

## Chronic heart failure in adults: diagnosis and management

**[D] Evidence review for mineralocorticoid receptor antagonist therapy for heart failure with preserved ejection fraction**

*NICE guideline NG106*

*Evidence review underpinning recommendation 1.5.4 in the NICE guideline*

*September 2025*

Final

This evidence review was developed by NICE



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# 1 Mineralocorticoid receptor antagonist therapy for heart failure with preserved left ventricular ejection fraction

## 1.1 Review question

What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists (finerenone, and spironolactone) in people with chronic heart failure with preserved ejection fraction?

### 1.1.1 Introduction

Heart failure was historically perceived by many as the clinical syndrome caused by the presence of left ventricular dysfunction, which includes a reduction in the left ventricular ejection fraction (LVEF) to  $\leq 40\%$ . For over 20 years, it has been recognised that a number of patients with the heart failure syndrome do not have a reduction of the LVEF. These patients are said to have heart failure with preserved ejection fraction (HFpEF), with LVEF  $\geq 50\%$ . In addition to the preserved LVEF, they must display structural abnormalities of the heart reflecting a rise in the diastolic left ventricular pressure, left ventricular hypertrophy, dilatation of the left atrium or a rise in the pulmonary artery pressure, as well as a rise in their natriuretic peptide level.

The trials that tried to replicate the evidence base we have for heart failure with reduced ejection fraction (HFrEF) in the population with HFpEF, resulted in neutral outcomes (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, mineralocorticoid receptor antagonist, beta-blocker, ivabradine and sacubitril-valsartan). Therefore, previous iterations of the guidelines could not provide any solid evidence-base for treating those with HFpEF, beyond diuretics and addressing their risk factors. However, with the advent of sodium-glucose co-transporter 2 inhibitors (SGLT2i) as therapeutic agents in HFrEF, interest arose in testing these agents in patients with HFpEF. Indeed, two pivotal trials demonstrated significant reduction of the risk of hospitalisation of patients with HFpEF when treated with either dapagliflozin and empagliflozin. New evidence is also now available on finerenone in patients with HFpEF. Thus, there is a need to re-appraise the evidence base for use of these agents in the treatment of HFpEF and to consider both their clinical and cost-effectiveness before making evidence-based clinical recommendations.

### 1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

**Table 1: PICO characteristics of review question**

<b>Population</b>	<ul style="list-style-type: none"><li>• Adults diagnosed with heart failure with preserved ejection fraction.</li><li>• Preserved ejection fraction heart failure is defined as left ventricular ejection fraction (LVEF) <math>\geq 50\%</math>, with abnormal cardiac biomarkers (B-type natriuretic peptides [BNP] or N-terminal pro-B-type natriuretic peptide level [NT-proBNP]) plus a structural issue in the heart including two or more of the following:<ul style="list-style-type: none"><li>○ Left atrial volume <math>&gt;34</math> ml/m<sup>2</sup> in sinus rhythm, or <math>&gt;40</math> ml/m<sup>2</sup> in atrial fibrillation</li><li>○ Ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E:e') <math>&gt;11</math></li><li>○ Left ventricular hypertrophy (<math>&gt;12</math> mm wall thickness)</li><li>○ Pulmonary arterial pressure <math>&gt;35</math> mmHg</li></ul></li></ul>
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	<p>Diagnosis should be made by a heart failure specialist or heart failure specialist team.</p> <p>Studies including an indirect population (for example mixed heart failure with a mildly reduced ejection fraction [HFmrEF] and heart failure with a preserved ejection fraction [HFpEF]) will only be included if <math>\geq 80\%</math> match the protocol criteria or there are subgroup data for the protocol population.</p> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Children</li> <li>• Acute heart failure in hospital</li> <li>• Heart failure with reduced or mildly reduced ejection fraction</li> <li>• Heart failure due to right heart dysfunction (e.g., pre-capillary pulmonary hypertension and primary right ventricular cardiomyopathies)</li> <li>• High output heart failure</li> <li>• Adult congenital heart disease</li> <li>• Primary heart valve disease</li> <li>• Acute myocardial infarction (within 3 months of the event)</li> <li>• Treatment with chemotherapy</li> </ul>
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• Mineralocorticoid receptor antagonists (spironolactone and finerenone)</li> </ul>
<b>Comparison</b>	<p>Placebo + usual chronic heart failure care or usual chronic heart failure care alone</p>
<b>Outcomes</b>	<p>All outcomes are considered equally important for decision making and therefore have all been rated as critical:</p> <ul style="list-style-type: none"> <li>• All-cause mortality (time-to-event)</li> <li>• Cardiovascular mortality (time-to-event)</li> <li>• Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value)</li> <li>• Unplanned hospitalisation or visits (heart failure-related) (time-to-event; including repeat events when reported) <ul style="list-style-type: none"> <li>○ All cause unplanned hospitalisation or visits will be included if heart failure-related is not reported in a study, but this will be downgraded for outcome indirectness</li> </ul> </li> </ul> <p>Adverse events (recorded as the number of people with at least one event, not the total number of events)</p> <ul style="list-style-type: none"> <li>• Withdrawal due to drug-related adverse events (dichotomous)</li> <li>• Acute Kidney Injury – serum creatinine rise of <math>\geq 50\%</math> over <math>\leq 7</math> days (dichotomous)</li> <li>• Hyponatraemia- serum sodium concentration <math>&lt; 135</math> mmol/L (dichotomous)</li> <li>• Hyperkalaemia- serum potassium concentration <math>\geq 5.5</math> mmol/L (dichotomous)</li> <li>• Falls (dichotomous)</li> <li>• Gynaecomastia (dichotomous)</li> </ul> <p>Time points for analysis:</p> <ul style="list-style-type: none"> <li>○ 12 months (pool all times <math>\geq 3</math> months, taking the closest to 12 months follow-up time from each study if multiple time points are reported)</li> </ul> <p>Exclude if follow-up <math>&lt; 3</math> months</p>
<b>Study design</b>	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>• Randomised controlled trials (RCTs)</li> <li>• Published systematic reviews of RCTs</li> <li>• Published network meta-analyses (NMAs) and individual participant data meta-analyses (IPDs).</li> </ul> <p>Exclusion:</p>

- Cross-over RCTs
- Non-randomised studies

### 1.1.3 Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual](#). Methods specific to this review question are described in the review protocol in appendix A.

#### Literature search methods

The searches for the effectiveness evidence were run on 01/11/2024 and re-run on 09/01/2025. The following databases were searched: Cochrane Database of Systematic Reviews (CDSR) (Wiley); Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Embase (Ovid); MEDLINE ALL (Ovid); and Epistemonikos. Limits were applied to remove animal studies, editorials, conference abstracts, empty registry entries and references not published in the English language. The National Guideline Centre (NGC) systematic review and randomised controlled trial search filters were used to limit to study types.

The searches for the cost effectiveness evidence (economic evaluations) were run on 12/02/2024 and re-run on 04/12/2024 and 13/01/2025. The following databases were searched: Embase (Ovid); MEDLINE ALL (Ovid); and INAHTA. Limits were applied to remove animal studies, editorials, conference abstracts, empty registry entries and references not published in the English language.

The searches for the cost effectiveness evidence (quality of life) were run on 25 07 2024 and re-run on 04/12/2024 and 13/01/2025. The following databases were searched: Embase (Ovid) and MEDLINE ALL (Ovid). Limits were applied to remove animal studies, editorials, conference abstracts, empty registry entries and references not published in the English language.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the [2015 PRESS Guideline Statement](#). Further details and full search strategies for each database are provided in Appendix B.

#### Review methods

Chronic heart failure is defined according to the following criteria:

- Symptoms (such as breathlessness, ankle swelling, and fatigue) with or without signs (such as elevated jugular venous pressure, pulmonary crackles, and peripheral oedema); and
- Elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion on imaging (such as pleural effusions, pulmonary oedema, ascites, lung comets); and
- Outpatient or stabilised after hospital admission.

However, for the purposes of this review, trials were not excluded on the basis of lacking corroboratory evidence from natriuretic peptides or imaging, as this would selectively exclude older trials.

Studies that were included and analysed in the previous update of the guideline and met the current protocol criteria were retained in this evidence review and pooled with newly identified studies where appropriate. The previously included studies were added to EPPI-

reviewer and any data available for the additional outcomes that were not in the previous protocol were also extracted. All outcomes were reassessed for risk of bias according to the Cochrane Risk of Bias 2 checklist for consistency with current methods.

Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

## 1.1.4 Effectiveness evidence

### 1.1.4.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of mineralocorticoid receptor antagonist (MRA) therapy versus placebo or usual care as treatment for patients with chronic heart failure with preserved ejection fraction.

Six RCT studies (across 13 study records) were included in the review; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). The included studies assessed 2 different MRA therapies – spironolactone and finerenone (which have been combined as a class grouping in this review) – and compared these to placebo. The protocol previously included eplerenone as an included intervention. On closer scrutiny, this medicine was identified as not licensed for CHF with preserved ejection fraction. Therefore, a protocol amendment has been made to remove eplerenone from the intervention list for this evidence review and studies investigating eplerenone as a therapy have been excluded. Although not currently licensed for CHF with preserved ejection fraction, finerenone has been included in the evidence review based on the knowledge that this medicine is in the regulatory pipeline for licensing in this population. To improve clarity on approach to inclusion of licensed medicines, the protocol has been amended to remove 'licensed' from the description of analysis groupings (see Appendix A1). The identified studies reported all relevant outcomes, except for falls and hyponatremia.

The FINEARTS-HF trial included adults with mildly reduced or preserved ejection fraction, but for this review only the data for the preserved ejection fraction subgroup were analysed in accordance with the review protocol. [The mildly reduced ejection fraction subgroup is included in review B.](#)

The TOPCAT trial included adults with LVEF  $\geq 45\%$ , but the full trial population was included in the analysis for this review because over 80% of participants had an LVEF  $\geq 50\%$ . A sensitivity analysis was undertaken using only the data from TOPCAT in those with an LVEF  $\geq 50\%$  in the pooled analysis to assess whether the estimates were different when strictly limited to preserved ejection fraction. The results can be seen in Table 4.

All included studies required participants to have symptomatic heart failure. Three of the studies (Docherty 2024, Kurrelmeyer 2014 and Pitt 2014) specified prior heart-failure hospitalisation or elevated natriuretic peptides within the trial inclusion criteria, in accordance with the universal definition of heart failure, while the remaining 3 studies did not.

To avoid excluding informative trials, a protocol deviation was agreed to allow inclusion of studies that did not use the presence of a structural issue with the heart as an inclusion criterion. Only one of the included studies (Docherty, 2024) matched the population definition listed in the protocol requiring at least two markers of a structural issue with the heart. Three studies (Edelmann, 2013; Kurrelmeyer, 2014;; Upadhya, 2017) required people to have one marker of a structural issue with the heart to be included, while two studies (Mottram, 2004; Pitt, 2014) did not specify any evidence of a structural heart issue being required for inclusion.

See also the study selection flow chart **Appendix C**, study evidence tables in **Appendix D**, forest plots in **Appendix E** and GRADE tables in **Appendix A**.

### 1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

### 1.1.5 Summary of studies included in the effectiveness evidence

**Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes
Docherty, 2024 [FINEARTS-HF]  Subsidiary paper: Solomon, 2024	20mg or 40 mg of finerenone per day, depending on the eGFR  Placebo	Participants with heart failure, NYHA class II–IV, aged 40 years or older with evidence of structural heart disease and elevated natriuretic peptides (NT-proBNP >300 pg/mL (or BNP >100 pg/mL) for patients in sinus rhythm or NT-proBNP >900 pg/mL (or BNP >300 pg/mL) for patients in atrial fibrillation)  Subgroup with LVEF ≥50% used for analysis (from Solomon 2024)  N=3821	<ul style="list-style-type: none"> <li>All-cause mortality</li> <li>Cardiovascular mortality</li> <li>Kansas City Cardiomyopathy Questionnaire</li> <li>Heart failure-related hospitalisation</li> <li>Discontinuation due to drug-related events</li> <li>Hyperkalaemia</li> </ul> Follow-up: 32 months
Edelmann, 2013 [ALDO-DHF]  Subsidiary paper: Edelmann, 2010	25 mg of spironolactone per day  Placebo	Adults with HFpEF with LVEF ≥50% and current heart failure symptoms between NYHA class II-III.  N=422	<ul style="list-style-type: none"> <li>All-cause mortality</li> <li>Minnesota Living with Heart Failure Questionnaire</li> <li>SF-36 Physical Functioning Score</li> <li>Hyperkalaemia</li> <li>Gynaecomastia</li> </ul> Follow-up: 12 months
Kurrelmeyer, 2014	25 mg of spironolactone per day  Placebo	Women with HFpEF with LVEF ≥50% and current heart failure symptoms between NYHA class II-III and B-type natriuretic peptide levels ≥62pg/mL  N=48	<ul style="list-style-type: none"> <li>All-cause mortality</li> <li>Kansas City Cardiomyopathy Questionnaire</li> <li>Heart failure-related hospitalisation</li> <li>Transient and serious hyperkalaemia</li> </ul> Follow-up: 6 months
Mottram, 2004	25 mg of spironolactone per day	Patients with diastolic heart failure with LVEF ≥50%, NYHA class II and hypertension requiring	<ul style="list-style-type: none"> <li>Gynaecomastia</li> </ul>

Study	Intervention and comparison	Population	Outcomes
	Placebo	antihypertensive medication and reported exertional dyspnoea.  N=30	Follow-up: 6 months
Pitt, 2014 [TOPCAT]  Subsidiary papers: Solomon, 2016 Desai, 2011 Lewis, 2016 Desai, 2018 Shah, 2013	15 to 45 mg of spironolactone per day  Placebo	People aged ≥ 50 years with symptomatic heart failure (>90% NYHA class II-IV) and LVEF ≥ 45% (>80% of participants had LVEF >50% based on data from Solomon 2016 so overall population meets the review protocol criteria).  Hospitalised for heart failure within previous 12 months; or BNP ≥100 pg/mL or NTproBNP ≥360 pg /mL.  N=3445	<ul style="list-style-type: none"> <li>All-cause mortality</li> <li>Cardiovascular mortality</li> <li>Kansas City Cardiomyopathy Questionnaire</li> <li>EQ-5D</li> <li>Heart failure-related hospitalisation</li> <li>Acute kidney injury (doubling of serum creatinine to a value beyond the upper reference limit)</li> <li>Hyperkalaemia</li> <li>Gynaecomastia</li> </ul> Follow-up: median 3.3 years
Upadhya, 2017	25 mg spironolactone per day  Placebo	Participants with confirmed HFpEF with LVEF ≥50%, heart failure clinical score from the National Health and Nutrition Examination Survey-I (NHANES) of ≥3; >90% NYHA class II-II  N=80	<ul style="list-style-type: none"> <li>Minnesota Living with Heart Failure Questionnaire</li> <li>All-cause hospitalisation</li> </ul> Follow-up: 9 months

BNP: B-type natriuretic peptides; EQ-5D: EuroQoL 5-dimensions questionnaire; HFpEF: Heart failure with a preserved ejection fraction; LVEF: Left ventricular ejection fraction; NYHA: New York Health Association; NT-proBNP: N-terminal pro-B-type natriuretic peptide level

See Appendix D for full evidence tables.

### 1.1.6 Summary of the effectiveness evidence

#### Primary analysis: overall population

**Table 3: Clinical evidence summary: MRA versus placebo**

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MRA
All-cause mortality (time-to-event)  Follow-up: 2.7 to 3.3 years	7266 (2 RCTs)	⊕⊕○○ Low <sup>a,b</sup>	HR 0.89 (0.79 to 1.0)	Not estimable	Not estimable

Outcomes Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MRA
All-cause mortality (dichotomous) Follow-up: 1 to 3.3 years	7714 (4 RCTs)	⊕○○○ Very low <sup>a,d</sup> ⊕⊕○○ Low <sup>a,c</sup>	RR 0.93 (0.84 to 1.03)	153 per 1,000	11 fewer per 1,000 (from 25 fewer to 5 more)
Cardiovascular mortality (time-to-event) Follow-up: 2.7 to 3.3 years	7266 (2 RCTs)	⊕⊕⊕○ Moderate <sup>b</sup>	HR 0.90 (0.77 to 1.06)	Not estimable	Not estimable
Cardiovascular mortality (dichotomous) Follow-up: 2.7 to 3.3 years	7266 (2 RCTs)	⊕⊕⊕○ Moderate <sup>c</sup>	RR 0.95 (0.81 to 1.10)	87 per 1,000	4 fewer per 1,000 (from 17 fewer to 9 more)
Minnesota Living with Heart Failure; change scores (score range: 0-105, lower scores are better) Follow-up: 9 to 12 months	461 (2 RCTs)	⊕⊕⊕○ Moderate <sup>d</sup>	-	The mean change in MLWHF was -1.5.	MD 0.86 lower (3.07 lower to 1.34 higher)
KCCQ overall summary score (OSS); change scores (score range: 0-100, higher scores are better) Follow-up: 12 months	3400 (1 RCT) Follow-up: 6 months to 12 months	⊕⊕⊕⊕ High	-	The change from baseline was not reported	MD 1.35 higher (0.21 higher to 2.49 higher)
KCCQ clinical summary score (CSS); change scores (score range: 0-100, higher scores are better) Follow-up: 6 months	48 (1 RCT)	⊕⊕○○ Low <sup>b,e</sup>	-	The mean change in KCCQ CSS was 7.60	MD 5.30 lower (15.52 lower to 4.92 higher)
KCCQ total symptom score (TSS); change scores (score range 0-100, higher scores are better) Follow-up: 12 months	3821 (1 RCT)	⊕○ Moderate <sup>a</sup>	-	The mean change in KCCQ TSS was 7.31	MD 1.90 higher (0.7 higher to 3.09 higher)
SF-36 Physical functioning; final score (score range: 0-100, higher scores are better) Follow-up: 12 months	381 (1 RCT)	⊕⊕○○ Low <sup>b,d</sup>	-	The mean SF-36 physical functioning final score was 66	MD 2 lower (6.72 lower to 2.72 higher)
EQ-VAS change score (score range: 0-100, higher scores are better)	3395 (1 RCT)	⊕⊕⊕⊕ High	-	NR	MD 0.47 higher (0.27 lower to 1.21 higher)

Outcomes Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MRA
Follow-up: 3.3 years					
Heart failure-related hospitalisation (time-to-event)	7266 (2 RCTs)	⊕⊕○○ Low <sup>a,b</sup>	HR 0.77 (0.69 to 0.87)	Not estimable	Not estimable
Follow-up: 2.7 years to 3.3 years					
Heart failure-related hospitalisation (total events)	7266 (2 RCTs)	⊕⊕⊕○ Moderate <sup>b</sup>	Rate ratio 0.79 (0.71 to 0.88)	121 per 1,000 participant years	25 fewer per 1,000 participant years (35 fewer to 15 fewer) <sup>g</sup>
Follow-up: 2.7 years to 3.3 years					
Heart failure-related hospitalisation (dichotomous)	7314 (3 RCTs)	⊕○○○ Very low <sup>a,b,c</sup>	RR 0.86 (0.77 to 0.95)	163 per 1,000	23 fewer per 1,000 (from 38 fewer to 8 fewer)
Follow-up: 6 months to 3.3 years					
All-cause hospitalisation (dichotomous)	71 (1 RCT)	⊕○○○ Very low <sup>b,c</sup>	RR 0.71 (0.30 to 1.71)	265 per 1,000	77 fewer per 1,000 (185 fewer to 188 more)
Follow-up: 9 months					
Withdrawal due to drug-related events (dichotomous)	3808 (1 RCT)	⊕⊕○○ Low <sup>a,b</sup>	RR 1.22 (0.85 to 1.74)	28 per 1,000	6 more per 1,000 (from 4 fewer to 21 more)
Follow-up: 32 months					
AKI - doubling of serum creatinine to a value beyond the upper reference limit (dichotomous)	3445 (1 RCT)	⊕⊕○○ Low <sup>b,f</sup>	RR 1.45 (1.16 to 1.81)	70 per 1,000	32 more per 1,000 (from 11 more to 57 more)
Follow-up: 3.3 years					
Hyperkalaemia – Serum potassium concentration ≥5.5mmol/L (dichotomous)	7575 (4 RCTs)	⊕⊕⊕⊕ High	RR 2.06 (1.81 to 2.36)	75 per 1,000	79 more per 1,000 (from 60 more to 101 more)
Follow-up: 6 months to 3.3 years					
Gynaecomastia in men or breast tenderness/enlargement in women (dichotomous)	3875 (3 RCTs)	⊕⊕⊕⊕ High	RR 7.53 (3.43 to 16.51)	4 per 1,000	24 more per 1,000 (from 9 more to 56 more)
Follow-up: 6 months to 3.3 years					

AKI: Acute kidney injury; EQ-VAS: EuroQoL visual analogue scale; HR: Hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: Mean difference; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial; RR: Relative risk; SF-36: Short Form-36 health survey

- a. Downgraded by 1 increment for risk of bias due to unexplained deviations from the trial protocol in the majority of the evidence (the FINEARTS-HF trial did not use the LVEF thresholds prespecified in the study protocol).
- b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes. KCCQ MID is 5; MLWHFQ MID is 5; SF36 physical summary score MID is 2; EQ5D VAS MID is 9.05.
- c. Downgraded by 1 increment as the majority of the evidence was indirect (due to reporting as number of events)
- d. Downgraded by 1 increment for risk of bias due to some concerns for the majority of the evidence: no information provided regarding allocation concealment.
- e. Downgraded by 1 increment for risk of bias due to some concerns for the majority of the evidence: differences between groups which could suggest a problem with the randomisation process and no information provided regarding allocation concealment.
- f. Downgraded by 1 increment for outcome indirectness due to the serum creatinine increase not being within the acute time frame specified in the protocol.
- g. Absolute difference calculated based on difference in number of events per person-year reported in the papers.

