2017	37	29 (18)	34	25 (18)		14.01%	4[-4.38,12.38]
Total ***	**264**		**247**			**100%**	**0.84[-2.3,3.98]**
Heterogeneity: Tau^2=0; Chi^2=0.93, df=2(P=0.63); I^2=0%							
Test for overall effect: Z=0.53(P=0.6)							



Favours MRA — Favours placebo/no treatm

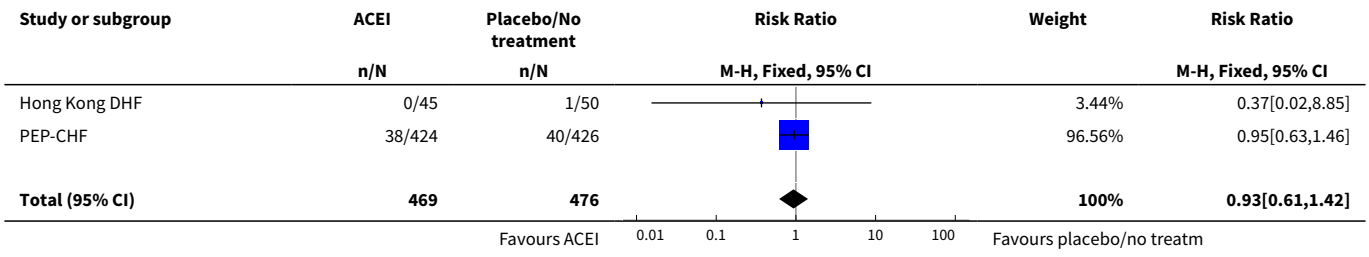
Analysis 2.9. Comparison 2 Mineralocorticoid receptor antagonists versus placebo or no treatment, Outcome 9 Withdrawal due to adverse event.

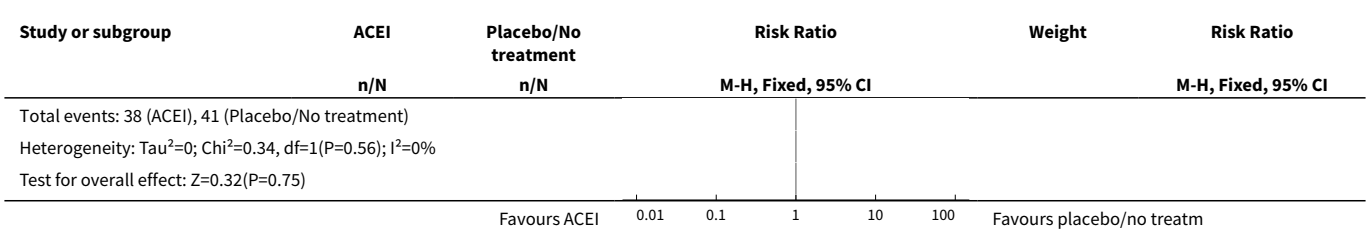


Comparison 3. Angiotensin converting enzyme inhibitors versus placebo or no treatment

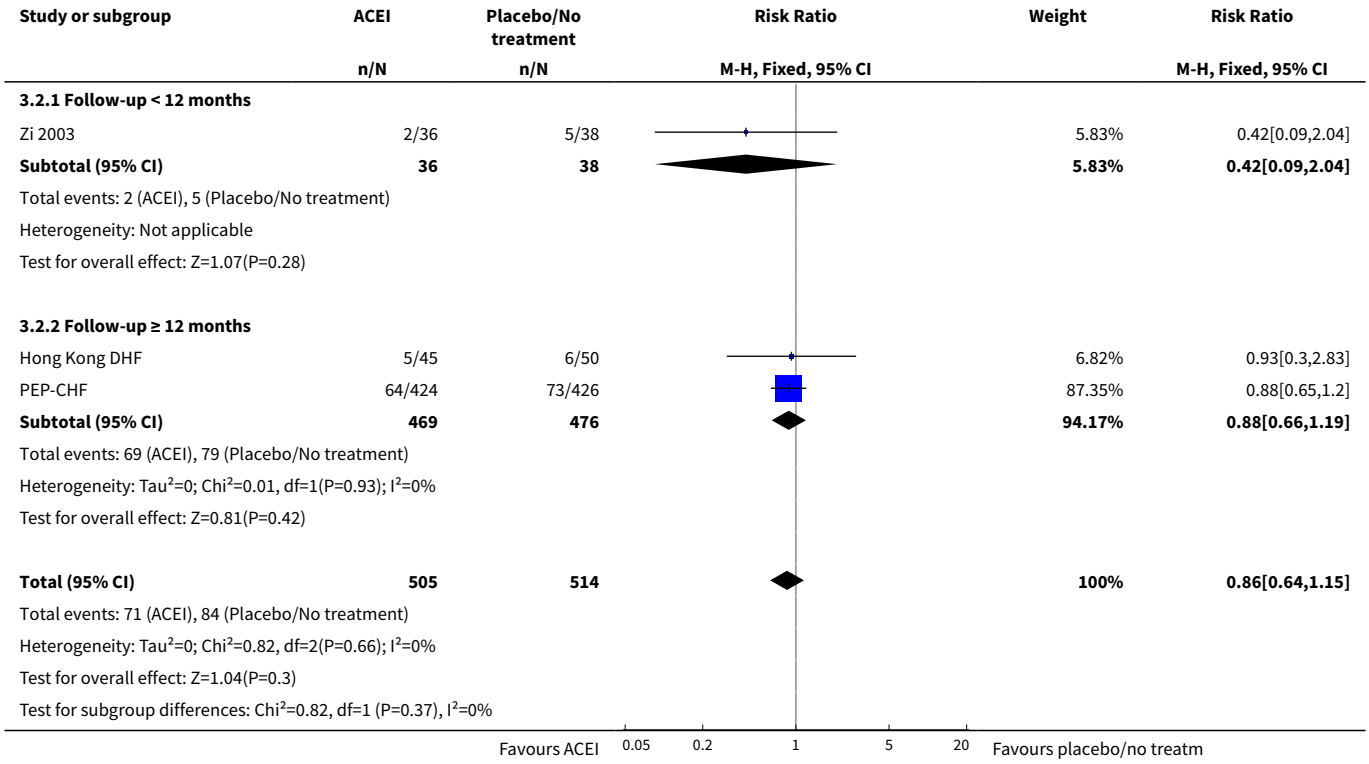
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Cardiovascular mortality (RR)	2	945	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.61, 1.42]
2 Heart failure hospitalisation (RR)	3	1019	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.64, 1.15]
2.1 Follow-up < 12 months	1	74	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.09, 2.04]
2.2 Follow-up ≥ 12 months	2	945	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.66, 1.19]
3 Hyperkalaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 All-cause mortality (RR)	4	1079	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.38]
5 Quality of life (Minnesota)	2	154	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-3.66, 3.48]
6 Withdrawal due to adverse event	3	1019	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.26, 9.00]

Analysis 3.1. Comparison 3 Angiotensin converting enzyme inhibitors versus placebo or no treatment, Outcome 1 Cardiovascular mortality (RR).

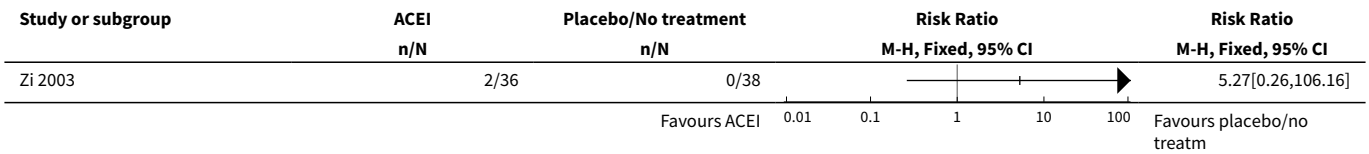




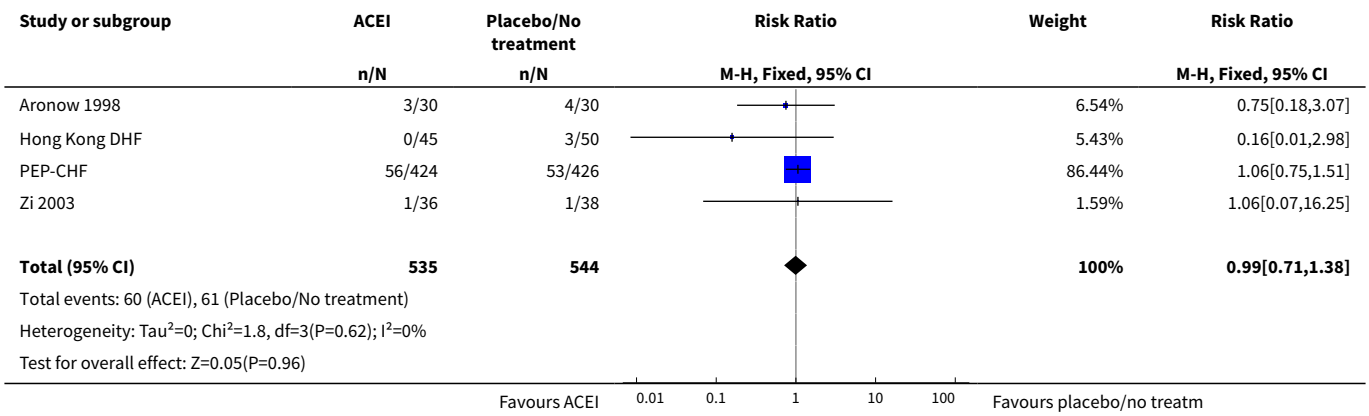
Analysis 3.2. Comparison 3 Angiotensin converting enzyme inhibitors versus placebo or no treatment, Outcome 2 Heart failure hospitalisation (RR).