### Sensitivity analysis: using TOPCAT subgroup with LVEF ≥50%

**Table 4: Clinical evidence summary: MRA versus placebo using TOPCAT subgroup with LVEF ≥50%**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MRA
All-cause mortality (time-to-event)	6745 (2 RCTs) Follow-up: 2.7 months to 3.3 years	⊕⊕⊕⊕ High	HR 0.92 (0.81 to 1.04)	Not estimable	Not estimable
Cardiovascular mortality (time-to-event)	6745 (2 RCTs) Follow-up: 2.7 months to 3.3 years	⊕⊕⊕○ Moderate <sup>a</sup>	HR 0.94 (0.79 to 1.12)	Not estimable	Not estimable
Heart failure-related hospitalisations (time-to-event)	6745 (2 RCTs) Follow-up: 2.7 months to 3.3 years	⊕⊕⊕○ Moderate <sup>a</sup>	HR 0.78 (0.69 to 0.89)	Not estimable	Not estimable

HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial

- a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25.

See Appendix F for full GRADE tables.

#### 1.1.7 Economic evidence

A single search was performed to identify economic evaluations of relevance to any of the questions in this guideline update that had been published since the last guideline (See the health economic review protocol in Appendix A and the literature search strategy in Appendix B). A further 15 studies included previously in the guideline were re-assessed for applicability and quality. Ten studies were excluded following the full-text review. Leaving no relevant studies to be included for this question.

### 1.1.7.1 Included studies

No health economic studies were included.

### 1.1.7.2 Excluded studies

Ten economic studies relating to this review question were identified but were excluded due to incorrect comparator and interventions. See Appendix J.2 for a list of excluded economic studies, with reason for exclusion.

See also the health economic study selection flow chart in Appendix G.

### 1.1.8 Summary of included economic evidence

No economic evidence was included.

### 1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis. However, the guideline model used to evaluate medicines for heart failure with reduced ejection fraction was adapted to inform this question. Model parameters unique to preserved ejection fraction analysis can be found in Table 5. For other methods and parameters see Economic analysis report on medicines for heart failure and reduced ejection fraction.

**Table 5: Key model parameters**

Parameter	Value	Source
All-cause mortality – baseline rate per year –0-5 years	0.052	Guideline review – Pitt et al 2014 [TOPCAT] – 274/1723 at 3.3 years – see Appendix D
All-cause mortality – Hazard ratio (MRA vs no medicine) – all years	0.89	Guideline review – see <b>Table 3</b>
Utility gain	zero	Assumed for simplicity but likely to be some improvement
Hospitalisation for heart failure – baseline -0-1 year	0.121	Guideline review – see <b>Table 3</b>
Hospitalisation for heart failure – rate ratio – all years	0.79	Guideline review – see <b>Table 3</b>
Cost per year (spironolactone)	£38.35	NHS drug tariff – see Table 7
Visits for initiation and titration	1 GP visit 2 GP nurse visits	Expert opinion – see 1.1.10 Unit costs
Additional follow-up visits per year	zero	Expert opinion
Treatment escalation per year	zero	Assumed

GP=general practitioner; MRA: Mineralocorticoid receptor antagonist

Even assuming no gain in quality of life, the model suggests that spironolactone is likely to be highly cost-effective (See Table 6).

**Table 6: Cost-effectiveness of MRAs for people with heart failure and preserved ejection fraction**

Strategy	Mean cost per person	Mean QALYs per person	Incremental cost per QALY gained (i.e. ICER)	Net health benefit at £20,000/QALY
No medicine	£5,661	6.126	-	5.84
Spirolactone	£8,115	6.430		6.02
Increment	£2,454	0.303	£8,099	0.18

*ICER: Incremental cost-effectiveness ratio; MRA: Mineralocorticoid receptor antagonist; QALY=quality-adjusted life-year*

### 1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of resource impact.

**Table 7 Unit cost of selected medicines – NHS drug tariff (27<sup>th</sup> March 2025)**

Class	Drug	Tablet s/pack	Price/ pack	Tablets per day	Cost per year at max dose	Dose	Indication
MRA	Spironolactone	28	£2.94	1	£38.35	Initially 25mg once daily, then adjusted according to response to 50mg once daily.	Moderate to severe heart failure (adjunct)
MRA	Finerenone	28	£36.68	2	£956.96	20mg once daily (CKD), 20mg or 40mg daily FINEARTS-HF trial dosage, cost based on 40mg	<b>[Off-label For HFpEF.]</b> Chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes [if serum-potassium ≤5 mmol/L and eGFR ≥60 mL/min/1.73 m <sup>2</sup> ]
SGLT2i	Dapagliflozin	28	£36.59	1	£477.30	10mg once daily.	Symptomatic chronic heart failure
SGLT2i	Empagliflozin	28	£36.59	1	£477.30	10mg once daily.	Symptomatic chronic heart failure

MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

In the absence of economic evidence, given there are differences in resource use in titration between treatments the resource use associated with titration and one year of treatment has been estimated to allow potential resource implications of any recommendation to be taken into consideration. The committee provided feedback on the expected resource use for treatment titration for each medicine in order to estimate the expected annual costs associated with treatment, to review alongside the health benefits identified in the effectiveness review. Resource use expected during the titration phase of treatment was collected based on the feedback of three GPs and four nurses. The total annual costs of treatments based on the mode (the most common response), minimum and maximum number of visits based on the responses collected are presented in Table 8. In addition to the costs presented below it is anticipated that tests for renal function and electrolytes would be undertaken for all treatments at baseline, after initiation and after dose step up for all treatments and then every 6 months for treatment initiation and for each step up of treatment.

It is assumed that:

- MRAs are initiated by a GP (assuming a duration of 15 minutes) at a cost of £74.10 (PSSRU 2023)
- SGLT2 inhibitors are initiated at a cardiology outpatient appointment at a cost of £186 (NHS National cost collection 2023/24)
- All other visits are by a Band 7 nurse assuming a cost of £37 based on a 30-minute visit (PSSRU 2023)

In addition to the costs presented below, it was anticipated that tests for renal function and electrolytes would be undertaken for all treatments at baseline, after initiation and after each dose increase. These tests would then be repeated every 6 months, or every 3 months for people with chronic kidney disease (CKD), following treatment initiation and each subsequent dose increase.

**Table 8: Annual costs associated with treatment and titration**

Drug class	Drug name	Cost per year at max dose	Total number of visits for titration Mode (min, max)	Total cost of visit Mode (min, max)	Total annual costs Mode (min, max)
MRA	Spironolactone	£38.35	3 (2, 3)	£148 (£111, £148)	£186 (£149, £186)
MRA	Finerenone	£956.96	3 (2, 3)	£148 (£111, £148)	£1105 (£1068, £1105)
SGLT2i	Dapagliflozin	£477.30	2 (1, 2)	£223 (£186, £223)	£700 (£663, £700)
SGLT2i	Empagliflozin	£477.30	2 (1, 2)	£223 (£186, £223)	£700 (£663, £700)

MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

### 1.1.12 The committee's discussion and interpretation of the evidence

#### The outcomes that matter most

The Committee considered all-cause mortality, cardiovascular mortality, health-related quality of life, heart failure-related hospitalisation or visits (or all-cause hospitalisation or visits if heart failure-related hospitalisation was not reported), withdrawal due to drug-related events, acute kidney injury, hyperkalaemia, and gynaecomastia. For the purpose of decision making, all outcomes were rated as critical. For the current review, there were no available outcome data for hyponatraemia and falls.

All-cause mortality, cardiovascular mortality, and heart failure-related hospitalisation or visits were preferred as time-to-event outcomes when reported in papers. However, the dichotomous data for these were also included, but downgraded for indirectness.

In the case of health-related quality of life measures using the Kansas City Cardiomyopathy Questionnaire overall summary scores, standard deviation values for the change scores were imputed. Whereas for the Kansas City Cardiomyopathy Questionnaire clinical summary scores, the change scores were calculated from reported baseline and final values.

### **The quality of the evidence**

Using the GRADE criteria, the outcomes had certainty ratings ranging from high to very low. Common reasons for downgrading the certainty ratings included imprecision and risk of bias due to limited allocation reporting, potential problems with the randomisation process, and unexplained deviations from the trial protocol.

The committee commented on concerns about the quality of evidence from the TOPCAT trial as issues have been previously noted about substantial regional differences in patients recruited in the Russia/Georgia region, amongst whom there were very few patients admitted to hospital, raising concerns about whether they truly had heart failure (see other factors the committee took into account).

A sensitivity analysis was performed to investigate whether limiting to adults with chronic heart failure and preserved ejection fraction at a strict threshold of LVEF  $\geq 50\%$  altered the results compared to using the overall population from the TOPCAT trial, which was used for the primary analysis.

There were no noted issues identified with heterogeneity among the outcomes of interest.

### **Benefits and harms**

#### **Overall analysis results**

The primary comparison presented in the evidence was the grouping of all mineralocorticoid receptor antagonists (MRAs) compared to placebo.

The committee noted a potential benefit for reduced all-cause and cardiovascular mortality, but the size of these benefits alone was not sufficient to recommend the use of MRAs in this population. However, the clinically important benefit of reduced heart failure-related hospitalisation (23% reduction in time-to-first event data, and 25 fewer heart failure hospitalisations per 1000 people over 1.8 years) added more certainty to the overall body of evidence suggesting a benefit of MRAs. The committee agreed that this outcome is important to patients and can be an indicator of prognosis and health status and can have negative consequences, especially in older people. Therefore, avoiding admissions was agreed to be very valuable.

Most quality of life outcomes, including the Minnesota Living with Heart Failure measure, the Kansas City Cardiomyopathy Questionnaire (overall summary score and total symptom score), EQ-VAS, and SF-36, demonstrated no clinically important difference with the addition of MRAs. The Kansas City Cardiomyopathy Questionnaire clinical summary score showed a clinically important benefit favouring placebo in a single small RCT.

The committee discussed the risk of harm from MRA use. The evidence demonstrated an increased risk for the development of hyperkalaemia, which was agreed to require careful monitoring and management, including changing the dose or stopping the administration of MRA as appropriate based on the potassium levels. However, the committee agreed that it was possible to manage this risk, and it should not preclude a recommendation for MRAs in this population. The evidence also suggested that gynaecomastia or breast enlargement and

tenderness may be associated specifically with spironolactone use. However, this adverse event was agreed not to be severe enough to cease MRA treatment for HFpEF in most cases. As gynaecomastia or breast enlargement or tenderness is only associated with spironolactone, finerenone could be considered as an alternative option. The cost-effectiveness of finerenone for treating heart failure with preserved or mildly reduced ejection fraction will be formally assessed by NICE later in 2025.!

### **Sensitivity analysis results**

Regarding the TOPCAT trial, the most robust results are from the overall study population, including all randomised participants. As over 80% of the trial population meets the protocol definition of HFpEF, the full trial results have been used for the primary analysis. The subgroup with LVEF  $\geq 50\%$ , strictly matching our protocol HFpEF definition, was analysed in a sensitivity analysis.

Data were available for this subgroup for the outcomes of all-cause mortality, cardiovascular mortality, and heart failure-related hospitalisation and were combined with data from other trials. The pooled estimates using the TOPCAT subgroup with LVEF  $\geq 50\%$  did not differ meaningfully from the pooled estimates using the full TOPCAT cohort, which increased the committee's confidence in the applicability of the findings from the primary analysis.

### **Summary**

The committee concluded that there was sufficient evidence to support a recommendation for the use of MRAs in adults with chronic heart failure and HFpEF based largely on the evidence of reduced heart failure-related hospitalisation, alongside an adverse event profile that was not severe enough to outweigh this benefit. However, due to the limited size of the evidence base, this was deemed insufficient to support an 'offer' level recommendation. and a 'consider' recommendation was agreed upon. Clinical judgement is important when selecting individual medicines to use within this class, including consideration of differences in side effect profiles.

### **Cost effectiveness and resource use**

No published economic evidence was available for the committee to review. This question was not prioritised for original modelling. The committee considered the balance between the costs and benefits of MRAs.

The only MRA licenced for this subpopulation at the time of writing is spironolactone. This is a generic medicine with a low acquisition cost. Even when accounting for titration and monitoring costs, the overall cost would be considerably lower than that of dapagliflozin and empagliflozin, which are the only other treatment options recommended by NICE for this population ([TA902](#) and [TA929](#)). Given that spironolactone is both a low cost treatment and likely to reduce the rate of hospitalisation and improved survival, it is likely to be a cost-effective treatment option. An original economic analysis was conducted that showed that spironolactone is likely to be highly cost-effective compared with no medicine using the trial evidence in people with preserved ejection fraction. This analysis is tentative, as some of the parameters came from a reduced ejection fraction population including demographics and longer-term outcomes.

The rest of the clinical evidence was for finerenone which is expected to have a more favourable side effect profile than spironolactone. The cost-effectiveness of finerenone for treating heart failure with preserved or mildly reduced ejection fraction will be formally assessed by NICE later in 2025.

Overall, the committee considered that this recommendation will expand the population treated with an MRA. Some patients with HFpEF will have been given an MRA with diuretic therapy for symptoms (eg hypertension or hypokalaemia) but it is expected that this

recommendation will cause a shift to more MRA prescribing in this group as standard care rather than an add-on if required. Given the low cost of the only MRA currently licenced in this population, spironolactone, this is not likely to represent a significant cost impact to the NHS.

### **Other factors the committee took into account**

The Committee emphasised the importance of excluding alternative diagnoses such as pre-capillary pulmonary hypertension or hypertrophic cardiomyopathy, which would benefit from an alternative treatment pathway. It is also important in ascertaining the diagnosis that corroborating factors indicative of chronic heart failure, such as elevated natriuretic peptides and structural heart abnormalities are sought and confirmed.

The committee noted that heart failure with preserved ejection fraction is a heterogenous syndrome and uncertainties exist regarding the diagnostic criteria.

The committee noted the importance of treating both cardiovascular and non-cardiovascular comorbidities, as well as signs and symptoms of heart failure. A frailty assessment may also be considered.

Dapagliflozin and empagliflozin should be offered in accordance with the NICE technology appraisals ([TA902](#) and [TA929](#)).

It was acknowledged that MRAs can be initiated in primary care but that the workload associated with monitoring for hyperkalaemia can be quite demanding and can also be a burden for patients, having to access blood test services frequently.

The committee discussed the widely-reported regional differences in outcomes from the TOPCAT trial. It was agreed that the risk of bias associated with a post hoc analysis (limiting to the Americas cohort) not linked to our agreed review protocol that excluded approximately 50% of the original trial cohort was too great to be used as a basis for NICE guideline recommendations when other data are available. However, the limitations of evidence from this trial were acknowledged, including that in the Russia/Georgia cohort all clinical event rates were markedly lower, and there was no detectable impact of spironolactone on any outcomes unlike in the Americas cohort where spironolactone did reduce mortality and hospitalisation. The committee agreed that the patients enrolled from Russia/Georgia did not reflect the morbidity and mortality rates that would be expected for people with symptomatic chronic heart failure and so their confidence in the evidence from this trial was reduced and they understood that the effect estimates may reduce the apparent benefit of MRAs when pooled with other trial data.

### **1.1.13 Recommendations supported by this evidence review**

This evidence review supports recommendation 1.5.4.

### **1.1.14 References**

#### **1.1.14.1 Clinical**

[Desai, Akshay S, Lewis, Eldrin F, Li, Rebecca et al. \(2011\) Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. American heart journal 162\(6\): 966-972e10](#)

[Desai, Akshay S, Liu, Jiankang, Pfeffer, Marc A et al. \(2018\) Incident Hyperkalemia, Hypokalemia, and Clinical Outcomes During Spironolactone Treatment of Heart Failure With Preserved Ejection Fraction: Analysis of the TOPCAT Trial. Journal of cardiac failure 24\(5\): 313-320](#)

[Docherty, Kieran F, Henderson, Alasdair D, Jhund, Pardeep S et al. \(2024\) Efficacy and Safety of Finerenone Across the Ejection Fraction Spectrum in Heart Failure with Mildly Reduced and Preserved Ejection Fraction: a Prespecified Analysis of The FINEARTS-HF Trial. Circulation](#)

[Edelmann, Frank, Schmidt, Albrecht G, Gelbrich, Gotz et al. \(2010\) Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure \(Aldo-DHF\). European journal of heart failure 12\(8\): 874-82](#)

[Edelmann, Frank, Wachter, Rolf, Schmidt, Albrecht G et al. \(2013\) Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 309\(8\): 781-91](#)

Kurrelmeyer KM, Ashton Y, Xu J EA (2014) Effects of spironolactone treatment in elderly women with heart failure and preserved left ventricular ejection fraction. Journal of Cardiac Failure : 560-8

[Lewis, Eldrin F, Kim, Hae-Young, Claggett, Brian et al. \(2016\) Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial. Circulation. Heart failure 9\(3\): e001937](#)

Mottram PM, Haluska B, Leano R EA (2004) Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. Circulation : 558-65

[Pitt, Bertram, Pfeffer, Marc A, Assmann, Susan F et al. \(2014\) Spironolactone for heart failure with preserved ejection fraction. The New England journal of medicine 370\(15\): 1383-92](#)

[Shah, Sanjiv J, Heitner, John F, Sweitzer, Nancy K et al. \(2013\) Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circulation. Heart failure 6\(2\): 184-92](#)

[Solomon, Scott D, Claggett, Brian, Lewis, Eldrin F et al. \(2016\) Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. European heart journal 37\(5\): 455-62](#)

[Solomon, Scott D, McMurray, John J V, Vaduganathan, Muthiah et al. \(2024\) Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. The New England journal of medicine 391\(16\): 1475-1485](#)

[Upadhyaya, B, Hundley, WG, Brubaker, PH et al. \(2017\) Effect of Spironolactone on Exercise Tolerance and Arterial Function in Older Adults with Heart Failure with Preserved Ejection Fraction. Journal of the American Geriatrics Society 65\(11\): 2374-2382](#)

#### **1.1.14.2 Economic**

No Economic studies were included for this review question.