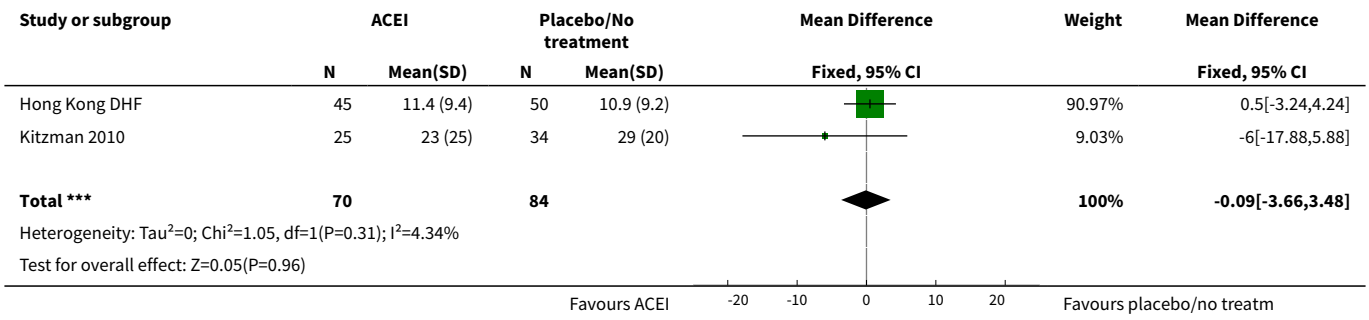
Analysis 3.3. Comparison 3 Angiotensin converting enzyme inhibitors versus placebo or no treatment, Outcome 3 Hyperkalaemia.



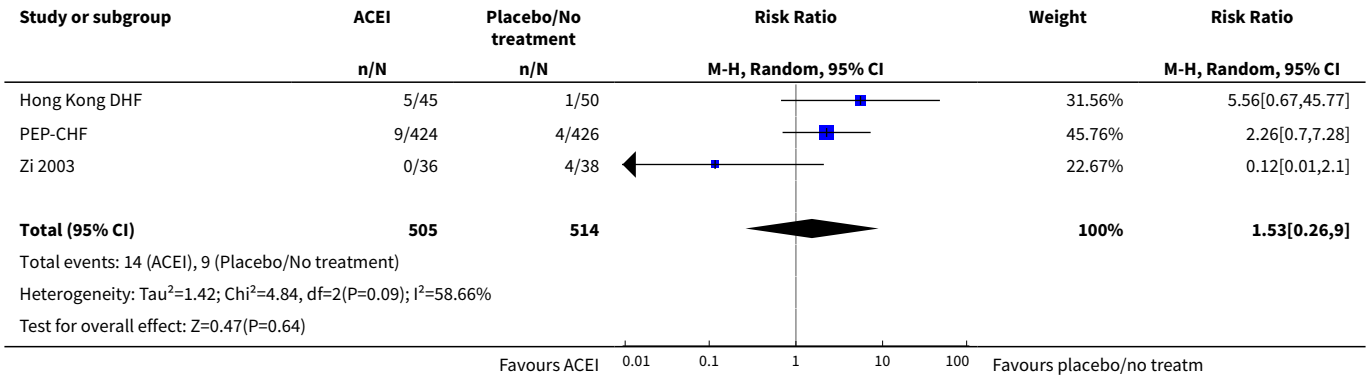
Analysis 3.4. Comparison 3 Angiotensin converting enzyme inhibitors versus placebo or no treatment, Outcome 4 All-cause mortality (RR).



Analysis 3.5. Comparison 3 Angiotensin converting enzyme inhibitors versus placebo or no treatment, Outcome 5 Quality of life (Minnesota).



Analysis 3.6. Comparison 3 Angiotensin converting enzyme inhibitors versus placebo or no treatment, Outcome 6 Withdrawal due to adverse event.

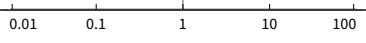


Comparison 4. Angiotensin receptor blockers versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular mortality (RR)	3	7254	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.14]
2 Cardiovascular mortality (HR)	2	5087	Hazard Ratio (Fixed, 95% CI)	1.00 [0.89, 1.13]
3 Heart failure hospitalisation (RR)	3	7254	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.02]
4 Heart failure hospitalisation (HR)	2	7148	Hazard Ratio (Fixed, 95% CI)	0.90 [0.80, 1.01]
5 Hyperkalaemia	2	7148	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.07, 3.33]
6 All-cause mortality (RR)	4	7964	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.11]
7 All-cause mortality (HR)	2	4838	Hazard Ratio (Fixed, 95% CI)	0.99 [0.88, 1.12]
8 Quality of life (Minnesota)	3	3117	Mean Difference (IV, Fixed, 95% CI)	0.41 [-0.86, 1.67]
9 Withdrawal due to adverse event	4	7406	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.09, 1.36]

Analysis 4.1. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 1 Cardiovascular mortality (RR).

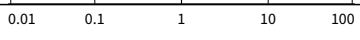
Study or subgroup	ARB n/N	placebo/no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-Preserved	170/1512	170/1508		35.93%	1[0.82,1.22]
Hong Kong DHF	1/56	1/50		0.22%	0.89[0.06,13.9]
I-PRESERVE	311/2067	302/2061		63.84%	1.03[0.89,1.19]
Total (95% CI)	**3635**	**3619**		**100%**	**1.02[0.9,1.14]**
Total events: 482 (ARB), 473 (placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=2(P=0.97); I^2=0%					
Test for overall effect: Z=0.26(P=0.79)					



Favours ARB — Favours placebo/no treatm

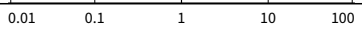
Analysis 4.2. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 2 Cardiovascular mortality (HR).

Study or subgroup	ARB N	placebo/no treatment N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
CHARM-Preserved	1512	1508	-0 (0.098)		41.38%	0.99[0.82,1.2]
I-PRESERVE	2067	0	0 (0.082)		58.62%	1.01[0.86,1.19]
Total (95% CI)					**100%**	**1[0.89,1.13]**



Favours ARB — Favours placebo/no treatm

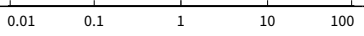
Study or subgroup	ARB	placebo/no treatment	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.87); I²=0%						
Test for overall effect: Z=0.03(P=0.98)						



Favours ARB — Favours placebo/no treatm

Analysis 4.3. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 3 Heart failure hospitalisation (RR).

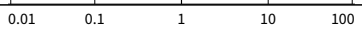
Study or subgroup	ARB	placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
CHARM-Preserved	241/1512	276/1508		44.63%	0.87[0.74,1.02]
Hong Kong DHF	6/56	6/50		1.02%	0.89[0.31,2.59]
I-PRESERVE	325/2067	336/2061		54.34%	0.96[0.84,1.11]
Total (95% CI)	**3635**	**3619**		**100%**	**0.92[0.83,1.02]**
Total events: 572 (ARB), 618 (placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=0.91, df=2(P=0.64); I²=0%					
Test for overall effect: Z=1.53(P=0.13)					



Favours ARB — Favours placebo/no treatm

Analysis 4.4. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 4 Heart failure hospitalisation (HR).

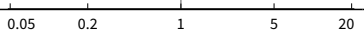
Study or subgroup	ARB	placebo/no treatment	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
CHARM-Preserved	1512	1508	-0.2 (0.085)		47.95%	0.85[0.72,1]
I-PRESERVE	2067	2061	-0.1 (0.081)		52.05%	0.95[0.81,1.11]
Total (95% CI)					**100%**	**0.9[0.8,1.01]**
Heterogeneity: Tau²=0; Chi²=0.9, df=1(P=0.34); I²=0%						
Test for overall effect: Z=1.78(P=0.07)						



Favours ARB — Favours placebo/no treatm

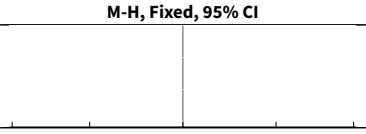
Analysis 4.5. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 5 Hyperkalaemia.

Study or subgroup	ARB	placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
CHARM-Preserved	22/1512	9/1508		50%	2.44[1.13,5.28]
I-PRESERVE	12/2067	9/2061		50%	1.33[0.56,3.15]
Total (95% CI)	**3579**	**3569**		**100%**	**1.88[1.07,3.33]**



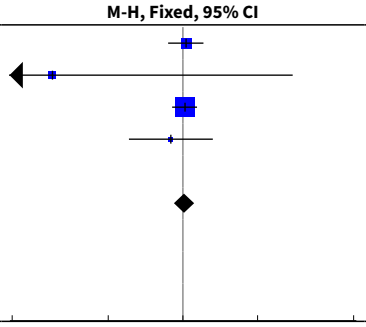
Favours ARB — Favours placebo/no treatm

Study or subgroup	ARB	placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Total events: 34 (ARB), 18 (placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=1.06, df=1(P=0.3); I²=5.32%					
Test for overall effect: Z=2.18(P=0.03)					



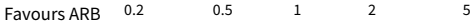
Analysis 4.6. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 6 All-cause mortality (RR).

Study or subgroup	ARB	placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
CHARM-Preserved	244/1512	237/1508		32.77%	1.03[0.87,1.21]
Hong Kong DHF	1/56	3/50		0.44%	0.3[0.03,2.77]
I-PRESERVE	445/2067	436/2061		60.3%	1.02[0.91,1.14]
SUPPORT	43/363	46/347		6.5%	0.89[0.61,1.32]
Total (95% CI)	**3998**	**3966**		**100%**	**1.01[0.92,1.11]**
Total events: 733 (ARB), 722 (placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=1.59, df=3(P=0.66); I²=0%					
Test for overall effect: Z=0.2(P=0.84)					



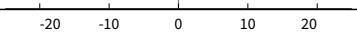
Analysis 4.7. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 7 All-cause mortality (HR).