#### **1.1.14.3 Other**

NHS England (2024) National Schedule of NHS Costs Year: 2023-24. Available from: <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>

NHS Business service authority (2025) Drug Tariff. Available at: <https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff>

Personal Social Services Research Unit. Unit Costs of Health and Social Care 2023. Published online 2024. Available from: <https://www.pssru.ac.uk/unitcostsreport/>

# Appendices

## Appendix A Review protocols

### A.1 Review protocol for mineralocorticoid receptor antagonist therapy for chronic heart failure with preserved ejection fraction

Field	Content
Review title	Mineralocorticoid receptor antagonist (MRA) therapy for chronic heart failure with preserved ejection fraction (HFpEF)
Review question	What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists (finerenone, and spironolactone) in people with chronic heart failure with preserved ejection fraction?
Objective	To review evidence on MRA therapy in patients with HFpEF as a basis for new recommendations on this class of drug for HFpEF patients.
Searches	<p>The following databases will be searched:</p> <ul style="list-style-type: none"><li>• Cochrane Central Register of Controlled Trials (CENTRAL)</li><li>• Cochrane Database of Systematic Reviews (CDSR)</li><li>• Embase</li><li>• MEDLINE</li><li>• Epistemonikos</li></ul> <p>Searches will be restricted by:</p> <ul style="list-style-type: none"><li>• Date limitations – from date of searches in 2018 update; 6th December 2017</li><li>• English language studies</li><li>• Human studies</li></ul> <p>Other searches: Inclusion lists of relevant systematic reviews</p>

Field	Content
	<p>As this is a short update the searches will not be re-run. Committee members will be asked to identify any trials they are aware of that may be published after the search date, and the publication status of these will be checked later in development. NICE evidence surveillance is also active on this topic suite, so any new trials with the potential for a substantial impact on the guideline due to possible requirements to change recommendations, can also be included. Any evidence identified by surveillance that does not have a substantial impact will be added in future update. The full search strategies will be published in the final review.</p> <p>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).</p> <p>Key paper: Solomon SD et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. <i>N Engl J Med.</i> 2024 Oct 24;391(16):1475-1485.</p>
Condition or domain being studied	Chronic heart failure with preserved ejection fraction.
Population	<p><b>Inclusion:</b> Adults diagnosed with heart failure due to left ventricular dysfunction with preserved ejection fraction. Preserved ejection fraction CHF is defined as LVEF <math>\geq 50\%</math> plus a structural issue in the heart including two or more of the following:</p> <ul style="list-style-type: none"> <li>• Left atrial volume <math>&gt; 34</math> ml/m<sup>2</sup> in sinus rhythm, or <math>&gt;40</math> ml/m<sup>2</sup> in atrial fibrillation</li> <li>• Ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E:e') <math>&gt;11</math></li> <li>• Left ventricular hypertrophy (<math>&gt;12</math> mm wall thickness),</li> <li>• Pulmonary arterial pressure <math>&gt;35</math> mmHg</li> </ul> <p>Diagnosis should be made by a heart failure specialist or heart failure specialist team.</p> <p>Studies including an indirect population (for example mixed HFmrEF and HFpEF) will only be included if <math>\geq 80\%</math> match the protocol criteria or there are subgroup data for the protocol population.</p> <p><b>Exclusion:</b></p> <ul style="list-style-type: none"> <li>• Children</li> <li>• Acute heart failure in hospital</li> <li>• Heart failure with reduced or mildly reduced EF</li> <li>• Heart failure due to right heart dysfunction (e.g., pre-capillary pulmonary hypertension and primary right ventricular cardiomyopathies)</li> <li>• High output heart failure</li> </ul>

Field	Content
	<ul style="list-style-type: none"> <li>• Adult congenital heart disease</li> <li>• Primary heart valve disease</li> <li>• Acute MI (within 3 months of the event)</li> <li>• Treatment with chemotherapy</li> </ul>
Intervention	<p><b>Inclusion:</b> Mineralocorticoid receptor antagonists (spironolactone and finerenone)</p> <p><b>Mode of delivery:</b> oral</p> <p><b>Analysis groupings:</b> a class effect will be assumed and all agents and doses within a class will be pooled.</p> <p>Background/concomitant treatment: studies in which participants are also receiving other pharmacological agents as background therapy (balanced between the randomised groups) will be included. This may include, for example, diuretics, statins, anticoagulants, and anti-arrhythmic agents, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan), angiotensin receptor antagonist / blocker (ARB), beta-adrenergic antagonist/blockers and SGLT2 inhibitors.</p> <p>[Eplerenone was removed as an included intervention because it is specifically licensed for CHF with reduced ejection fraction]</p>
Comparator	Placebo + usual CHF care or usual CHF care alone
Types of study to be included	<p><b>Inclusion:</b></p> <ul style="list-style-type: none"> <li>• RCTs</li> <li>• Published systematic reviews of RCTs</li> <li>• Published individual participant data meta-analyses (IPDs).</li> </ul> <p><b>Exclusion:</b></p> <ul style="list-style-type: none"> <li>• Cross-over RCTs</li> <li>• Non-randomised studies</li> </ul>

Field	Content
	Note: Post hoc subgroup analyses from RCTs may have to be considered for inclusion if there is insufficient evidence from prespecified analyses based on GC discussion.
Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available
Context	This review will partially update NICE guideline NG106.
Primary outcomes (critical outcomes)	<p>All outcomes are considered equally important for decision making and therefore have all been rated as critical:</p> <ul style="list-style-type: none"> <li>• All-cause mortality (time-to-event)</li> <li>• Cardiovascular mortality (time-to-event)</li> <li>• Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value)</li> <li>• Unplanned hospitalisation or visits (HF-related) (time-to-event; including repeat events when reported)</li> <li>• all cause unplanned hospitalisation or visits will be included if HF-related is not reported in a study, but this will be downgraded for outcome indirectness</li> </ul> <p>Adverse events (recorded as the number of people with at least one event, not the total number of events)</p> <ul style="list-style-type: none"> <li>• Withdrawal due to drug-related adverse events (dichotomous)</li> <li>• Acute Kidney Injury – serum creatinine rise of <math>\geq 50\%</math> over <math>\leq 7</math> days (dichotomous)</li> <li>• Hyponatraemia – serum sodium concentration <math>&lt; 135</math> mmol/L (dichotomous)</li> <li>• Hyperkalaemia – serum potassium concentration <math>\geq 5.5</math> mmol/L (dichotomous)</li> <li>• Falls – (dichotomous)</li> <li>• Gynaecomastia (dichotomous)</li> </ul> <p>Time points for analysis: 12 months (pool all times <math>\geq 3</math> months, taking the closest to 12 months follow-up time from each study if multiple time points are reported) Exclude if follow-up <math>&lt; 3</math> months</p> <p>The COMET database was searched for relevant core outcome sets and one consensus document published in 2013 was identified, which was used to inform the GC discussions on protocol outcomes (<a href="https://onlinelibrary.wiley.com/doi/epdf/10.1093/eurjhf/hft095">https://onlinelibrary.wiley.com/doi/epdf/10.1093/eurjhf/hft095</a>).</p>

Field	Content
	<p>Indirect outcome definitions</p> <p>If continuous data are not available, dichotomous outcome data for quality of life scales will be accepted but downgraded for outcome indirectness. For KCCQ this should be based on the threshold of an improvement of 5 points, which is the accepted MID. Only one threshold will be reported per study.</p> <p>Adverse events that are similar to the protocol definitions will be considered for inclusion and, if sufficiently similar, will be included but downgraded for outcome indirectness.</p>
<p>Data extraction (selection and coding)</p>	<p>EndNote will be used for reference management, sifting, citations and bibliographies.</p> <p>All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.</p> <p>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see <a href="#">Developing NICE guidelines: the manual</a> section 6.4).</p> <p>10% of all evidence reviews are quality assured by a senior technical analyst. This includes checking:</p> <ul style="list-style-type: none"> <li>• papers were included /excluded appropriately</li> <li>• a sample of the data extractions</li> <li>• correct methods are used to synthesise data</li> <li>• a sample of the risk of bias assessments</li> </ul> <p>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.</p>
<p>Risk of bias (quality) assessment</p>	<p>Risk of bias will be assessed using the appropriate checklist as described in <a href="#">Developing NICE guidelines: the manual</a>.</p> <ul style="list-style-type: none"> <li>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)</li> <li>• Randomised Controlled Trial: Cochrane RoB (2.0)</li> </ul>

Field	Content										
Strategy for data synthesis	<ul style="list-style-type: none"> <li>• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences.</li> <li>• For time-to-event outcomes, if sufficient information is provided, hazard ratios will be reported but dichotomous data will also be extracted. Only one measure will be considered for decision making. This will be agreed with the committee taking into account the proportion of studies that report sufficient data to calculate the risk ratio and the hazard ratio, in order to maximise the available pooled data. If there are differences in effect estimates between the two measures, potential reasons for this will be considered in the interpretation of the evidence.</li> <li>• Heterogeneity between the studies in effect measures will be assessed using the I<sup>2</sup> statistic and visually inspected. An I<sup>2</sup> value greater than 40% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.</li> <li>• GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome.</li> <li>• The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a></li> <li>• Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.</li> </ul>										
Analysis of sub-groups	<p><b>Subgroups that will be investigated if heterogeneity is present:</b></p> <ul style="list-style-type: none"> <li>• Renal function (eGFR &lt;30mL/min; eGFR 30-60mL/min; eGFR &gt;60mL/min)</li> <li>• Presence or absence of type 2 diabetes</li> <li>• MRA type (steroidal and non-steroidal)</li> </ul>										
Type and method of review	<table border="0"> <tr> <td><input checked="" type="checkbox"/></td> <td>Intervention</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Diagnostic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Prognostic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Qualitative</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Epidemiologic</td> </tr> </table>	<input checked="" type="checkbox"/>	Intervention	<input type="checkbox"/>	Diagnostic	<input type="checkbox"/>	Prognostic	<input type="checkbox"/>	Qualitative	<input type="checkbox"/>	Epidemiologic
<input checked="" type="checkbox"/>	Intervention										
<input type="checkbox"/>	Diagnostic										
<input type="checkbox"/>	Prognostic										
<input type="checkbox"/>	Qualitative										
<input type="checkbox"/>	Epidemiologic										

Field	Content		
	<input type="checkbox"/>	Service Delivery	
	<input type="checkbox"/>	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	October 2024		
Anticipated completion date	September 2025		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Piloting of the study selection process	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Formal screening of search results against eligibility criteria	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Data extraction	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Risk of bias (quality) assessment	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Data analysis	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Named contact	5a. Named contact Guideline Development Team NGC		
	5b Named contact e-mail chfiatreatment@nice.org.uk		

Field	Content
	5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
Review team members	From NICE: Dr Sharon Swain Mrs Eleanor Samarasekera Dr Lisa Miles Ms Annette Chalker Mr David Wonderling Mr Alfredo Mariani Ms Kirsty Luckham Ms Jemma Deane Mr Daniel Davies
Funding sources/sponsor	Development of this systematic review is being funded by NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of <a href="#">Developing NICE guidelines: the manual</a> . Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
Other registration details	NA
Reference/URL for published protocol	NA
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

Field	Content
	notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Heart failure; pharmacological; mineralocorticoid receptor antagonists.
Details of existing review of same topic by same authors	NA
Current review status	<input type="checkbox"/> Ongoing <input checked="" type="checkbox"/> Completed but not published <input type="checkbox"/> Completed and published <input type="checkbox"/> Completed, published and being updated <input type="checkbox"/> Discontinued
Additional information	N/A
Details of final publication	<a href="http://www.nice.org.uk">www.nice.org.uk</a>

CHF: Chronic heart failure; COMET: Core outcome measures in effectiveness trials; EF: Ejection fraction; eGFR: estimated glomerular filtration rate; EPPI: Evidence for Policy & Practice Information Centre; ESC: European society of cardiology; GC: guideline committee; LVEF: left ventricular ejection fraction; MI: Myocardial infarction MID: minimally important difference; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; SGLT2: Sodium-glucose co-transporter 2

## A.1 Health economic review protocol

	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocol above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).

<b>All questions – health economic evidence</b>	
	<p>Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)</p> <p>Unpublished reports will not be considered unless submitted as part of a call for evidence.</p> <p>Studies must be in English.</p>
Search strategy	<p>A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated, the search will be run from December 2017, which was the cut-off date for the searches conducted for NICE guideline NG106.</p>
Review strategy	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2010, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.</p> <p>Studies published after 2010 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).{NICE2014}</p> <p><b>Inclusion and exclusion criteria</b></p> <p>If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’ then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.</p> <p>If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.</p> <p>If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.</p> <p><b>Where there is discretion</b></p> <p>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies</p>

	<b>All questions – health economic evidence</b>
	<p>excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.</p> <p>The health economist will be guided by the following hierarchies.</p> <p>Setting:</p> <ul style="list-style-type: none"> <li>UK NHS (most applicable).</li> <li>OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).</li> <li>OECD countries with predominantly private health insurance systems (for example, Switzerland).</li> </ul> <p>Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.</p> <p>Health economic study type:</p> <ul style="list-style-type: none"> <li>Cost–utility analysis (most applicable).</li> <li>Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).</li> <li>Comparative cost analysis.</li> </ul> <p>Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.</p> <p>Year of analysis:</p> <ul style="list-style-type: none"> <li>The more recent the study, the more applicable it will be.</li> <li>Studies published in 2010 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2010 will be rated as 'Not applicable'.</li> <li>Studies published before 2010 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.</li> </ul> <p>Quality and relevance of effectiveness data used in the health economic analysis:</p> <ul style="list-style-type: none"> <li>The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.</li> </ul>

## Appendix B Literature search strategies

What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists (eplerenone, finerenone, and spironolactone) in people with chronic heart failure with preserved ejection fraction?

### Background and development

#### Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review.

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. [PRESS 2015 Guideline Statement](#). *Journal of Clinical Epidemiology*, 75, 40-46).

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. [PRISMA-S](#). *Systematic Reviews*, 10(1), 39).

#### Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

#### Prior work

The search terms for the population and intervention were compared to the searches for previous NICE guidance ([NG106](#)). Modifications were made to these original search strategies for the specifications in the review protocol.

#### Search limits and other restrictions

##### Formats

Limits were applied in adherence to standard NICE practice (as set out in the [Identifying the evidence chapter](#) of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results

- Theses and dissertations
- Papers not published in the English language.

### **Date limits**

A date limit of 1<sup>st</sup> December 2017 to current was applied, as stated in the review protocol from when searches were conducted for [NG106](#).

### **Search filters and classifiers**

#### **Effectiveness searches**

The National Guideline Centre (NGC) systematic review and randomised controlled trial search filters were applied in MEDLINE and Embase.

#### **Cost effectiveness searches**

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

Glanville J et al. (2009) [Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE](#). Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

The National Guideline Centre (NGC) Quality of Life filter was applied in MEDLINE and Embase strategies.

### **Key decisions**

The effectiveness search strategy was developed to find evidence for the specified population and intervention.

The cost-effectiveness searches used population only terminology.

Searches were adapted to suit different database functionality and were re-run as originally written.

### **Effectiveness searches**

#### **Database results**

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	1 <sup>st</sup> November 2024	Wiley	Issue 11 of 12, November 2024	3
Cochrane Central Register of Controlled Trials (CENTRAL)	1 <sup>st</sup> November 2024	Wiley	Issue 10 of 12, October 2024	481
Embase	1 <sup>st</sup> November 2024	Ovid	<1974 to 2024 October 31>	1981
MEDLINE	1 <sup>st</sup> November 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to October 31, 2024>	600
Epistemonikos	1 <sup>st</sup> November 2024	<a href="#">Epistemonikos</a>	01/11/2024	14

### Re-run search results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	9 <sup>th</sup> January 2025	Wiley	Issue 1 of 12, January 2025	0
Cochrane Central Register of Controlled Trials (CENTRAL)	9 <sup>th</sup> January 2025	Wiley	Issue 12 of 12, December 2024	14
Embase	9 <sup>th</sup> January 2025	Ovid	<1974 to 2025 January 07>	78
MEDLINE	9 <sup>th</sup> January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 06, 2025>	40
Epistemonikos	9 <sup>th</sup> January 2025	<a href="#">Epistemonikos</a>	09/01/2025	0

### Search strategy history

#### Database name: Cochrane Database of Systematic Reviews (CDSR)

Searches	
ID	Search Hits

Searches		
#1	MeSH descriptor: [Heart Failure] explode all trees	14855
#2	MeSH descriptor: [Cardiomyopathy, Dilated] this term only	675
#3	MeSH descriptor: [Shock, Cardiogenic] this term only	497
#4	MeSH descriptor: [Ventricular Dysfunction] explode all trees	2938
#5	MeSH descriptor: [Cardiac Output, Low] this term only	458
#6	((heart or cardia* or cardio* or myocard* or ventric*) NEAR/2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")):ti	20210
#7	((congestive or acute or decompensat* or chronic or left) NEAR/2 "heart failure"):ti,ab	13946
#8	((cardia* or cardio*) NEAR/2 (renal or reno) NEAR/2 syndrome*):ti,ab	36
#9	(cardiorenal NEAR/2 syndrome*):ti,ab	135
#10	((cardiac or heart) NEAR/2 (edema* or oedema*)):ti,ab	148
#11	((dilated or congestive or idiopathic) NEAR/2 cardiomyopath*):ti,ab	1155
#12	((cardiogenic or cardiocirculatory) NEAR/2 (shock or collapse)):ti,ab	1400
#13	((("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) NEAR/2 (failure* or insufficien* or dysfunction*)):ti,ab	5664
#14	((("mid range" or mild* or minimal* or normal or preserved or reduced) NEAR/3 ("ejection fraction" or EF or LVEF)):ti,ab	5429
#15	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd):ti,ab	2745
#16	((low or subnormal or depressed) NEAR/2 (cardiac NEAR/2 output)):ti,ab	456
#17	(forward NEAR/2 failure*):ti,ab	9
#18	{OR #1-#17}	34535
#19	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees	954
#20	((mineralocorticoid* or aldosterone*) NEAR/2 (antagonist* or block* or inhibit*)):ti,ab	1814
#21	(aldactone* or spironolactone* or eplerenone* or inspra*):ti,ab	2488
#22	(finerenone* or kerendia*):ti,ab	214
#23	{OR #19-#22}	3873
#24	#18 AND #23	1382
#25	conference:pt or (clinicaltrials or trialsearch):so	789605
#26	#24 NOT #25 with Cochrane Library publication date Between Dec 2017 and Nov 2024, in Cochrane Reviews, Cochrane Protocols, Trials	484

### Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches		
ID	Search	Hits
#1	MeSH descriptor: [Heart Failure] explode all trees	14855
#2	MeSH descriptor: [Cardiomyopathy, Dilated] this term only	675
#3	MeSH descriptor: [Shock, Cardiogenic] this term only	497
#4	MeSH descriptor: [Ventricular Dysfunction] explode all trees	2938
#5	MeSH descriptor: [Cardiac Output, Low] this term only	458
#6	((heart or cardia* or cardio* or myocard* or ventric*) NEAR/2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")):ti	20210
#7	((congestive or acute or decompensat* or chronic or left) NEAR/2 "heart failure"):ti,ab	13946
#8	((cardia* or cardio*) NEAR/2 (renal or reno) NEAR/2 syndrome*):ti,ab	36

Searches	
#9	(cardiorenal NEAR/2 syndrome*):ti,ab 135
#10	((cardiac or heart) NEAR/2 (edema* or oedema*)):ti,ab 148
#11	((dilated or congestive or idiopathic) NEAR/2 cardiomyopath*):ti,ab 1155
#12	((cardiogenic or cardiocirculatory) NEAR/2 (shock or collapse)):ti,ab 1400
#13	("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) NEAR/2 (failure* or insufficien* or dysfunction*):ti,ab 5664
#14	("mid range" or mild* or minimal* or normal or preserved or reduced) NEAR/3 ("ejection fraction" or EF or LVEF):ti,ab 5429
#15	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd):ti,ab 2745
#16	((low or subnormal or depressed) NEAR/2 (cardiac NEAR/2 output)):ti,ab 456
#17	(forward NEAR/2 failure*):ti,ab 9
#18	{OR #1-#17} 34535
#19	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees 954
#20	((mineralocorticoid* or aldosterone*) NEAR/2 (antagonist* or block* or inhibit*)):ti,ab 1814
#21	(aldactone* or spironolactone* or eplerenone* or inspra*):ti,ab 2488
#22	(finerenone* or kerendia*):ti,ab 214
#23	{OR #19-#22} 3873
#24	#18 AND #23 1382
#25	conference:pt or (clinicaltrials or trialsearch):so 789605
#26	#24 NOT #25 with Cochrane Library publication date Between Dec 2017 and Nov 2024, in Cochrane Reviews, Cochrane Protocols, Trials 484

### Database name: Embase

Searches	
1	heart failure/ or acute heart failure/ or cardiogenic shock/ or cardiopulmonary insufficiency/ or cardiorenal syndrome/ or exp diastolic dysfunction/ or forward heart failure/ or exp systolic dysfunction/ 434174
2	exp congestive heart failure/ 134250
3	heart ventricle failure/ or exp heart left ventricle failure/ 43878
4	dilated cardiomyopathy/ 3239
5	((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 180422
6	((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 126896
7	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 761
8	(cardiorenal adj2 syndrome*).tw.2460
9	((cardiac or heart) adj2 (edema* or oedema*)).tw. 1671
10	((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw. 36476
11	((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw. 30980
12	("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw. 84405
13	((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw. 54521
14	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw. 21653
15	((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw. 6393
16	(forward adj2 failure*).tw. 129
17	or/1-16 646926

<b>Searches</b>		
18	exp mineralocorticoid antagonist/	112709
19	((mineralocorticoid* or aldosterone*) adj2 (antagonist* or block* or inhibit*).tw.	12712
20	(aldactone* or spironolactone* or eplerenone* or inspra*).tw.	14566
21	(finerenone* or kerendia*).tw.	711
22	or/18-21	117919
23	17 and 22	29505
24	random*.ti,ab.	2138572
25	factorial*.ti,ab.	50723
26	(crossover* or cross over*).ti,ab.	133243
27	((doubl* or singl*) adj blind*).ti,ab.	289427
28	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1347905
29	crossover procedure/	80219
30	single blind procedure/	56921
31	randomized controlled trial/	851675
32	double blind procedure/	225422
33	or/24-32	3139232
34	Systematic review/	494746
35	Meta-Analysis/	335609
36	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	411548
37	((systematic* or evidence*) adj3 (review* or overview*).ti,ab.	520867
38	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	72536
39	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	115813
40	(search* adj4 literature).ab.	141923
41	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	519352
42	cochrane.jw.	25487
43	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	7831
44	or/34-43	1060019
45	33 or 44	3883630
46	23 and 45	5652
47	limit 46 to english language	5437
48	Nonhuman/ not human/	5559343
49	47 not 48	5353
50	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	6052709
51	49 not 50	4444
52	(letter or editorial).pt.	2176300
53	51 not 52	4365
54	limit 53 to dc=20171201-20241101	1981

**Database name: MEDLINE**

<b>Searches</b>		
1	exp Heart Failure/	156793
2	Cardiomyopathy, Dilated/	17636
3	Shock, Cardiogenic/	11520

Searches		
4	exp Ventricular Dysfunction/	44833
5	Cardiac Output, Low/	5629
6	((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti.	118348
7	((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw.	78658
8	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw.	349
9	(cardiorenal adj2 syndrome*).tw.	1433
10	((cardiac or heart) adj2 (edema* or oedema*)).tw.	1264
11	((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw.	22891
12	((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw.	16498
13	("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*).tw.	45532
14	((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw.	25433
15	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw.	9733
16	((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw.	4189
17	(forward adj2 failure*).tw.	78
18	or/1-17	308296
19	exp Mineralocorticoid Receptor Antagonists/	10960
20	((mineralocorticoid* or aldosterone*) adj2 (antagonist* or block* or inhibit*)).tw.	8276
21	(aldactone* or spironolactone* or eplerenone* or inspra*).tw.	8063
22	(finerenone* or kerendia*).tw.	467
23	or/19-22	18337
24	18 and 23	4934
25	Randomized Controlled Trial/	624428
26	controlled clinical trial.pt.	95629
27	randomi#ed.ti,ab.	863168
28	placebo.ab.	253145
29	randomly.ti,ab.	446457
30	Clinical Trials as topic.sh.	203705
31	trial.ti.	321313
32	or/25-31	1700228
33	Meta-Analysis/	210854
34	exp Meta-Analysis as Topic/	31151
35	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	325375
36	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	435285
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	58947
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	96924
39	(search* adj4 literature).ab.	113616
40	(medline or pubmed or cochrane or embase or psychlit or psychlit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	427904
41	cochrane.jw.	16858
42	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	4231
43	or/33-42	800982

Searches			
44	32 or 43	2315785	
45	24 and 44	1485	
46	limit 45 to english language	1380	
47	animals/ not humans/	5238019	
48	46 not 47	1327	
49	limit 48 to (letter or historical article or comment or editorial or news or case reports)	47	
50	48 not 49	1280	
51	limit 50 to ed=20171201-20241101	517	
52	limit 50 to dt=20171201-20241101	549	
53	51 or 52	600	

### Database name: Epistemonikos

Searches	
Search 1	
title:("heart failure") AND title:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	1
abstract:("heart failure") AND abstract:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	5
Search 2	
title:(HFnEF OR HFmrEF OR HFpEF OR HFREF OR lvsd) AND title:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	0
abstract:(HFnEF OR HFmrEF OR HFpEF OR HFREF OR lvsd) AND abstract:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	0
Search 3	
title:("left ventricular" OR "left ventricle" OR lv OR systolic* OR diastolic*) AND title:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	0
abstract:("left ventricular" OR "left ventricle" OR lv OR systolic* OR diastolic*) AND abstract:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	8
Search 4	
title:("cardiorenal syndrome" OR "heart edema" OR "heart oedema") AND title:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	0
abstract:("cardiorenal syndrome" OR "heart edema" OR "heart oedema") AND abstract:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*)	0
Search 5	

<b>Searches</b>
<p>title:(cardiomyopath*) AND title:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*) 0</p> <p>abstract:(cardiomyopath*) AND abstract:(mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia*) 0</p> <p>14</p> <p>Limited from 2017-current; publication type: systematic review; Cochrane review: no; Systematic Review Question: interventions</p>

### Additional search methods

Studies identified in the previous update of this guideline and from systematic review reference lists were also added to the items retrieved.

### Cost-effectiveness searches

#### Database results – Economic Evaluations

<b>Databases</b>	<b>Date searched</b>	<b>Database platform</b>	<b>Database segment or version</b>	<b>No. of results downloaded</b>
Embase	12 <sup>th</sup> February 2024	Ovid	Embase <1974 to 2024 February 09>	4631
MEDLINE	12 <sup>th</sup> February 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to February 09, 2024>	1799
HTA	12 <sup>th</sup> February 2024	CRD	Up to 2018	8
NHS Economic Evaluation Database (NHS EED) (legacy database)	12 <sup>th</sup> February 2024	CRD	Up to 2015	0
INAHTA	12 <sup>th</sup> February 2024	<a href="#">INAHTA</a>	12/02/2024	91

#### Database results – Quality of Life

<b>Databases</b>	<b>Date searched</b>	<b>Database platform</b>	<b>Database segment or version</b>	<b>No. of results downloaded</b>
Embase	25 <sup>th</sup> July 2024	Ovid	Embase <1974 to 2024 July 24>	4213
MEDLINE	25 <sup>th</sup> July 2024	Ovid	Ovid MEDLINE(R)	2546

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
			ALL 1946 to July 24, 2024	

### Re-run search results – Economic Evaluations – Update 1

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	4 <sup>th</sup> December 2024	Ovid	Embase <1974 to 2024 December 03>	921
MEDLINE	4 <sup>th</sup> December 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to December 02, 2024>	273
INAHTA	4 <sup>th</sup> December 2024	<a href="#">INAHTA</a>	4/12/2024	25

HTA AND NHS EED are legacy databases and were not re-run due as no new records have been added

### Re-run search results – Economic Evaluations – Update 2

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	13 <sup>th</sup> January 2025	Ovid	Embase <1974 to 2025 January 10>	112
MEDLINE	13 <sup>th</sup> January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 10, 2025>	56
INAHTA	13 <sup>th</sup> January 2025	<a href="#">INAHTA</a>	13/01/2025	28

HTA AND NHS EED are legacy databases and were not re-run due as no new records have been added

**Re-run search results – Quality of Life – Update 1**

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	4 <sup>th</sup> December 2024	Ovid	Embase <1974 to 2024 December 03>	187
MEDLINE	4 <sup>th</sup> December 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to December 02, 2024>	104

**Re-run search results – Quality of Life – Update 2**

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	13 <sup>th</sup> January 2025	Ovid	Embase <1974 to 2025 January 10>	43
MEDLINE	13 <sup>th</sup> January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 10, 2025>	29

**Search strategy history****Database name: Embase economic evaluation**

Searches	
1	heart failure/ or acute heart failure/ or cardiogenic shock/ or cardiopulmonary insufficiency/ or cardiorenal syndrome/ or exp diastolic dysfunction/ or forward heart failure/ or exp systolic dysfunction/ 408023
2	exp congestive heart failure/ 127929
3	heart ventricle failure/ or exp heart left ventricle failure/ 42366
4	dilated cardiomyopathy/ 1707
5	((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 172522
6	((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 122466
7	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 732
8	(cardiorenal adj2 syndrome*).tw.2306
9	((cardiac or heart) adj2 (edema* or oedema*)).tw. 1605

Searches		
10	((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw.	35276
11	((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw.	28677
12	((("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw.	81493
13	((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw.	50358
14	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw.	19634
15	((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw.	6190
16	(forward adj2 failure*).tw.	126
17	or/1-16	613437
18	Health economics/	36277
19	exp health care cost/	348767
20	exp Fee/	44635
21	exp Budget/	34309
22	Funding/	81371
23	budget*.ti,ab.	48615
24	cost*.ti.	198234
25	(economic* or pharmaco?economic*).ti.	78306
26	(price* or pricing*).ti,ab.	75356
27	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	296991
28	(financ* or fee or fees).ti,ab.	234068
29	(value adj2 (money or monetary)).ti,ab.	4233
30	or/18-29	1088021
31	17 and 30	19541
32	limit 31 to english language	18944
33	Nonhuman/ not human/	5382202
34	32 not 33	18821
35	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5832293
36	34 not 35	12844
37	(letter or editorial).pt.	2103817
38	36 not 37	11605
39	limit 38 to dc=20171201-20240229	4631

#### Database name: Medline economic evaluation

Searches		
1	exp Heart Failure/	151655
2	Cardiomyopathy, Dilated/	17386
3	Shock, Cardiogenic/	11068
4	exp Ventricular Dysfunction/	43989
5	Cardiac Output, Low/	5620
6	((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti.	113028
7	((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw.	76267
8	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw.	339
9	(cardiorenal adj2 syndrome*).tw.	1334

Searches		
10	((cardiac or heart) adj2 (edema* or oedema*)).tw.	1229
11	((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw.	22225
12	((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw.	15449
13	("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*).tw.	44123
14	((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw.	23261
15	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw.	8567
16	((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw.	4107
17	(forward adj2 failure*).tw.	77
18	or/1-17	297032
19	Economics/	27523
20	Value of life/	5821
21	exp "Costs and Cost Analysis"/	268686
22	exp Economics, Hospital/	25795
23	exp Economics, Medical/	14419
24	Economics, Nursing/	4013
25	Economics, Pharmaceutical/	3125
26	exp "Fees and Charges"/	31453
27	exp Budgets/	14189
28	budget*.ti,ab.	36835
29	cost*.ti.	147915
30	(economic* or pharmaco?economic*).ti.	62859
31	(price* or pricing*).ti,ab.	55101
32	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	216581
33	(financ* or fee or fees).ti,ab.	166449
34	(value adj2 (money or monetary)).ti,ab.	3136
35	or/19-34	754861
36	18 and 35	5374
37	limit 36 to english language	5088
38	animals/ not humans/	5160739
39	37 not 38	5054
40	limit 39 to (letter or historical article or comment or editorial or news or case reports)	351
41	39 not 40	4703
42	limit 41 to ed=20171201-20240229	1516
43	limit 41 to dt=20171201-20240229	1616
44	42 or 43	1799

#### Database name: HTA economic evaluation

Searches		
Line	Search	Hits
1	MeSH DESCRIPTOR heart failure EXPLODE ALL TREES	832
2	MeSH DESCRIPTOR Cardiomyopathy, Dilated	23
3	MeSH DESCRIPTOR Shock, Cardiogenic	23
4	MeSH DESCRIPTOR Ventricular Dysfunction EXPLODE ALL TREES	165

Searches		
5	MeSH DESCRIPTOR Cardiac Output, Low	24
6	((((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or stand still))):TI	786
7	((((congestive or acute or decompensat* or chronic or left) adj2 heart failure))	741
8	((((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*))	1
9	((cardiorenal adj2 syndrome*))	0
10	((((cardiac or heart) adj2 (edema* or oedema*)))	2
11	((((dilated or congestive or idiopathic) adj2 cardiomyopath*))	48
12	((((cardiogenic or cardiocirculatory) adj2 (shock or collapse)))	78
13	((((left ventricular or left ventricle or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*))	203
14	((((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)))	52
15	((HFNEF or HFmrEF or HFpEF or HFrEF or lvsd))	21
16	((((low or subnormal or depressed) adj2 (cardiac adj2 output)))	23
17	((forward adj2 failure*))	0
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1516
19	* IN NHSEED	17613
20	#18 AND #19	434
21	* IN HTA	17351
22	#18 AND #21	260
23	* FROM 2017 TO 2024	506
24	#20 AND #23	0
25	#22 AND #23	8

#### Database name: INAHTA economic evaluation

Searches		
Line	Query	Hits
20	#19 AND #18	91
19	* FROM 2017 TO 2024	4504
18	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	411
17	(forward) AND (failure*)	4
16	(low or subnormal or depressed) AND (cardiac output)	6
15	(HFNEF or HFmrEF or HFpEF or HFrEF or lvsd)	4
14	(mid range or mild* or minimal* or normal or preserved or reduced) AND (ejection fraction or EF or LVEF)	30
13	("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) AND (failure* or insufficien* or dysfunction*)	88
12	(cardiogenic or cardiocirculatory) AND (shock or collapse)	19
11	(dilated or congestive or idiopathic) AND (cardiomyopath*)	15
10	(cardiac or heart) AND (edema* or oedema*)	11
9	(cardiorenal) AND (syndrome*)	0
8	(cardia* or cardio*) AND (renal or reno) AND (syndrome*)	3
7	(congestive or acute or decompensat* or chronic or left) AND ("heart failure")	220

Searches	
6	(heart or cardia* or cardio* or myocard* or ventric*)[Title] AND (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")[Title] 219
5	"Cardiac Output, Low"[mh] 3
4	"Ventricular Dysfunction"[mhe] 31
3	"Shock, Cardiogenic"[mh] 9
2	"Cardiomyopathy, Dilated"[mh] 5
1	"Heart Failure"[mhe] 222

### Database name: Embase Quality of Life

Searches	
1	heart failure/ or acute heart failure/ or cardiogenic shock/ or cardiopulmonary insufficiency/ or cardiorenal syndrome/ or exp diastolic dysfunction/ or forward heart failure/ or exp systolic dysfunction/ 425492
2	exp congestive heart failure/ 132098
3	heart ventricle failure/ or exp heart left ventricle failure/ 43359
4	dilated cardiomyopathy/ 2734
5	((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 177876
6	((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 125543
7	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 751
8	(cardiorenal adj2 syndrome*).tw.2413
9	((cardiac or heart) adj2 (edema* or oedema*)).tw. 1649
10	((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw. 36128
11	((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw. 30219
12	((("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw. 83514
13	((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw. 53242
14	(HF <sub>n</sub> EF or HF <sub>mr</sub> EF or HF <sub>p</sub> EF or HF <sub>r</sub> EF or lv <sub>sd</sub> ).tw. 20999
15	((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw. 6339
16	(forward adj2 failure*).tw. 129
17	or/1-16 636045
18	quality adjusted life year/ 38081
19	quality of life index/ 3307
20	short form 12/ or short form 20/ or short form 36/ or short form 8/ 53248
21	sickness impact profile/ 2414
22	(quality adj2 (wellbeing or well being)).ti,ab. 4300
23	sickness impact profile.ti,ab. 1252
24	disability adjusted life.ti,ab. 7479
25	(qal* or qtime* or qwb* or daly*).ti,ab. 37019
26	(euroqol* or eq5d* or eq 5*).ti,ab. 33319
27	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. 142937
28	(health utility* or utility score* or disutilit* or utility value*).ti,ab. 10493
29	(hui or hui1 or hui2 or hui3).ti,ab. 3375
30	(health* year* equivalent* or hye or hyes).ti,ab. 210
31	discrete choice*.ti,ab. 5215

Searches		
32	rosser.ti,ab.	145
33	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.	18387
34	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.	53543
35	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.	532
36	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.	13992
37	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.	1678
38	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.	5346
39	or/18-38	294233
40	17 and 39	7697
41	limit 40 to english language	7556
42	Nonhuman/ not human/	5499187
43	41 not 42	7515
44	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5991243
45	43 not 44	4363
46	(letter or editorial).pt.	2151720
47	45 not 46	4213