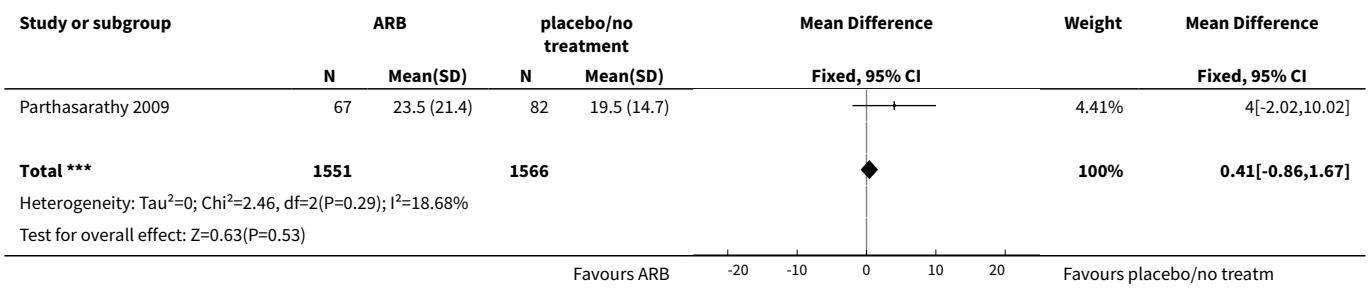
Study or subgroup	ARB	placebo/no treatment	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
I-PRESERVE	2067	2061	0 (0.065)		91.61%	1[0.88,1.14]
SUPPORT	363	347	-0.1 (0.215)		8.39%	0.9[0.59,1.37]
Total (95% CI)					**100%**	**0.99[0.88,1.12]**
Heterogeneity: Tau²=0; Chi²=0.22, df=1(P=0.64); I²=0%						
Test for overall effect: Z=0.14(P=0.89)						



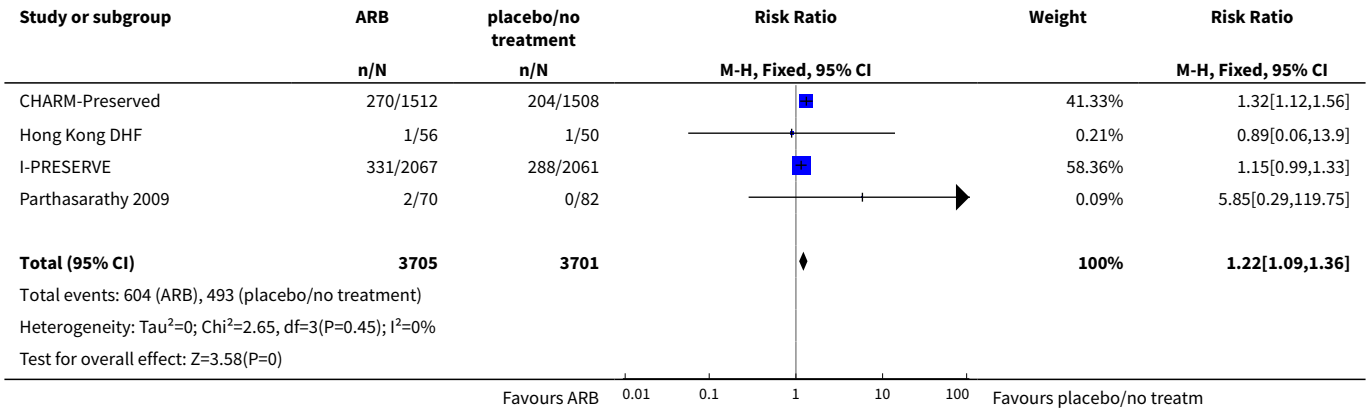
Analysis 4.8. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 8 Quality of life (Minnesota).

Study or subgroup	ARB		placebo/no treatment		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Hong Kong DHF	56	9.4 (9.7)	50	10.9 (9.2)		12.32%	-1.5[-5.1,2.1]
I-PRESERVE	1428	32.1 (18.9)	1434	31.6 (18.9)		83.27%	0.5[-0.89,1.89]





Analysis 4.9. Comparison 4 Angiotensin receptor blockers versus placebo or no treatment, Outcome 9 Withdrawal due to adverse event.



APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Heart Failure] explode all trees

#2 ((heart or cardia* or myocardial) near/3 (failure or insufficienc* or decompensat*)):ab,ti,kw

#3 #1 or #2

#4 MeSH descriptor: [Ventricular Dysfunction] explode all trees

#5 MeSH descriptor: [Ventricular Function] explode all trees

#6 ((preserved or normal or greater) near/5 ("ejection fraction" or "EF" or "LVEF")):ab,ti,kw

#7 ("preserved systolic function" or "normal systolic function" or "HFpEF" or "HF-pEF" or "HFnEF" or "HF-nEF" or "DHF" or diastolic*):ab,ti,kw

#8 #4 or #5 or #6 or #7

#9 #3 and #8

#10 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees

#11 (beta near/2 (antagonist* or block* or receptor*)):ab,ti,kw

#12 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone or cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxy benazepril or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol or Betapace or Blocadren or Bystolic or Cartrol or Coreg or Corgard or Inderal or Kerlone or Levatol or Lopressor or Normodyne or Sectral or Tenormin or Toprol or Trandate or Visken or Zebeta):ab,ti,kw

#13 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees

#14 ((angiotensin* or dipeptidyl* or 'kininase ii') near/3 (convert* or enzyme or inhibit* or recept* or block*)):ab,ti,kw

#15 (ace near/1 inhibit*):ab,ti,kw

#16 acei:ab,ti,kw

#17 (alacepril or altiopril or ancovenin or benazepril* or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril* or epicaptopril or fasidotril* or fosinopril or foroxymithine or gemopatrilat or idrapril or ilepatril or imidapril* or indolapril or libenzapril or lisinopril or moexipril* or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or sampatrilat or saralasin or "s nitrosocaptopril" or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril):ab,ti,kw

#18 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees

#19 (angiotensin near/3 ('receptor antagonist*' or "receptor block*")):ab,ti,kw

#20 (arb or arbs):ab,ti,kw

#21 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or fimasartan or fonsartan or forasartan or irbesartan or "KT3-671" or losartan or milfasartan or olmesartan or pomisartan or pratosartan or ripisartan or saprisartan or sparsentan or tasosartan or telmisartan or Losartan or zolasartan or Edarbi or Blopress or Atacand or Amias or Ratacand or Eprozar or Aprovel or Karvea or Avapro or Cozaar or Benicar or Olmecip or Micardis or Diovan):ab,ti,kw

#22 MeSH descriptor: [Neprilysin] this term only and with qualifier(s): [Antagonists & inhibitors - AI]

#23 (neprilysin near/1 (inhibit* or antagonist*)):ab,ti,kw

#24 arni:ab,ti,kw

#25 (sacubitril or sacubitrilat or lbq657 or "lbq 657" or ahu377 or "ahu 377" or entresto or lcz696 or "lcz 696")

#26 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees

#27 ((mineralocorticoid or aldosterone) near/3 (antagonist* or block* or inhibit*)):ab,ti,kw

#28 ("canrenoic acid" or canrenone or eplerenone or finerenone or "oxprenoate potassium" or spironolactone or aldactone or contaren or inspra or luvion or phanurane or spiroletan):ab,ti,kw

#29 {or #10-#28}

#30 #9 and #29

MEDLINE (Ovid)

1. exp Heart Failure/

2. ((heart or cardia* or myocardial) adj3 (failure or insufficienc* or decompensat*)).tw.

3. 1 or 2

4. exp Ventricular Dysfunction/

5. exp Ventricular Function/

6. ((preserved or normal or greater) adj5 (ejection fraction or EF or LVEF)).tw.

7. (preserved systolic function or normal systolic function or HFpEF or HF-pEF or HFnEF or HF-nEF or DHF or diastolic*).tw.

8. 4 or 5 or 6 or 7

9. 3 and 8

10. exp Adrenergic beta-Antagonists/

11. (beta adj2 (antagonist* or block* or receptor*)).tw.

12. (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone or cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol or Betapace or Blocadren or Bystolic or Cartrol or Coreg or Corgard or Inderal or Kerlone or Levatol or Lopressor or Normodyne or Sectral or Tenormin or Toprol or Trandate or Visken or Zebeta).mp.

13. exp Angiotensin-Converting Enzyme Inhibitors/

14. ((angiotensin* or dipeptidyl* or kininase ii) adj3 (convert* or enzyme or inhibit* or recept* or block*)).tw.

15. (ace adj inhibit*).tw.

16. acei.tw.

17. (alacepril or altiopril or ancovenin or benazepril* or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril* or epicaptopril or fasidotril* or fosinopril or foroxymithine or gemopatrilat or idrapril or ilepatril or imidapril* or indolapril or libenzapril or lisinopril or moexipril* or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or sampatrilat or saralasin or s nitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).mp.

18. exp Angiotensin Receptor Antagonists/

19. (angiotensin adj3 (receptor antagonist* or receptor block*)).tw.

20. (arb or arbs).tw.

21. (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or fimasartan or fonsartan or forasartan or irbesartan or KT3-671 or losartan or milfasartan or olmesartan or pomisartan or pratosartan or ripisartan or saprisartan or sparsentan or tasosartan or telmisartan or valsartan or zolasartan or Edarbi or Blopress or Atacand or Amias or Ratacand or Eprozar or Aprovel or Karvea or Avapro or Cozaar or Benicar or Olmecip or Micardis or Diovan).mp.

22. Neprilysin/ai [Antagonists & Inhibitors]

23. (neprilysin adj (inhibit* or antagonist*)).tw.

24. arni.tw.