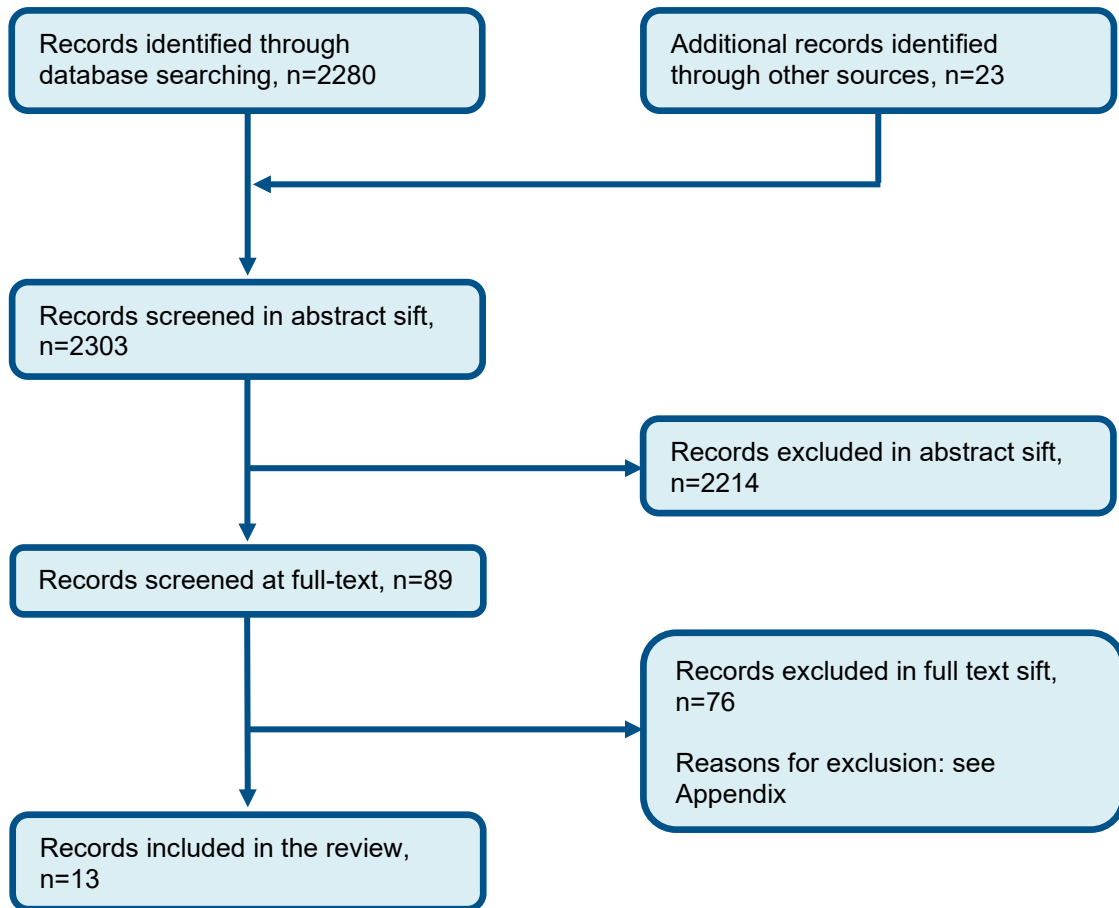
#### Database name: Medline Quality of Life

Searches		
1	exp Heart Failure/	154898
2	Cardiomyopathy, Dilated/	17552
3	Shock, Cardiogenic/	11354
4	exp Ventricular Dysfunction/	44539
5	Cardiac Output, Low/	5624
6	((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti.	116177
7	((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw.	77705
8	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw.	344
9	(cardiorenal adj2 syndrome*).tw.	1393
10	((cardiac or heart) adj2 (edema* or oedema*)).tw.	1245
11	((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw.	22625
12	((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw.	16063
13	("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*).tw.	44962
14	((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw.	24530
15	(HF <sub>n</sub> EF or HF <sub>m</sub> rEF or HF <sub>p</sub> EF or HF <sub>r</sub> EF or lv <sub>s</sub> d).tw.	9242
16	((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw.	4154
17	(forward adj2 failure*).tw.	78
18	or/1-17	303908
19	quality-adjusted life years/	16609
20	sickness impact profile/	7337
21	(quality adj2 (wellbeing or well being)).ti,ab.	3238
22	sickness impact profile.ti,ab.	1089
23	disability adjusted life.ti,ab.	6213

Searches		
24	(qal* or qtime* or qwb* or daly*).ti,ab.	21833
25	(euroqol* or eq5d* or eq 5*).ti,ab.	18468
26	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.	80463
27	(health utility* or utility score* or disutilit* or utility value*).ti,ab.	5869
28	(hui or hui1 or hui2 or hui3).ti,ab.	2105
29	(health* year* equivalent* or hye or hyes).ti,ab.	86
30	discrete choice*.ti,ab.	3659
31	rosser.ti,ab.	111
32	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.	12305
33	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.	32728
34	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.	458
35	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.	8739
36	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.	1004
37	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.	4065
38	or/19-37	171196
39	18 and 38	2674
40	limit 39 to english language	2588
41	animals/ not humans/	5207441
42	40 not 41	2582
43	limit 42 to (letter or historical article or comment or editorial or news or case reports)	36
44	42 not 43	2546

## Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of MRAs for heart failure with preserved ejection fraction



## Appendix D Effectiveness evidence

Desai, 2011

### Bibliographic Reference

Desai, Akshay S; Lewis, Eldrin F; Li, Rebecca; Solomon, Scott D; Assmann, Susan F; Boineau, Robin; Clausell, Nadine; Diaz, Rafael; Fleg, Jerome L; Gordeev, Ivan; McKinlay, Sonja; O'Meara, Eileen; Shaburishvili, Tamaz; Pitt, Bertram; Pfeffer, Marc A; Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction.; American heart journal; 2011; vol. 162 (no. 6); 966-972e10

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	Pitt, 2014 is the primary trial
<b>Other publications associated with this study included in review</b>	Solomon, 2016, Lewis, 2016, Desai, 2018, Pfeffer, 2015, and Shah, 2013
<b>Trial name / registration number</b>	TOPCAT/ NCT00094302
<b>Study setting</b>	266 centres in the United States, Canada, Russia, Republic of Georgia, Argentina, and Brazil
<b>Study dates</b>	Not specified

<b>Sources of funding</b>	the National Heart, Lung, and Blood Institute
<b>Inclusion criteria</b>	<p>Aged <math>\geq 50</math> years</p> <p>Heart failure signs and symptoms</p> <p>LVEF <math>\geq 45\%</math> confirmed within 6 months before randomisation</p> <p>Systolic blood pressure <math>&lt; 140</math> mm Hg or <math>\leq 160</math> mm Hg and on treatment with <math>\geq 3</math> antihypertensive medications</p> <p>Serum potassium <math>&lt; 5.0</math> mmol/L</p> <p>Hospitalisation for which management of heart failure was a major component within 1 year before randomisation or elevated natriuretic peptides within 60 days before randomisation (BNP <math>\geq 100</math> pg/mL or NT-proBNP <math>\geq 360</math> pg/mL)</p>
<b>Exclusion criteria</b>	<p>Severe systemic illness with life expectancy <math>&lt; 3</math> years from randomisation</p> <p>Severe chronic obstructive pulmonary disease (ie requiring home oxygen or chronic oral steroid therapy)</p> <p>Known restrictive/ infiltrative cardiomyopathy, hypertrophic cardiomyopathy or constrictive pericarditis.</p> <p>Hemodynamically significant valvular heart disease (ie valvular disease anticipated to require surgical correction during the trial)</p> <p>Atrial fibrillation with a resting heart rate <math>&gt; 90</math> beat/min</p> <p>Systolic blood pressure <math>&gt; 160</math> mm Hg</p> <p>History of hyperkalaemia (<math>\geq 5.5</math> mmol/L within the last 6 months or <math>\geq 5.0</math> mmol/L in the last 2 weeks)</p> <p>Severe renal dysfunction, defined as eGFR <math>&lt; 30</math> mL/min per <math>1.73\text{m}^2</math> or serum creatinine <math>\geq 2.5</math> mg/dL</p> <p>MI, coronary artery bypass graft surgery or stroke within 90 days before randomisation; percutaneous coronary intervention within 30 days before randomisation</p> <p>Use of aldosterone antagonist or potassium sparing diuretic within 14 days before randomisation</p>

<b>Recruitment / selection of participants</b>	Recruitment based on screening eligibility based on review of medical records by study staff at or before the baseline visit.
<b>Intervention(s)</b>	Spironolactone initiated at 15 mg once daily. All patients tolerating this dose without adverse effects are up-titrated to the target dose of 30 mg once daily. Additional up-titration to a maximum dose of 45 mg once daily is permitted at the site investigator's discretion on or after the 4-month visit.
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	Subgroup analysis will be conducted according to baseline characteristics including history of hospitalisation for HF within the year before randomisation, EF, age, gender, race, ethnicity, history of hypertension, history of diabetes, NYHA functional class, baseline systolic blood pressure, concomitant CV medications, pulse pressure, eGFR, body mass index, prior history of myocardial infarction, and geographic region.
<b>Number of participants</b>	3168 (as of 2 September 2011)
<b>Duration of follow-up</b>	Projected follow-up 3.75 years
<b>Indirectness</b>	None
<b>Method of analysis</b>	Intention-to-treat

Desai, 2018

**Bibliographic Reference** Desai, Akshay S; Liu, Jiankang; Pfeffer, Marc A; Claggett, Brian; Fleg, Jerome; Lewis, Eldrin F; McKinlay, Sonja; O'Meara, Eileen; Shah, Sanjiv J; Sweitzer, Nancy K; Solomon, Scott; Pitt, Bertram; Incident Hyperkalemia, Hypokalemia, and Clinical Outcomes During Spironolactone Treatment of Heart Failure With Preserved Ejection Fraction: Analysis of the TOPCAT Trial.; Journal of cardiac failure; 2018; vol. 24 (no. 5); 313-320

## Study details

<b>Secondary publication of another included study- see primary study for details</b>	See Pitt, 2014 (primary study)
<b>Other publications associated with this study included in review</b>	Solomon, 2016, Desai, 2011, Lewis, 2016, and Shah, 2013
<b>Trial name / registration number</b>	See Pitt, 2014
<b>Study location</b>	The Americas, Russia, and Georgia
<b>Additional comments</b>	Moderate hyperkalaemia ( $\geq 5.5$ mmol/l)

## Study arms

Spironolactone (N = 1722)

Placebo (N = 1723)

## Outcomes

### Dichotomous outcomes

Outcome	Spironolactone, , N = 1722	Placebo, , N = 1723
<b>Hyperkalaemia - The Americas</b>	n = 211 ; % = 23.8	n = 72 ; % = 8.2
No of events		
<b>Hyperkalaemia - Russia/ Georgia</b>	n = 97 ; % = 11.6	n = 75 ; % = 8.9
No of events		

### Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

#### Dichotomous outcomes: Hyperkalaemia: The Americas: Spironolactone versus Placebo at 3.3 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Docherty, 2024

**Bibliographic Reference** Docherty, Kieran F; Henderson, Alasdair D; Jhund, Pardeep S; Claggett, Brian L; Desai, Akshay S; Mueller, Katharina; Viswanathan, Prabhakar; Scalise, Andrea; Lam, Carolyn S P; Senni, Michele; Shah, Sanjiv J; Voors, Adriaan A; Zannad,

Faiez; Pitt, Bertram; Vaduganathan, Muthiah; Solomon, Scott D; McMurray, John Jv; Efficacy and Safety of Finerenone Across the Ejection Fraction Spectrum in Heart Failure with Mildly Reduced and Preserved Ejection Fraction: a Prespecified Analysis of The FINEARTS-HF Trial.; Circulation; 2024

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	Solomon, 2024
<b>Trial name / registration number</b>	FINEARTS-HF/ NCT04435626.
<b>Study location</b>	Asia, Eastern Europe, Western Europe, Oceania, North America, and Latin America (37 countries total)
<b>Study setting</b>	Trial centre
<b>Study dates</b>	14 September 2020 to 10 January 2023
<b>Sources of funding</b>	Bayer
<b>Inclusion criteria</b>	<p>Participants aged 40 years or older</p> <p>NYHA class II-IV</p> <p>Treatment with a diuretic for 30 days or longer before randomisation</p> <p>LVEF of <math>\geq 40\%</math> with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy) measured within 12 months of screening.</p>

	Elevated natriuretic peptide levels (NT-proBNP >300 pg/mL [or BNP >100 pg/mL] for patients in sinus rhythm or NT-proBNP >900 pg/mL [or BNP >300 pg/mL] for patients in atrial fibrillation), measured within 90 days in those with a recent worsening HF event within 90 days of randomization, or measured 30 days before randomization in those without a recent worsening heart failure event.
<b>Exclusion criteria</b>	eGFR <25 ml/min/1.73 m <sup>2</sup> , serum/plasma potassium >5.0 mmol/L at screening or randomization symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or randomization
<b>Recruitment / selection of participants</b>	Not specified
<b>Intervention(s)</b>	Finerenone was administered at a maximum dose of 20 mg or 40 mg once daily, depending on the baseline estimated glomerular filtration rate (eGFR).
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	LVEF status
<b>Number of participants</b>	5993 participants with LVEF data available (3821 with relevant LVEF status ≥50% used)
<b>Duration of follow-up</b>	32 months (12 months for KCCQ-TSS)
<b>Method of analysis</b>	Intention-to-treat
<b>Additional comments</b>	Patient totals: <ul style="list-style-type: none"> <li>LVEF 50-60% finerenone group = 1329</li> </ul>

- LVEF 50-60% placebo group = 1345
- LVEF >60% finerenone group= 575
- LVEF >60% placebo group = 572

## Study arms

Finerenone (N = 3003)

Finerenone was administered at a maximum dose of 20 mg or 40 mg once daily, depending on the baseline estimated glomerular filtration rate (eGFR).

Placebo (N = 2998)

Placebo

## Characteristics

Study-level characteristics

Characteristic	Study (N = 3821)
% Female	n = NA ; % = NA
Sample size	
% Female - LVEF $\geq$ 50 to <60%	n = 1368 ; % = 51.2
Sample size	
% Female - LVEF >60%	n = 679 ; % = 59.2

<b>Characteristic</b>	<b>Study (N = 3821)</b>
Sample size	
<b>Age</b>	NA (NA)
Mean (SD)	
<b>Age - LVEF <math>\geq</math>50 to &lt;60%</b>	73.3 (9.1)
Mean (SD)	
<b>Age - LVEF &gt;60%</b>	73.5 (9.2)
Mean (SD)	
<b>Ethnicity</b>	n = NA ; % = NA
Sample size	
<b>Ethnicity - Asian: LVEF <math>\geq</math>50 to &lt;60%:</b>	n = 359 ; % = 13.4
Sample size	
<b>Ethnicity - Asian: LVEF &gt;60%</b>	n = 205 ; % = 17.9
Sample size	
<b>Ethnicity - Black: LVEF <math>\geq</math>50 to &lt;60%</b>	n = 36 ; % = 1.3
Sample size	
<b>Ethnicity - Black: LVEF &gt;60%</b>	n = 29 ; % = 2.5
Sample size	

Characteristic	Study (N = 3821)
<b>Ethnicity - Other: LVEF <math>\geq</math>50 to &lt;60%</b> Sample size	n = 94 ; % = 3.5
<b>Ethnicity - Other: LVEF &gt;60%</b> Sample size	n = 30 ; % = 2.6
<b>Ethnicity - White: LVEF <math>\geq</math>50 to &lt;60%</b> Sample size	n = 2185 ; % = 81.7
<b>Ethnicity - White: LVEF &gt;60%</b> Sample size	n = 883 ; % = 77
<b>NYHA class</b> Sample size	n = NA ; % = NA
<b>NYHA class - Class II: LVEF <math>\geq</math>50 to &lt;60%</b> Sample size	n = 1828 ; % = 68.4
<b>NYHA class - Class II: LVEF &gt;60%</b> Sample size	n = 815 ; % = 71.1
<b>NYHA class - Class III/IV: LVEF <math>\geq</math>50 to &lt;60%</b> Sample size	n = 846 ; % = 31.6
<b>NYHA class - Class III/IV: LVEF &gt;60%</b>	n = 331 ; % = 28.9

<b>Characteristic</b>	<b>Study (N = 3821)</b>
Sample size	
<b>Type 2 diabetes</b>	n = NA ; % = NA
Sample size	
<b>Type 2 diabetes - LVEF <math>\geq</math>50 to &lt;60%</b>	n = 1097 ; % = 41
Sample size	
<b>Type 2 diabetes - LVEF &gt;60%</b>	n = 472 ; % = 41.2
Sample size	
<b>Atrial fibrillation</b>	n = NA ; % = NA
Sample size	
<b>Atrial fibrillation - LVEF <math>\geq</math>50 to &lt;60%</b>	n = 1099 ; % = 41.1
Sample size	
<b>Atrial fibrillation - LVEF &gt;60%</b>	n = 421 ; % = 36.7
Sample size	
<b>Previous heart failure hospitalisation</b>	n = NA ; % = NA
Sample size	
<b>Previous heart failure hospitalisation - LVEF <math>\geq</math>50 to &lt;60%</b>	n = 1582 ; % = 59.2
Sample size	

<b>Characteristic</b>	<b>Study (N = 3821)</b>
<b>Previous heart failure hospitalisation - LVEF &gt;60%</b> Sample size	n = 583 ; % = 50.8
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>)</b> Mean (SD)	NA (NA)
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>) - LVEF ≥50 to &lt;60%</b> Mean (SD)	61 (19.3)
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>) - LVEF &gt;60%</b> Mean (SD)	59.6 (19.4)
<b>Background (non-randomised) heart failure medications</b> Sample size	n = NA ; % = NA
<b>Background (non-randomised) heart failure medications - Beta blocker: LVEF ≥50 to &lt;60%</b> Sample size	n = 2242 ; % = 83.8
<b>Background (non-randomised) heart failure medications - Beta-blocker: LVEF &gt;60%</b> Sample size	n = 927 ; % = 80.8
<b>Background (non-randomised) heart failure medications - ACE inhibitor: LVEF ≥50 to &lt;60%</b> Sample size	n = 890 ; % = 33.3
<b>Background (non-randomised) heart failure medications - ACE inhibitor: LVEF &gt;60%</b>	n = 392 ; % = 34.2

Characteristic	Study (N = 3821)
Sample size	
<b>Background (non-randomised) heart failure medications - Angiotensin-receptor blockers: LVEF <math>\geq</math>50 to &lt;60%</b>	n = 1016 ; % = 38
Sample size	
<b>Background (non-randomised) heart failure medications - Angiotensin-receptor blocker: LVEF &gt;60%</b>	n = 465 ; % = 40.5
Sample size	
<b>Background (non-randomised) heart failure medications - ARNI: LVEF <math>\geq</math>50 to &lt;60%</b>	n = 145 ; % = 5.4
Sample size	
<b>Background (non-randomised) heart failure medications - ARNI: LVEF &gt;60%</b>	n = 27 ; % = 2.4
Sample size	
<b>Background (non-randomised) heart failure medications - SGLT2i: LVEF <math>\geq</math>50 to &lt;60%</b>	n = 366 ; % = 13.7
Sample size	
<b>Background (non-randomised) heart failure medications - SGLT2i: LVEF &gt;60%</b>	n = 113 ; % = 9.9
Sample size	
<b>Background (non-randomised) heart failure medications - Loop diuretic: LVEF <math>\geq</math>50 to &lt;60%</b>	n = 2318 ; % = 86.7
Sample size	
<b>Background (non-randomised) heart failure medications - Loop diuretic: LVEF &gt;60%</b>	n = 943 ; % = 82.2
Sample size	

## Outcomes

Study timepoints

Baseline

32 month

Hazard ratios and rate ratios

Outcome	Finerenone vs Placebo, 32 month, N2 = 1917, N1 = 1904
<b>All-cause mortality - LVEF <math>\geq</math>50 to &lt;60%</b> Finerenone n = 1329, placebo n = 1345 Hazard ratio/95% CI	0.85 (0.7 to 1.04) <sup>a</sup>
<b>All-cause mortality - LVEF &gt;60%</b> Finerenone n = 575, placebo n = 572 Hazard ratio/95% CI	1.0 (0.74 to 1.34) <sup>a</sup>
<b>Cardiovascular death - LVEF <math>\geq</math>50 to &lt;60%</b> Finerenone n = 1329, placebo n = 1345 Hazard ratio/95% CI	0.9 (0.67 to 1.2) <sup>a</sup>
<b>Cardiovascular death - LVEF &gt;60%</b> Finerenone n = 575, placebo n = 572	0.95 (0.61 to 1.46) <sup>a</sup>

Outcome	Finerenone vs Placebo, 32 month, N2 = 1917, N1 = 1904
Hazard ratio/95% CI	
<b>First worsening heart failure event - LVEF <math>\geq</math>50 to &lt;60%</b>	0.78 (0.65 to 0.94) <sup>a</sup>
Finerenone n = 1329, placebo n = 1345	
Hazard ratio/95% CI	
<b>First worsening heart failure event - LVEF &gt;60%</b>	0.69 (0.51 to 0.93) <sup>a</sup>
Finerenone n = 575, placebo n = 572	
Hazard ratio/95% CI	
<b>Heart failure-related hospitalisation (total events) - LVEF <math>\geq</math>50 to &lt;60%</b>	0.73 (0.59 to 0.91) <sup>a</sup>
Finerenone n = 1329, placebo n = 1345	
Rate ratio/95% CI	
<b>Heart failure-related hospitalisation (total events) – LVEF &gt;60%</b>	0.79 (0.57 to 1.09) <sup>a</sup>
Finerenone n = 575, placebo n = 572	
Rate ratio/95% CI	

<sup>a</sup>Hazard ratio or rate ratio adjusted for the following baseline variables: randomized treatment (finerenone or placebo), age, sex, estimated glomerular filtration rate, New York Heart Association (NYHA) functional class, heart rate, systolic blood pressure, body mass index, (log)NT-proBNP (N-terminal pro-B-type natriuretic peptide), and a history of type 2 diabetes, previous heart failure (HF) hospitalization, atrial fibrillation, or myocardial infarction

## Contrast outcomes

<b>Outcome</b>	<b>Finerenone vs Placebo, 12 month,</b>
<b>Kansas City Cardiomyopathy Questionnaire – total symptom score - LVEF ≥50 to &lt;60%</b>	1.37 (-0.07 to 2.82)
Mean difference in change from baseline	
Finerenone n = 1329, placebo n = 1345	
<b>Kansas City Cardiomyopathy Questionnaire – total symptom score - LVEF &gt;60%</b>	3.02 (0.91 to 5.14)
Mean difference in change from baseline	
Finerenone n = 575, placebo n = 572	

## Dichotomous outcomes

<b>Outcome</b>	<b>Finerenone, 32 month, N = 1904</b>	<b>Placebo, 32 month, N = 1917</b>
<b>All-cause mortality - LVEF ≥50 to &lt;60%</b>	n = 202 ; % = 15.2	n = 228 ; % = 17
Finerenone at 32 months, n=1329		
Placebo at 32 months, n=1345		
No of events		
<b>All-cause mortality - LVEF &gt;60%</b>	n = 96 ; % = 16.7	n = 93 ; % = 16.3
Finerenone at 32 months, n=575		
Placebo at 32 months, n=572		
No of events		

<b>Outcome</b>	<b>Finerenone, 32 month, N = 1904</b>	<b>Placebo, 32 month, N = 1917</b>
<b>Cardiovascular mortality - LVEF <math>\geq</math>50 to <math>&lt;</math>60%</b> Finerenone at 32 months, n=1329 Placebo at 32 months, n=1345 No of events	n = 93 ; % = 7	n = 96 ; % = 7.1
<b>Cardiovascular mortality - LVEF <math>\geq</math>60%</b> Finerenone at 32 months, n=575 Placebo at 32 months, n=572 No of events	n = 46 ; % = 8	n = 45 ; % = 7.9
<b>Discontinuation due to drug-related events - LVEF <math>\geq</math>50 to <math>&lt;</math>60%</b> Finerenone at 32 months, n=1323 Placebo at 32 months, n=1342 No of events	n = 43 ; % = 3.3	n = 38 ; % = 2.8
<b>Discontinuation due to drug-related events - LVEF <math>&gt;</math>60%</b> Finerenone at 32 months, n=572 Placebo at 32 months, n=571 No of events	n = 21 ; % = 3.7	n = 15 ; % = 2.6
<b>Potassium (<math>&gt;</math>5.5 mmol/l) - LVEF <math>\geq</math>50 to <math>&lt;</math>60%</b> Finerenone at 32 months, n=1275	n = 182 ; % = 14.3	n = 87 ; % = 6.7

<b>Outcome</b>	<b>Finerenone, 32 month, N = 1904</b>	<b>Placebo, 32 month, N = 1917</b>
Placebo at 32 months, n=1298 No of events		
<b>Potassium (&gt;5.5 mmol/l) - LVEF &gt;60%</b> Finerenone at 32 months, n=558 Placebo at 32 months, n=551 No of events	n = 70 ; % = 12.5	n = 35 ; % = 6.4
<b>Heart failure-related hospitalisation - LVEF ≥50 to &lt;60%</b> Finerenone at 32 months, n=1329 Placebo at 32 months, n=1345 No of events	n = 219; % = 16.5	n = 249; % = 18.5
<b>Heart failure-related hospitalisation - LVEF &gt;60%</b> Finerenone at 32 months, n=575 Placebo at 32 months, n=572 No of events	n = 85; % = 14.8	n = 105; % = 18.4

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Hazard ratios: All-cause mortality: LVEF≥50to<60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: All-cause mortality: LVEF>60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Cardiovascular death: LVEF≥50to<60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Cardiovascular death: LVEF>60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: First worsening heart failure event: LVEF ≥50 to <60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: First worsening heart failure event: LVEF>60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Heart failure-related hospitalisation (total events): LVEF $\geq$ 50 to <60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Heart failure-related hospitalisation (total events): LVEF>60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire – total symptom score: LVEF $\geq$ 50to<60%: Finerenone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire – total symptom score: LVEF>60%: Finerenone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Potassium (>5.5mmol/l): LVEF≥50to<60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Potassium (>5.5mmol/l): LVEF>60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Discontinuation due to drug-related events: LVEF≥50to<60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Discontinuation due to drug-related events: LVEF>60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: All-cause mortality: LVEF≥50to<60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Partially applicable <i>(outcome indirectness: reported as dichotomous) not time-to-event.</i>

Dichotomous outcomes: All-cause mortality: LVEF>60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns <i>(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)</i>
Overall bias and Directness	Overall Directness	Partially applicable <i>(outcome indirectness: reported as dichotomous)</i>

Dichotomous outcomes: Cardiovascular mortality: Cardiovascular mortality: LVEF $\geq$ 50to<60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns (LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)
Overall bias and Directness	Overall Directness	Partially applicable (outcome indirectness: reported as dichotomous)

Dichotomous outcomes: Cardiovascular mortality: Cardiovascular mortality: LVEF $\geq$ 60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns (LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)
Overall bias and Directness	Overall Directness	Partially applicable (outcome indirectness: reported as dichotomous)

Dichotomous outcomes: Heart failure-related hospitalisation: LVEF $\geq$ 50to<60%: Finerenone versus Placebo at 32 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)
Overall bias and Directness	Overall Directness	Partially applicable (outcome indirectness: reported as dichotomous)

Dichotomous outcomes: Heart failure-related hospitalisation: LVEF $\geq$ 60%: Finerenone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)
Overall bias and Directness	Overall Directness	Partially applicable (outcome indirectness: reported as dichotomous)

Edelmann, 2010

#### **Bibliographic Reference**

Edelmann, Frank; Schmidt, Albrecht G; Gelbrich, Gotz; Binder, Lutz; Herrmann-Lingen, Christoph; Halle, Martin; Hasenfuss, Gerd; Wachter, Rolf; Pieske, Burkert; Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure (Aldo-DHF).; European journal of heart failure; 2010; vol. 12 (no. 8); 874-82

#### **Study details**

<b>Secondary publication of another included study- see primary study for details</b>	Edelmann, 2013
<b>Other publications associated with this study included in review</b>	NA

<b>Trial name / registration number</b>	Aldo-DHF/ NCT00094302
<b>Study location</b>	Germany and Austria
<b>Study setting</b>	Study centres
<b>Study dates</b>	Not specified
<b>Sources of funding</b>	The Competence Network of Heart Failure funded by the Federal Ministry of Education and Research (BMBF), FKZ 01GI0205. Aldo-DHF is funded by the German Federal Ministry of Education and Research—Health Research (DLR Project Management Organizations).
<b>Inclusion criteria</b>	<p>Current heart failure symptoms consistent with NYHA classes II or III</p> <p>Left ventricular ejection fraction (LVEF) <math>\geq</math> 50% at rest</p> <p>Echocardiographic evidence of diastolic dysfunction (Grade <math>\geq</math> I) or atrial fibrillation</p> <p>Peak VO<sub>2</sub> <math>\leq</math> 25mL/kg/min</p> <p>Males and females aged <math>\geq</math> 50 years</p> <p>Written informed consent</p>
<b>Exclusion criteria</b>	<p>Prior documented systolic heart failure (LVEF <math>\leq</math> 40%)</p> <p>Significant coronary artery disease (current angina pectoris or ischaemia on stress tests; untreated coronary stenosis <math>\geq</math> 50%)</p> <p>Myocardial infarction or CABG within the last 3 months</p> <p>Definite or probable pulmonary disease (VC <math>\leq</math> 80% or FEV<sub>1</sub> <math>\leq</math> 80% of reference values on spirometry)</p> <p>Severe obesity (BMI <math>\geq</math> 36 kg/m<sup>2</sup>)</p>

	<p>Significant renal dysfunction (creatinine <math>\geq</math> 1.8 mg/dL)</p> <p>Significant hypotension (blood pressure <math>\leq</math> 90 mmHg systolic and/or <math>\leq</math> 50 mmHg diastolic)</p> <p>Mental disorders suspected to interact with study outcome</p> <p>Any patient characteristic that may interfere with adherence to the study protocol, such as dementia, substance abuse, history of non-compliance with prescribed medications, or medical appointments</p> <p>Significant laboratory abnormalities (potassium <math>\geq</math> 5.1 mmol/L; haemoglobin <math>\leq</math> 11g/dL, haematocrit <math>\leq</math> 33%)</p> <p>Changes in concomitant medication within the last 2 weeks prior to screening visit</p> <p>Known contraindications for spironolactone or prior documented intolerance to an aldosterone receptor antagonist</p> <p>Concomitant therapy with a potassium-sparing diuretic (e.g. triamterene, amiloride), potassium substitution, high-dose acetylsalicylic acid (.500 mg/d) or permanent intake of non-steroidal anti-inflammatory agents, digitalis</p> <p>Insulin-dependent diabetes mellitus with a history of ketoacidosis</p> <p>Suspected metabolic acidosis</p> <p>Pregnant or nursing women</p> <p>Women with child bearing potency without effective contraception (except for implants, hormonal depot injections, combined oral contraceptives, IUDs or vasectomized partner)</p> <p>Concomitant participation in other clinical trials</p> <p>Therapy with an aldosterone receptor antagonist within the last 3 months</p> <p>Participation in another clinical trial within the last 30 days</p>
<b>Recruitment / selection of participants</b>	Recruitment noted, but described in detail.
<b>Intervention(s)</b>	Spironolactone 25 mg once daily

<b>Comparator</b>	Placebo
<b>Population subgroups</b>	Patients with diastolic heart failure
<b>Number of participants</b>	Aiming to recruit 420 participants
<b>Duration of follow-up</b>	6, 12, and 18 months
<b>Indirectness</b>	None
<b>Method of analysis</b>	Primary analysis will be carried out by the Mann–Whitney U-test.

Edelmann, 2013

**Bibliographic Reference** Edelmann, Frank; Wachter, Rolf; Schmidt, Albrecht G; Kraigher-Krainer, Elisabeth; Colantonio, Caterina; Kamke, Wolfram; Duvinage, Andre; Stahrenberg, Raoul; Durstewitz, Kathleen; Loffler, Markus; Dungen, Hans-Dirk; Tschope, Carsten; Herrmann-Lingen, Christoph; Halle, Martin; Hasenfuss, Gerd; Gelbrich, Gotz; Pieske, Burkert; Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial.; JAMA; 2013; vol. 309 (no. 8); 781-91

Study details

<b>Secondary publication of another included</b>	NA
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<b>study- see primary study for details</b>	
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	Aldo-DHF/ ISRCTN94726526
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	Germany and Austria
<b>Study setting</b>	Trial centres
<b>Study dates</b>	March 2007 to April 2012
<b>Sources of funding</b>	This work was supported by the German-Austrian Heart Failure Study Group and the German Competence Network of Heart Failure. Aldo-DHF was funded by the Federal Ministry of Education and Research Grant 01GI0205 (clinical trial program Aldo-DHF [FKZ 01KG0506]). The University of Gottingen was the formal sponsor.
<b>Inclusion criteria</b>	Men and women aged 50 years or older Current heart failure symptoms consistent with NYHA class II or III LVEF of 50% or greater Echocardiographic evidence of diastolic dysfunction (grade $\geq 1$ ) or atrial fibrillation at presentation Maximum exercise capacity (peak VO <sub>2</sub> ) of 25 mL/kg/min or less

<b>Exclusion criteria</b>	<p>Prior documented reduced LVEF <math>\leq 40\%</math></p> <p>Significant coronary artery disease (current angina pectoris or ischemia on stress tests, untreated coronary stenosis <math>&gt;50\%</math>)</p> <p>Myocardial infarction or coronary artery bypass graft surgery 3 months or less prior to enrollment</p> <p>Clinically relevant pulmonary disease (vital capacity <math>&lt;80\%</math> or forced expiratory volume in 1 second <math>&lt;80\%</math> of reference values on spirometry)</p> <p>Significant laboratory abnormalities (potassium <math>\geq 5.1</math> mmol/L; hemoglobin <math>\leq 11</math> g/dL; hematocrit <math>\leq 33\%</math>; serum creatinine <math>&gt;1.8</math> mg/dL; or estimated glomerular filtration rate [eGFR]<math>&lt;30</math> mL/min/1.73 m<sup>2</sup>, calculated using the Modification of Diet in Renal Disease formula: <math>186 \times \{\text{serum creatinine [in micromoles per liter]} / 88.4\} \times 1.154^{\text{age [in years]}} - 0.203 \times 1.21</math> [if patient is black]<math>\times 0.742</math> [if patient is female]), k</p> <p>Known contraindications for spironolactone or known intolerance to or therapy with a mineralocorticoid receptor antagonist within the last 3 months</p> <p>Concomitant therapy with a potassium-sparing diuretic</p> <p>Potassium supplementation</p>
<b>Recruitment / selection of participants</b>	Recruitment procedures were noted , but not described in detail.
<b>Intervention(s)</b>	Spironolactone 25mg/day
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	Patients were categorized into subgroups by each of the following variables at baseline (median split for continuous variables): age, sex, body mass index, systolic blood pressure, heart rate, NYHA class (II or III), grade of diastolic function (I vs all other), criteria for diastolic heart failure according to European Society of Cardiology criteria (Paulus positive or negative), and eGFR

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<b>Number of participants</b>	422 patients
<b>Duration of follow-up</b>	12 months
<b>Indirectness</b>	None
<b>Method of analysis</b>	All analyses were based on the intention-to-treat principle.
<b>Additional comments</b>	Aldo-DHF was not powered to evaluate the effect of spironolactone on heart failure hospitalisations or mortality Total for quality of life outcomes: Spironolactone n=194 Placebo n=187

## Study arms

Spironolactone (N = 213)

Spironolactone 25mg/day

Placebo (N = 209)

Matching placebo

## Characteristics

Arm-level characteristics

Chronic heart failure: evidence review for MRAs for heart failure with preserved ejection fraction (September 2025)

<b>Characteristic</b>	<b>Spironolactone (N = 213)</b>	<b>Placebo (N = 209)</b>
<b>% Female</b> Sample size	n = 111 ; % = 52	n = 110 ; % = 53
<b>Age</b> Mean (SD)	67 (8)	67 (8)
<b>NYHA class</b> Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>NYHA class - NYHA class II</b> Sample size	n = 180 ; % = 85	n = 183 ; % = 88
<b>NYHA class - NYHA class III</b> Sample size	n = 59 ; % = 14	n = 26 ; % = 12
<b>Heart failure aetiology</b> Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Heart failure aetiology - Coronary heart disease</b> Sample size	n = 92 ; % = 43	n = 78 ; % = 37
<b>Heart failure aetiology - Hypertension</b> Sample size	n = 197 ; % = 92	n = 190 ; % = 91
<b>Heart failure aetiology - Hyperlipidaemia</b>	n = 130 ; % = 61	n = 143 ; % = 68

<b>Characteristic</b>	<b>Spironolactone (N = 213)</b>	<b>Placebo (N = 209)</b>
Sample size		
<b>LVEF</b>	67 (8%)	67 (8%)
Custom value		
<b>Type 2 diabetes</b>	n = 36 ; % = 17	n = 34 ; % = 16
Sample size		
<b>Atrial fibrillation</b>	n = 13 ; % = 6	n = 9 ; % = 4
Sample size		
<b>Previous heart failure hospitalisation</b>	n = 111 ; % = 52	n = 110 ; % = 53
Sample size		
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>)</b>	79 (19)	78 (18)
Mean (SD)		
<b>Background (non-randomised) heart failure medications</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Background (non-randomised) heart failure medications - Beta-blockers</b>	n = 146 ; % = 69	n = 156 ; % = 75
Sample size		
<b>Background (non-randomised) heart failure medications - Diuretics</b>	n = 118 ; % = 55	n = 109 ; % = 52
Sample size		

Characteristic	Spirolactone (N = 213)	Placebo (N = 209)
<b>Background (non-randomised) heart failure medications - ACEI/ARB</b>	n = 167 ; % = 78	n = 156 ; % = 75
Sample size		
<b>Background (non-randomised) heart failure medications - Calcium-antagonists</b>	n = 47 ; % = 22	n = 58 ; % = 28
Sample size		
<b>Background (non-randomised) heart failure medications - Lipid-lowering drugs</b>	n = 112 ; % = 53	n = 118 ; % = 56
Sample size		

## Outcomes

Study timepoints

Baseline

12 month

Dichotomous outcomes

Outcome	Spirolactone, 12 month, N = 204	Placebo, 12 month, N = 196
<b>All-cause mortality</b>	n = 1 ; % = 1	n = 0 ; % = 0
No of events		

Outcome	Spironolactone, 12 month, N = 204	Placebo, 12 month, N = 196
<b>Potassium</b> Ever increased >5.0mmol/L No of events	n = 44 ; % = 21	n = 22 ; % = 11
<b>Gynaecomastia</b> No of events	n = 9 ; % = 4	n = 1 ; % = NR

## Continuous outcomes

Outcome	Spironolactone, Baseline, N = 213	Spironolactone, 12 month, N = 194	Placebo, Baseline, N = 209	Placebo, 12 month, N = 187
<b>Minnesota Living with Heart Failure Questionnaire</b> Mean (95% CI)	NA (NA to NA)	21 (19 to 24)	NA (NA to NA)	21 (18 to 23)
<b>SF-36 Physical Functioning score</b> Mean (95% CI)	NA (NA to NA)	64 (61 to 68)	NA (NA to NA)	66 (63 to 69)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: All-cause mortality: Spironolactone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Outcome indirectness: reported as dichotomous not time-to-event.)