25. (Sacubitril or "ahu 377" or ahu377 or Sacubitrilat or lbq657 or "lbq 657" or ahu377 or "ahu 377" or Entresto or lcz696 or "lcz 696").mp.

26. exp Mineralocorticoid Receptor Antagonists/

27. ((mineralocorticoid or aldosterone) adj3 (antagonist* or block* or inhibit*)).tw.

28. (canrenoic acid or canrenone or eplerenone or finerenone or oxprenoate potassium or spironolactone or Aldactone or Contaren or Inspra or Luvion or Phanurane or Spiroletan).mp.

29. or/10-28

30. 9 and 29

31. randomized controlled trial.pt.

32. controlled clinical trial.pt.

33. randomized.ab.

34. placebo.ab.

35. drug therapy.fs.

36. randomly.ab.

37. trial.ab.

38. groups.ab.

39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. exp animals/ not humans.sh.

41. 39 not 40

42. 30 and 41

Embase

#33 #31 AND #32
#32 random*:ab,ti OR placebo* OR ((double NEXT/1 blind*):ab,ti)
#31 #10 AND #30
#30 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28OR #29
#29 'canrenoic acid' OR canrenone OR eplerenone OR finerenone OR 'oxprenoate potassium' OR spironolactone OR aldactone OR contaren OR inspra OR luvion OR phanurane OR spiroletan
#28 ((mineralocorticoid OR aldosterone) NEAR/3 (antagonist* OR block* OR inhibit*)):ab,ti
#27 'mineralocorticoid antagonist'/exp
#26 sacubitril OR sacubitrilat OR lbq657 OR 'lbq 657' OR 'ahu377' OR 'ahu 377' OR entresto OR lcz696 OR 'lcz 696'
#25 arni:ab,ti
#24 (neprilysin NEAR/1 (inhibit* OR antagonist*)):ab,ti
#23 'enkephalinase inhibitor'/exp
#22 abitesartan OR azilsartan OR candesartan OR elisartan OR embusartan OR eprosartan OR fimasartan OR fonsartan OR forasartanOR irbesartan OR 'kt3-671' OR losartan OR milfasartan OR olmesartan OR pomisartan OR pratosartan OR ripisartan OR saprisartanOR sparsentan OR tasosartan OR telmisartan OR valsartan OR zolasartan OR edarbi OR blopress OR atacand OR amias OR ratacandOR eprozar OR aprovel OR karvea OR avapro OR cozaar OR benicar OR olmecip OR micardis OR diovan
#21 arb:ab,ti OR arbs:ab,ti
#20 (angiotensin NEAR/3 ('receptor antagonist*' OR 'receptor block*')):ab,ti
#19 'angiotensin receptor antagonist'/exp
#18 alacepril OR altiopril OR ancovenin OR benazepril* OR captopril OR ceranapril OR ceronapril OR cilazapril OR deacetylalacepril OR delapril OR derapril OR enalapril* OR epicaptopril OR fasidotril* OR fosinopril OR foroxymithine OR gemopatrilat OR idrapril OR ilepatril OR imidapril* OR indolapril OR libenzapril OR lisinopril OR moexipril* OR omapatrilat OR pentopril* OR perindopril* OR pivopril OR quinapril* OR ramipril* OR rentiapril OR sampatrilat OR saralasin OR 's nitrosocaptopril' OR spirapril* OR temocapril*OR teprotide OR trandolapril* OR utibapril* OR zabicipril* OR zofenopril* OR aceon OR accupril OR altace OR capoten OR lotensinOR mavik OR monopril OR prinivil OR univas OR vasotec OR zestril
#17 acei:ab,ti
#16 (ace NEAR/1 inhibit*):ab,ti
#15 ((angiotensin* OR dipeptidyl* OR 'kininase ii') NEAR/3 (convert* OR enzyme OR inhibit* OR recept* OR block*)):ab,ti
#14 'dipeptidyl carboxypeptidase inhibitor'/exp
#13 acebutolol OR adimolol OR afurolol OR alprenolol OR amosulalol OR arotinolol OR atenolol OR befunolol OR betaxolol OR bevantololOR bisoprolol OR bopindolol OR bornaprolol OR brefonalol OR bucindolol OR bucumolol OR bufetolol OR bufuralol OR bunitrolol OR bunolol OR bupranolol OR butofilolol OR butoxamine OR carazolol OR carteolol OR carvedilol OR celiprolol OR cetamolol OR chlortalidone OR cloranolol OR cyanoiodopindolol OR cyanopindolol OR deacetylmetipranolol OR diacetolol OR dihydroalprenololOR dilevalol OR epanolol OR esmolol OR exaprolol OR falintolol OR flestolol OR flusoxolol OR hydroxybenzylpinodolol OR hydroxycarteolol