Continuous outcomes: Minnesota Living with Heart Failure Questionnaire: Spironolactone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: SF-36 Physical Functioning score: Spironolactone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Potassium: Spironolactone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Threshold of >5.0 mmol/l does not match the protocol)

Dichotomous outcomes: Gynaecomastia: Spironolactone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kurrelmeyer KM, Ashton Y, Xu J, 2014

**Bibliographic Reference** Kurrelmeyer KM, Ashton Y, Xu J EA; Effects of spironolactone treatment in elderly women with heart failure and preserved left ventricular ejection fraction.; Journal of Cardiac Failure ; 2014; (no. 20); 560-8

Study details

<b>Secondary publication of another included</b>	NA
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<b>study- see primary study for details</b>	
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NCT00206232
<b>Study location</b>	US
<b>Study setting</b>	Methodist Hospital
<b>Study dates</b>	2004-2008
<b>Sources of funding</b>	Women's Fund; Houston, Texas.
<b>Inclusion criteria</b>	<p>≥18 years or older with a previous diagnosis of HFpEF</p> <p>Had to have a blood pressure ≤150/95mm Hg for 4 weeks before enrollment and the ability to walk ≥50 m at the time of enrollment</p> <p>Treatment with an ACEI, or ARB if ACEI intolerant, was required for ≥4 weeks before enrollment.</p>
<b>Exclusion criteria</b>	<p>Current treatment with spironolactone or eplerenone</p> <p>Previous intolerance to spironolactone</p> <p>Creatinine &gt;2.5 mg/dL</p> <p>Serum potassium &gt;5.0 mEq/L</p>

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	Significant valvular disease Pericardial disease Severe chronic lung disease with cor pulmonale Unstable angina or myocardial infarction $\leq 4$ 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 Pregnant or lactating women
<b>Recruitment / selection of participants</b>	Not specified
<b>Intervention(s)</b>	Spironolactone (25mg/day)
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	NA
<b>Number of participants</b>	48
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	None

<b>Method of analysis</b>	Comparisons between placebo and spironolactone groups were made with the use of the Wilcoxon Mann-Whitney test for continuous variables and Fisher exact test for categoric variables
<b>Additional comments</b>	No deaths or HF hospitalisation during the 6-month study period. Adverse events were evaluated at every study visit but were not reported in the paper. There was no clinically important difference in sodium, blood urea nitrogen, or creatinine between the two groups.

## Study arms

Spironolactone (N = 24)

Spironolactone 25mg/day

Placebo (N = 24)

Placebo

## Characteristics

### Arm-level characteristics

<b>Characteristic</b>	<b>Spironolactone (N = 24)</b>	<b>Placebo (N = 24)</b>
<b>% Female</b>	n = 24 ; % = 100	n = 24 ; % = 100
Sample size		
<b>Age</b>	66.3 (2.2)	76.4 (1.6)
Mean (SD)		
<b>NYHA class</b>	n = NA ; % = NA	n = NA ; % = NA

<b>Characteristic</b>	<b>Spironolactone (N = 24)</b>	<b>Placebo (N = 24)</b>
Sample size		
<b>NYHA class - NYHA class II</b>	n = 8 ; % = 33	n = 16 ; % = 67
Sample size		
<b>NYHA class - NYHA class III</b>	n = 10 ; % = 42	n = 14 ; % = 58
Sample size		
<b>Heart failure aetiology</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Heart failure aetiology - Coronary artery disease</b>	n = 9 ; % = 37.5	n = 8 ; % = 33.3
Sample size		
<b>Heart failure aetiology - Hypertension</b>	n = 21 ; % = 87.5	n = 19 ; % = 79.2
Sample size		
<b>LVEF</b>	62.5 (1.2)	62.9 (1.2)
Mean (SD)		
<b>Type 2 diabetes</b>	n = 12 ; % = 50	n = 6 ; % = 25
Sample size		
<b>Atrial fibrillation</b>	n = 6 ; % = 25	n = 6 ; % = 25
Sample size		

<b>Characteristic</b>	<b>Spironolactone (N = 24)</b>	<b>Placebo (N = 24)</b>
<b>Previous heart failure hospitalisation</b> Sample size	n = 14 ; % = 58.3	n = 13 ; % = 54.2
<b>Background (non-randomised) heart failure medications</b> Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Background (non-randomised) heart failure medications - ACE-inhibitor</b> Sample size	n = 17 ; % = 70.8	n = 16 ; % = 66.7
<b>Background (non-randomised) heart failure medications - Angiotensin receptor blocker</b> Sample size	n = 7 ; % = 29.2	n = 9 ; % = 37.5
<b>Background (non-randomised) heart failure medications - Beta-blocker</b> Sample size	n = 15 ; % = 62.5	n = 15 ; % = 62.5
<b>Background (non-randomised) heart failure medications - Thiazide or loop diuretic</b> Sample size	n = 20 ; % = 83.3	n = 18 ; % = 75
<b>Background (non-randomised) heart failure medications - Digoxin</b> Sample size	n = 3 ; % = 12.5	n = 2 ; % = 8.3
<b>Background (non-randomised) heart failure medications - Calcium-antagonists</b> Sample size	n = 6 ; % = 25	n = 7 ; % = 29.2
<b>Background (non-randomised) heart failure medications - Nitrates</b>	n = 13 ; % = 54.2	n = 8 ; % = 33.3

Characteristic	Spirinolactone (N = 24)	Placebo (N = 24)
Sample size		
<b>Background (non-randomised) heart failure medications - Oral anticoagulants</b>	n = 5 ; % = 20.8	n = 5 ; % = 20.8
Sample size		
<b>Background (non-randomised) heart failure medications - Aspirin</b>	n = 6 ; % = 25	n = 8 ; % = 33.3
Sample size		
<b>Background (non-randomised) heart failure medications - Lipid lowering drug</b>	n = 13 ; % = 54.2	n = 14 ; % = 58.3
Sample size		

## Outcomes

Study timepoints

Baseline

6 month

## Dichotomous outcomes

Outcome	Spirinolactone , 6 month, N = 24	Placebo, 6 month, N = 24
<b>Deaths</b>	n = 0	n = 0
No of events		

Outcome	Spironolactone , 6 month, N = 24	Placebo, 6 month, N = 24
<b>Heart-failure related hospitalisation</b>	n = 0	n = 0
No of events		
<b>Transient and serious hyperkalaemia</b>	n = 4	n = 1
No of events		

## Continuous outcomes

Outcome	Spironolactone , Baseline, N = 24	Spironolactone , 6 month, N = 24	Placebo, Baseline, N = 24	Placebo, 6 month, N = 24
<b>Kansas City Cardiomyopathy Questionnaire</b>	46.2± 5.5	48.5± 5.5	54.2± 4.4	61.8± 5.2
Mean (SEM)				
Custom value				

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: Deaths: Spironolactone versus Placebo at 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)</i>
Overall bias and Directness	Overall Directness	Partially applicable <i>(Outcome indirectness: reported as dichotomous not time-to-event.)</i>

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire: Spironolactone versus Placebo at 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Heart failure-related hospitalisation: Spironolactone versus Placebo at 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)</i>
Overall bias and Directness	Overall Directness	Partially applicable <i>(Outcome indirectness: reported as dichotomous not time-to-event.)</i>

Dichotomous outcomes: Transient and serious hyperkalaemia: Spironolactone versus Placebo at 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns <i>(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)</i>
Overall bias and Directness	Overall Directness	Directly applicable

Lewis, 2016

**Bibliographic Reference** Lewis, Eldrin F; Kim, Hae-Young; Claggett, Brian; Spertus, John; Heitner, John F; Assmann, Susan F; Kenwood, Christopher T; Solomon, Scott D; Desai, Akshay S; Fang, James C; McKinlay, Sonia A; Pitt, Bertram A; Pfeffer, Marc A; Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial.; Circulation. Heart failure; 2016; vol. 9 (no. 3); e001937

Study details

<b>Secondary publication of another included study- see primary study for details</b>	Pitt, 2014 is the primary study
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<b>Other publications associated with this study included in review</b>	Solomon, 2016, Desai, 2018, Pfeffer, 2015, and Shah, 2013
<b>Trial name / registration number</b>	TOPCAT/ NCT00094302.
<b>Indirectness</b>	None

### Study arms

Spironolactone (N = 1722)

15 to 45 mg/day

Placebo (N = 1723)

Placebo

### Outcomes

Study timepoints

12 month

Contrast outcomes

Outcome	Spirolactone vs placebo , 12 month,
<b>Kansas City Cardiomyopathy Questionnaire</b> – overall summary score change from baseline Mean difference (SE) <b>N = 3400</b>	1.36 (0.44)
<b>EQ-5D</b> VAS change from baseline Mean difference (SE) <b>N = 3395</b>	0.47 (0.38)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire overall summary score: Spirolactone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: EQ-5D VAS: Spirolactone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Mottram PM, Haluska B, Leano R, 2004

**Bibliographic Reference** Mottram PM, Haluska B, Leano R EA; Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure.; Circulation ; 2004; (no. 110); 558-65

#### Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	Not specified
<b>Study location</b>	Australia
<b>Study setting</b>	Community setting

<b>Study dates</b>	February 2002 to October 2002
<b>Sources of funding</b>	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.
<b>Inclusion criteria</b>	Patients had to have hypertension requiring antihypertensive medication and report exertional dyspnea (NYHA class II) but no history of angina or myocardial infarction
<b>Exclusion criteria</b>	Patients taking angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or spironolactone. Patients with renal impairment or hyperkalemia at baseline. Patients with pulmonary disease, ischemic heart disease, abnormal regional or global resting LV systolic function, or significant valvular dysfunction.
<b>Recruitment / selection of participants</b>	Participants were recruited from the community (non-hospital, ambulatory population in southeast Queensland).
<b>Intervention(s)</b>	Spironolactone (25mg/day)
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	NA
<b>Number of participants</b>	30 patients
<b>Duration of follow-up</b>	6 months
<b>Indirectness</b>	Hypertensive diastolic heart disease population

<b>Method of analysis</b>	Linear regression was used to determine correlations between variables. In combination with respective t tests, multivariate analyses represented the primary endpoints.
<b>Additional comments</b>	Serum potassium reported at baseline, but no significant changes were noted at 6 months.  Creatinine reported as mean value, not as number of participants with AKI.

## Study arms

Spirolactone (N = 15)

25mg/d

Placebo (N = 15)

Matching placebo

## Characteristics

Arm-level characteristics

<b>Characteristic</b>	<b>Spirolactone (N = 15)</b>	<b>Placebo (N = 15)</b>
<b>% Female</b>	n = 9 ; % = 60	n = 10 ; % = 66
Sample size		
<b>Age</b>	61 (6)	62 (5)

<b>Characteristic</b>	<b>Spironolactone (N = 15)</b>	<b>Placebo (N = 15)</b>
Mean (SD)		
<b>NYHA class</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>NYHA class - NYHA class II</b>	n = 15 ; % = 100	n = 15 ; % = 100
Sample size		
<b>LVEF</b>	68 ±5%	67 ±4%
Custom value		
<b>Type 2 diabetes</b>	n = 1 ; % = NR	n = 0 ; % = 0
Sample size		
<b>Background (non-randomised) heart failure medications</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Background (non-randomised) heart failure medications - Calcium channel blocker</b>	n = 8 ; % = NA	n = 9 ; % = NA
Sample size		
<b>Background (non-randomised) heart failure medications - Diuretic</b>	n = 6 ; % = NA	n = 4 ; % = NA
Sample size		
<b>Background (non-randomised) heart failure medications - Beta-blocker</b>	n = 6 ; % = NA	n = 3 ; % = NA
Sample size		

## Outcomes

Study timepoints

Baseline

6 month

Dichotomous outcomes

Outcome	Spironolactone, 6 month, N = 15	Placebo, 6 month, N = 15
<b>Gynaecomastia</b>	n = 1	n = 0
No of events		

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcome: Gynaecomastia: Spironolactone versus Placebo at 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Pitt, 2014

**Bibliographic Reference** Pitt, Bertram; Pfeffer, Marc A; Assmann, Susan F; Boineau, Robin; Anand, Inder S; Claggett, Brian; Clausell, Nadine; Desai, Akshay S; Diaz, Rafael; Fleg, Jerome L; Gordeev, Ivan; Harty, Brian; Heitner, John F; Kenwood, Christopher T; Lewis, Eldrin F; O'Meara, Eileen; Probstfield, Jeffrey L; Shaburishvili, Tamaz; Shah, Sanjiv J; Solomon, Scott D; Sweitzer, Nancy K; Yang, Song; McKinlay, Sonja M; Spironolactone for heart failure with preserved ejection fraction.; The New England journal of medicine; 2014; vol. 370 (no. 15); 1383-92

### Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	Solomon 2016, Lewis 2016, Desai 2011, Desai 2018, Pfeffer 2015, and Shah 2013
<b>Trial name / registration number</b>	TOPCAT/NCT00094302
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study location</b>	United States, Canada, Brazil, Argentina, Russia, and Georgia
<b>Study setting</b>	Affiliated trial centre
<b>Study dates</b>	10 August 2006 to 31 January 2012

<b>Sources of funding</b>	National Heart, Lung, and Blood Institute
<b>Inclusion criteria</b>	<p>Patients aged 50 years or older</p> <p>Had at least one sign and one symptom of heart failure on a prespecified list of clinically defined signs and symptoms</p> <p>LVEF of 45% or more</p> <p>Controlled systolic blood pressure</p> <p>Serum potassium level of less than 5.0 mmol per litre</p> <p>Had a history of hospitalisation within the past 12 months, with management of heart failure a major component of the care provided</p> <p>An elevated natriuretic peptide level within 60 days before randomization (a brain natriuretic peptide [BNP] level <math>\geq 100</math> pg per milliliter or an N-terminal pro-BNP [NT-proBNP] level <math>\geq 360</math> pg per ml)</p>
<b>Exclusion criteria</b>	<p>Severe systemic illness with a life expectancy of less than 3 years</p> <p>Severe renal dysfunction</p>
<b>Recruitment / selection of participants</b>	Not specified
<b>Intervention(s)</b>	<p>Spironolactone</p> <p>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.</p>
<b>Comparator</b>	Placebo

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<b>Population subgroups</b>	22 prespecified subgroups
<b>Number of participants</b>	3445 participants
<b>Duration of follow-up</b>	Mean follow-up was 3.3 years
<b>Indirectness</b>	None
<b>Method of analysis</b>	Intention-to-treat principle
<b>Additional comments</b>	Adverse events not estimable. Total number of adverse events in spironolactone group was 2395 and 2387 in the placebo group.

## Study arms

Spironolactone (N = 1722)

15 to 45 mg/day

Placebo (N = 1723)

Placebo

## Characteristics

Arm-level characteristics

<b>Characteristic</b>	<b>Spironolactone (N = 1722)</b>	<b>Placebo (N = 1723)</b>
<b>% Female</b> Sample size	n = 888 ; % = 51.6	n = 887 ; % = 51.5
<b>Age</b> Median (IQR)	68.7 (61 to 76.4)	68.7 (60.7 to 75.5)
<b>Ethnicity</b> Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Ethnicity - white</b> Sample size	n = 1525 ; % = 88.6	n = 1537 ; % = 89.2
<b>NYHA class</b> Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>NYHA class - NYHA class I</b> Sample size	n = 56 ; % = 3.3	n = 53 ; % = 3.1
<b>NYHA class - NYHA class II</b> Sample size	n = 1090 ; % = 63.3	n = 1104 ; % = 64.1
<b>NYHA class - NYHA class III</b> Sample size	n = 568 ; % = 33	n = 553 ; % = 32.1
<b>NYHA class - NYHA class IV</b>	n = 7 ; % = 0.4	n = 8 ; % = 0.5

Characteristic	Spirolactone (N = 1722)	Placebo (N = 1723)
Sample size		
<b>LVEF</b>	56 (51 to 61)	56 (51 to 62)
Median (IQR)		
<b>Previous heart failure hospitalisation</b>	n = 1232 ; % = 71.5	n = 1232 ; % = 71.5
Sample size		
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>)</b>	65.3 (53.9 to 79.2)	65.5 (53.5 to 79.1)
Median (IQR)		

## Outcomes

Study timepoints

Baseline

3.3 year

Hazard ratios

Outcome	Spirolactone vs Placebo, Baseline, N2 = 1723, N1 = 1722	Spirolactone vs Placebo, 3.3 year, N2 = 1723, N1 = 1722
<b>All-cause mortality</b>	NA (NA to NA)	0.89 (0.75 to 1.05) <sup>a</sup>
Hazard ratio/95% CI		

<b>Outcome</b>	<b>Spironolactone vs Placebo, Baseline, N2 = 1723, N1 = 1722</b>	<b>Spironolactone vs Placebo, 3.3 year, N2 = 1723, N1 = 1722</b>
<b>CV-related mortality</b> Hazard ratio/95% CI	NA (NA to NA)	0.89 (0.72 to 1.1) <sup>a</sup>
<b>Hospitalisation for heart failure</b> Hazard ratio/95% CI	NA (NA to NA)	0.8 (0.67 to 0.96) <sup>a</sup>

<sup>a</sup> Hazard ratio adjusted for age (as a continuous variable), diabetes history at baseline (insulin-treated, not insulin-treated, or no history of diabetes), and whether or not the participant had been hospitalised for heart failure as a major component in the six months prior to enrolment

#### Dichotomous outcomes

<b>Outcome</b>	<b>Spironolactone, 3.3 year, N = 1722</b>	<b>Placebo, 3.3 year, N = 1723</b>
<b>All-cause mortality</b> No of events	n = 252 ; % = 14.6	n = 274 ; % = 15.9
<b>CV death</b> No of events	n = 160 ; % = 9.3	n = 176 ; % = 10.2
<b>Hospitalisation for heart failure</b> No of events	n = 206 ; % = 12	n = 245 ; % = 14.2
<b>Hyperkalaemia</b> No of events	n = 322; % = 18.7	n = 157; % = 9.1

<b>Outcome</b>	<b>Spironolactone, 3.3 year, N = 1722</b>	<b>Placebo, 3.3 year, N = 1723</b>
Acute kidney injury (doubling of serum creatinine to a value beyond the upper reference limit No of events	n = 175; % = 10.2	n = 121; % = 7