OR hydroxymetoprolol OR indenolol OR iodocyanopindolol OR iodopindolol OR iprocrolol OR isoxaprolol OR labetalol OR landiolol OR levobunolol OR levomoprolol OR medroxalol OR mepindolol OR methylthiopropranolol OR metipranololOR metoprolol OR moprolol OR nadolol OR nebivolol OR nifenalol OR nipradilol OR oxprenolol OR pafenolol OR pamatolol OR penbutolol OR pindolol OR practolol OR primidolol OR prizidilol OR procinolol OR pronetalol OR propranolol OR proxodolol OR ridazolol OR salcardolol OR soquinolol OR sotalol OR spirendolol OR talinolol OR tertatolol OR tienoxolol OR tilisolol OR timolol OR tolamolol OR toliprolol OR tribendilol OR xibenolol OR betapace OR blocadren OR bystolic OR cartrol OR coreg OR corgard OR inderal OR kerlone OR levatol OR lopressor OR normodyne OR sectral OR tenormin OR toprol OR trandate OR visken OR zebeta
#12 (beta NEAR/2 (antagonist* OR block* OR receptor*)):ab,ti
#11 'beta adrenergic receptor blocking agent'/exp
#10 #3 AND #9
#9 #4 OR #5 OR #6 OR #7 OR #8
#8 'preserved systolic function':ab,ti OR 'normal systolic function':ab,ti OR hfpef:ab,ti OR 'hf-pef':ab,ti OR hfnef:ab,ti OR 'hf-nef':ab,ti OR dhf:ab,ti OR diastolic*:ab,ti
#7 ((preserved OR normal OR greater) NEAR/5 ('ejection fraction' OR ef OR lvef)):ab,ti
#6 'systolic dysfunction'/exp
#5 'diastolic dysfunction'/exp
#4 'heart ventricle function'/de
#3 #1 OR #2
#2 ((heart OR cardia* OR myocardial) NEAR/3 (failure OR insufficienc* OR decompensat*)):ab,ti
#1 'heart failure'/exp

ClinicalTrials.gov

Advanced Search--Limited to study type: interventional studies

("heart failure" AND ("preserved ejection fraction" OR "normal ejection fraction" OR "preserved systolic function" OR "normal systolic function")) OR "diastolic heart failure" OR "HFpEF" OR "HF-pEF" OR "HFnEF" OR "HF-nEF" OR "DHF"

WHO International Clinical Trials Registry Platform (ICTRP) Search Portal

Standard Search

heart failure AND preserved ejection fraction OR heart failure AND normal ejection fraction OR

heart failure AND preserved systolic function OR heart failure AND normal systolic function OR

diastolic heart failure OR HFpEF OR HF-pEF OR HFnEF OR HF-nEF OR DHF

CONTRIBUTIONS OF AUTHORS

NM: selection of studies, data extraction, analysis, GRADE assessment, co-wrote the manuscript.

KM: selection of studies, GRADE assessment.

JT: contributed to review design, approved the final version.

CD: contributed to review design, GRADE assessment, approved the final version.

TL: guarantor of review, designed the review, data extraction, analysis, GRADE assessment, co-wrote the manuscript.

DECLARATIONS OF INTEREST

NM: none known.

KM: none known.

JT: none known.

CD: has received sponsorship from Servier, Roche and Novartis to attend cardiology conferences, payment from GE Healthcare to give lectures on heart failure, and has served as a paid consultant to Servier and Vifor.

TL: has received research grants from Pfizer and has served as an unpaid consultant to GSK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We originally planned to include participants with LVEF ≥ 40% but changed this to LVEF > 40%, since this is a more frequently used cut-off in clinical trials.

We originally limited our population to symptomatic heart failure (NYHA class > I) at enrolment; however, this criterion was removed to include people with diagnosis of heart failure in whom symptoms had improved the functional class.

We added a clarification regarding the exclusion of cross-over trials.

We originally planned to include withdrawals due to adverse events in the 'Summary of findings' table. This was changed because this outcome was frequently reported inconsistently, which limits the applicability of a pooled analysis. Instead, we added hyperkalaemia to the 'Summary of findings' table because this adverse event outcome has relevance for clinical decision making. For the same reason, hyperkalaemia was switched from secondary to primary outcomes and withdrawals due to adverse events was switched from primary to secondary outcomes.

We did not pre specify which scale for quality of life we would focus on in the 'Summary of findings' table. To aid comparisons across the 'Summary of findings' tables we chose to include the Minnsota Living with Heart Failure Questionnaire and not the standardised mean difference across two scales which applied only to MRA versus placebo or no treatment comparison.

INDEX TERMS

Medical Subject Headings (MeSH)

*Stroke Volume; Adrenergic beta-Antagonists [*therapeutic use]; Angiotensin Receptor Antagonists [*therapeutic use]; Angiotensin-Converting Enzyme Inhibitors [*therapeutic use]; Chronic Disease; Heart Failure [*drug therapy] [mortality]; Hospitalization; Mineralocorticoid Receptor Antagonists [*therapeutic use]; Neprilysin [antagonists & inhibitors]; Quality of Life; Randomized Controlled Trials as Topic; Renin-Angiotensin System [*drug effects]

MeSH check words

Humans