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Hazard ratios: All-cause mortality: Spironolactone versus Placebo at 3.3 years

<b>Section</b>	<b>Question</b>	<b>Answer</b>
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: CV-related mortality: Spironolactone versus Placebo at 3.3 years

<b>Section</b>	<b>Question</b>	<b>Answer</b>
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Hospitalisation for heart failure: Spironolactone versus Placebo at 3.3 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: All-cause mortality: Spironolactone versus Placebo at 3.3 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable ( <i>Outcome indirectness: reported as dichotomous not time-to-event.</i> )

Dichotomous outcomes: CV death: Spironolactone versus Placebo at 3.3 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable ( <i>Outcome indirectness: reported as dichotomous not time-to-event.</i> )

Dichotomous outcomes: hospitalisation for heart failure: Spironolactone versus Placebo at 3.3 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable ( <i>Outcome indirectness: reported as dichotomous not time-to-event.</i> )

Dichotomous outcomes: Hyperkalaemia: Spironolactone versus Placebo at 3.3 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: AKI (doubling serum Creatinine): Spironolactone versus Placebo at 3.3 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable <i>Outcome indirectness - Serum creatinine increase not being within the acute time frame specified in the protocol</i>

Shah, 2013

**Bibliographic Reference**

Shah, Sanjiv J; Heitner, John F; Sweitzer, Nancy K; Anand, Inder S; Kim, Hae-Young; Harty, Brian; Boineau, Robin; Clausell, Nadine; Desai, Akshay S; Diaz, Rafael; Fleg, Jerome L; Gordeev, Ivan; Lewis, Eldrin F; Markov, Valetin; O'Meara, Eileen; Kobulia, Bondo; Shaburishvili, Tamaz; Solomon, Scott D; Pitt, Bertram; Pfeffer, Marc A; Li, Rebecca; Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial.; *Circulation. Heart failure*; 2013; vol. 6 (no. 2); 184-92

## Study details

<b>Secondary publication of another included study- see primary study for details</b>	See Pitt, 2014 (primary study)
<b>Other publications associated with this study included in review</b>	Solomon, 2016, Lewis, 2016, Desai, 2018, Pfeffer, 2015
<b>Trial name / registration number</b>	TOPCAT/ NCT00094302

## Characteristics

## Study-level characteristics

<b>Characteristic</b>	<b>Study (N = 3445)</b>
<b>% Female</b>	n = 1775 ; % = 52

<b>Characteristic</b>	<b>Study (N = 3445)</b>
Sample size	
<b>Age</b>	68.6 (9.6)
Mean (SD)	
<b>Ethnicity</b>	n = NA ; % = NA
Sample size	
<b>Ethnicity - Native American/ Alaskan native</b>	n = 10 ; % = NR
Sample size	
<b>Ethnicity - Asian</b>	n = 19 ; % = 1
Sample size	
<b>Ethnicity - Black/African-American</b>	n = 302 ; % = 9
Sample size	
<b>Ethnicity - Hispanic</b>	n = 321 ; % = 9
Sample size	
<b>Ethnicity - Native Hawaiian/ Other Pacific Islander</b>	n = 1 ; % = NR
Sample size	
<b>Ethnicity - White</b>	n = 3062 ; % = 89
Sample size	

<b>Characteristic</b>	<b>Study (N = 3445)</b>
<b>Ethnicity - Other</b> Sample size	n = 70 ; % = 2
<b>Type 2 diabetes</b> Sample size	n = 1114 ; % = 32
<b>Atrial fibrillation</b> Sample size	n = 1213 ; % = 35
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>)</b> Mean (SD)	67.7 (20.1)
<b>Background (non-randomised) heart failure medications</b> Sample size	n = NA ; % = NA
<b>Background (non-randomised) heart failure medications - Diuretic</b> Sample size	n = 2817 ; % = 82
<b>Background (non-randomised) heart failure medications - Angiotensin Converting Enzyme (ACE) inhibitors</b> Sample size	n = 2251 ; % = 65
<b>Background (non-randomised) heart failure medications - Angiotensin-receptor blockers</b> Sample size	n = 688 ; % = 20
<b>Background (non-randomised) heart failure medications - ACEi or ARB</b>	n = 2889 ; % = 84

<b>Characteristic</b>	<b>Study (N = 3445)</b>
Sample size	
<b>Background (non-randomised) heart failure medications - Beta-blocker</b>	n = 2676 ; % = 78
Sample size	
<b>Background (non-randomised) heart failure medications - Calcium channel blocker</b>	n = 1295 ; % = 38
Sample size	
<b>Background (non-randomised) heart failure medications - Hypoglycemic agent</b>	n = 963 ; % = 28
Sample size	
<b>Background (non-randomised) heart failure medications - Aspirin</b>	n = 2250 ; % = 65
Sample size	
<b>Background (non-randomised) heart failure medications - Statin</b>	n = 1817 ; % = 53
Sample size	
<b>Background (non-randomised) heart failure medications - Warfarin</b>	n = 791 ; % = 23
Sample size	
<b>Background (non-randomised) heart failure medications - Long-acting nitrate</b>	n = 501 ; % = 15
Sample size	
<b>Background (non-randomised) heart failure medications - Other cardiovascular medications</b>	n = 1542 ; % = 45
Sample size	

Characteristic	Study (N = 3445)
<b>Device therapy</b>	n = NA ; % = NA
Sample size	
<b>Device therapy - Pacemaker</b>	n = 269 ; % = 8
Sample size	

Solomon, 2016

**Bibliographic Reference**

Solomon, Scott D; Claggett, Brian; Lewis, Eldrin F; Desai, Akshay; Anand, Inder; Sweitzer, Nancy K; O'Meara, Eileen; Shah, Sanjiv J; McKinlay, Sonja; Fleg, Jerome L; Sopko, George; Pitt, Bertram; Pfeffer, Marc A; Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction.; European heart journal; 2016; vol. 37 (no. 5); 455-62

**Study details**

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	Lewis 2016, Desai 2011, Desai 2018, Pfeffer 2015, and Shah 2013

<b>Trial name / registration number</b>	TOPCAT/ NCT00094302
<b>Study location</b>	United States, Canada, Brazil, Argentina, Russia, and Georgia (Specific information provided for the Americas and Russia/ Georgia)
<b>Study setting</b>	Affiliated trial centre
<b>Study dates</b>	10 August 2006 to 31 January 2012
<b>Sources of funding</b>	This work was funded by the National Heart, Lung, and Blood Institute and National Institutes of Health (contract HHSN268200425207C)
<b>Inclusion criteria</b>	<p>Patients aged 50 years or older</p> <p>Had at least one sign and one symptom of heart failure on a prespecified list of clinically defined signs and symptoms</p> <p>LVEF of 45% or more</p> <p>Controlled systolic blood pressure</p> <p>Serum potassium level of less than 5.0 mmol per litre</p> <p>Had a history of hospitalisation within the past 12 months, with management of heart failure a major component of the care provided</p> <p>An elevated natriuretic peptide level within 60 days before randomization (a brain natriuretic peptide [BNP] level <math>\geq 100</math> pg per milliliter or an N-terminal pro-BNP [NT-proBNP] level <math>\geq 360</math> pg per ml)</p>
<b>Exclusion criteria</b>	<p>Severe systemic illness with a life expectancy of less than 3 years</p> <p>Severe renal dysfunction</p>

<b>Recruitment / selection of participants</b>	Not specified
<b>Intervention(s)</b>	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.
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	LVEF status and trial location (ie The Americas and Russia/ Georgia)
<b>Number of participants</b>	3444 participants
<b>Duration of follow-up</b>	3.4 years median
<b>Indirectness</b>	None
<b>Method of analysis</b>	Intention-to-treat principle
<b>Additional comments</b>	

## Study arms

Spironolactone (N = 1722)

Placebo (N = 1723)

## Characteristics

### Study-level characteristics

<b>Characteristic</b>	<b>Study (N = 3444)</b>
<b>% Female</b> Sample size	n = NA ; % = NA
<b>% Female - LVEF 50-54.99%</b> Sample size	n = 345 ; % = 48.5
<b>% Female - LVEF 55-59.99%</b> Sample size	n = 449 ; % = 51.1
<b>% Female - LVEF &gt;60%</b> Sample size	n = 791 ; % = 59.3
<b>Age</b> Mean (SD)	NA (NA)
<b>Age - LVEF 50-54.99%</b> Mean (SD)	68 (10)

<b>Characteristic</b>	<b>Study (N = 3444)</b>
<b>Age - LVEF 55-59.99%</b> Mean (SD)	69 (10)
<b>Age - LVEF &gt;60%</b> Mean (SD)	70 (10)
<b>Ethnicity</b> Sample size	n = NA ; % = NA
<b>Ethnicity - Black - LVEF 50-54.99%</b> Sample size	n = 52 ; % = 7.3
<b>Ethnicity - Black- LVEF 55-59.99%</b> Sample size	n = 74 ; % = 8.3
<b>Ethnicity - Black: LVEF &gt;60%</b> Sample size	n = 138 ; % = 10.4
<b>NYHA class</b> Sample size	n = NA ; % = NA
<b>NYHA class - Class I: LVEF 50-54.99%</b> Sample size	n = 21 ; % = 2.9
<b>NYHA class - Class I: LVEF 55-59.99%</b>	n = 23 ; % = 2.6

Characteristic	Study (N = 3444)
Sample size	
<b>NYHA class - Class I: LVEF <math>\geq</math>60%</b>	n = 47 ; % = 3.5
Sample size	
<b>NYHA class - Class II: LVEF 50-54.99%</b>	n = 474 ; % = 66.6
Sample size	
<b>NYHA class - Class II: LVEF 55-59.99%</b>	n = 580 ; % = 66.2
Sample size	
<b>NYHA class - Class II: LVEF &gt;60%</b>	n = 822 ; % = 61.8
Sample size	
<b>NYHA class - Class III: LVEF 50-54.99%</b>	n = 217 ; % = 30.5
Sample size	
<b>NYHA class - Class III: LVEF 55-59.99%</b>	n = 268 ; % = 30.6
Sample size	
<b>NYHA class - Class III: LVEF <math>\geq</math>60%</b>	n = 455 ; % = 34.2
Sample size	
<b>NYHA class - Class IV: LVEF 50-54.99%</b>	n = 0 ; % = 0
Sample size	

Characteristic	Study (N = 3444)
<b>NYHA class - Class IV: LVEF 55-59.99%</b> Sample size	n = 5 ; % = 0.6
<b>NYHA class - Class IV: LVEF ≥60%</b> Sample size	n = 7 ; % = 0.5
<b>LVEF</b> Sample size	n = NA ; % = NA
<b>LVEF - LVEF 50-54.99%</b> Sample size	n = 712 ; % = NR
<b>LVEF - LVEF: 55-59.99%</b> Sample size	n = 879 ; % = NR
<b>LVEF - LVEF ≥60%</b> Sample size	n = 1333 ; % = NR
<b>Type 2 diabetes</b> Sample size	n = NA ; % = NA
<b>Type 2 diabetes - LVEF 50-54.99%</b> Sample size	n = 195 ; % = 27.4
<b>Type 2 diabetes - LVEF: 55-59.99%</b>	n = 285 ; % = 32.5

<b>Characteristic</b>	<b>Study (N = 3444)</b>
Sample size	
<b>Type 2 diabetes - LVEF &gt;60%</b>	n = 489 ; % = 36.7
Sample size	
<b>Previous heart failure hospitalisation</b>	n = NA ; % = NA
Sample size	
<b>Previous heart failure hospitalisation - LVEF: 50-54.99%</b>	n = 537 ; % = 75.4
Sample size	
<b>Previous heart failure hospitalisation - LVEF: 55-59.99%</b>	n = 662 ; % = 75.5
Sample size	
<b>Previous heart failure hospitalisation - LVEF &gt;60%</b>	n = 916 ; % = 68.7
Sample size	
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>) LVEF 50-54.99%</b>	68 (21.4)
Mean (SD)	
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>) - LVEF: 55-59.99%</b>	68 (19.9)
Mean (SD)	
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>) - LVEF &gt;60%</b>	66.5 (19.6)
Mean (SD)	

<b>Characteristic</b>	<b>Study (N = 3444)</b>
<b>Background (non-randomised) heart failure medications</b>	n = NA ; % = NA
Sample size	
<b>Background (non-randomised) heart failure medications - ACE/ARB - LVEF: 50-54.99%</b>	n = 620 ; % = 87.1
Sample size	
<b>Background (non-randomised) heart failure medications - ACE/ARB :LVEF 55-59.99%</b>	n = 749 ; % = 85.3
Sample size	
<b>Background (non-randomised) heart failure medications - ACE/ARB: LVEF ≥60%</b>	n = 1073 ; % = 80.6
Sample size	
<b>Background (non-randomised) heart failure medications - Beta-blockers: LVEF: 50-54.99%</b>	n = 577 ; % = 81
Sample size	
<b>Background (non-randomised) heart failure medications - Beta-blockers: LVEF: 55-59.99%</b>	n = 682 ; % = 77.7
Sample size	
<b>Background (non-randomised) heart failure medications - Beta-blockers: LVEF ≥60%</b>	n = 1010 ; % = 75.8
Sample size	
<b>Background (non-randomised) heart failure medications - Diuretics: LVEF: 50-54.99%</b>	n = 603 ; % = 84.77
Sample size	
<b>Background (non-randomised) heart failure medications - Diuretics: LVEF 55-59.99%</b>	n = 717 ; % = 81.7

Characteristic	Study (N = 3444)
Sample size	
<b>Background (non-randomised) heart failure medications - Diuretics: LVEF <math>\geq</math>60%</b>	n = 1101 ; % = 82.7
Sample size	

## Outcomes

Study timepoints

Baseline

3.4 year

Hazard ratios

Outcome	Spironolactone vs Placebo, 3.4 year, N2 = 1723, N1 = 1722
<b>All-cause mortality - LVEF: 50-54.99%</b>	0.96 (0.66 to 1.41)
Hazard ratio/95% CI	total n = 712
<b>All-cause mortality - LVEF: 55-59.99%</b>	1.09 (0.78 to 1.53)
Hazard ratio/95% CI	total n = 879
<b>All-cause mortality - LVEF &gt;60%</b>	0.88 (0.66 to 1.17)
Hazard ratio/95% CI	total n = 1333

<b>Outcome</b>	<b>Spirolactone vs Placebo, 3.4 year, N2 = 1723, N1 = 1722</b>
<b>Cardiovascular mortality - LVEF 50-54.99%</b> Hazard ratio/95% CI	0.95 (0.6 to 1.51) total n = 712
<b>Cardiovascular mortality - LVEF 55-59.99%</b> Hazard ratio/95% CI	1.09 (0.7 to 1.68) total n = 879
<b>Cardiovascular mortality - LVEF ≥60%</b> Hazard ratio/95% CI	0.9 (0.62 to 1.29) total n = 1333
<b>Heart failure-related hospitalisation - LVEF 50-54.99%</b> Hazard ratio/95% CI	0.7 (0.47 to 1.04) total n = 712
<b>Heart failure-related hospitalisation - LVEF 55-59.99%</b> Hazard ratio/95% CI	0.73 (0.49 to 1.08) total n = 879
<b>Heart failure-related hospitalisation - LVEF ≥60%</b> Hazard ratio/95% CI	0.98 (0.74 to 1.3) total n = 1333

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Hazard ratios: All-cause mortality: LVEF:50-54.99%-Spirolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: All-cause mortality: LVEF:55-59.99%: Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: All-cause mortality: LVEF>60%: Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Cardiovascular mortality: LVEF 50-54.99%; Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Cardiovascular mortality: LVEF 55-59.99%: Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Cardiovascular mortality: LVEF $\geq$ 60%: Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Heart failure-related hospitalisation: LVEF 50-54.99%: Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Heart failure-related hospitalisation: LVEF 55-59.99%: Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Heart failure-related hospitalisation: LVEF≥60%: Spironolactone versus Placebo at 3.4 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Solomon, 2024

#### **Bibliographic Reference**

Solomon, Scott D; McMurray, John J V; Vaduganathan, Muthiah; Claggett, Brian; Jhund, Pardeep S; Desai, Akshay S; Henderson, Alasdair D; Lam, Carolyn S P; Pitt, Bertram; Senni, Michele; Shah, Sanjiv J; Voors, Adriaan A; Zannad, Faiez; Abidin, Imran Zainal; Alcocer-Gamba, Marco Antonio; Atherton, John J; Bauersachs, Johann; Chang-Sheng, Ma; Chiang, Chern-En; Chioncel, Ovidiu; Chopra, Vijay; Comin-Colet, Josep; Filippatos, Gerasimos; Fonseca, Candida; Gajos, Grzegorz; Golland, Sorel; Goncalvesova, Eva; Kang, Seokmin; Katova, Tzvetana; Kosiborod, Mikhail N; Latkovskis, Gustavs; Lee, Alex Pui-Wai; Linssen, Gerard C M; Llamas-Esperon, Guillermo; Mareev, Vyacheslav; Martinez, Felipe A; Melenovsky, Vojtech; Merkely, Bela; Nodari, Savina; Petrie, Mark C; Saldarriaga, Clara Ines; Saraiva, Jose Francisco Kerr; Sato, Naoki; Schou, Morten; Sharma, Kavita; Troughton, Richard; Udell, Jacob A; Ukkonen, Heikki; Vardeny, Orly; Verma, Subodh; von Lewinski, Dirk; Voronkov, Leonid; Yilmaz, Mehmet Birhan; Zieroth, Shelley; Lay-Flurrie, James; van Gameren, Ilse; Amarante, Flaviana; Kolkhof, Peter; Viswanathan, Prabhakar; Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction.; The New England journal of medicine; 2024; vol. 391 (no. 16); 1475-1485

## Study details

<b>Secondary publication of another included study- see primary study for details</b>	NA
<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	FINEARTS-HF/ NCT04435626.
<b>Study location</b>	Asia, Eastern Europe, Western Europe, Oceania, North America, and Latin America (37 countries total)
<b>Study setting</b>	Trial centre
<b>Study dates</b>	14 September 2020 to 10 January 2023
<b>Sources of funding</b>	Bayer
<b>Inclusion criteria</b>	<p>Participant must be aged 40 years and older, at the time of signing the informed consent.</p> <p>Diagnosis of heart failure with NYHA class II–IV, ambulatory or hospitalized primarily for heart failure (if a hospitalized patient cannot be randomized as an in-patient, randomization as soon as possible after discharge is encouraged)</p> <p>On diuretic treatment for at least 30 days prior to randomization</p>

	<p>Documented LVEF of <math>\geq 40\%</math> measured by any modality within the last 12 months, at the latest at screening; if several values are available, the most recent one shall be reported. If LVEF was not measured in the past 12 months, a new measurement may be done at screening</p> <p>Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least 1 of the following findings: o LAD <math>\geq 3.8</math>cm, LAA <math>\geq 20</math>cm<sup>2</sup> , LAVI <math>&gt; 30</math> mL/m<sup>2</sup> , LVMI <math>\geq 115</math> g/m<sup>2</sup> (♂) / 95 g/m<sup>2</sup> (♀), septal thickness or posterior wall thickness <math>\geq 1.1</math> cm</p> <p>NT-proBNP <math>\geq 300</math> pg/mL (BNP <math>\geq 100</math> pg/mL) in sinus rhythm and patient does not have an ongoing diagnosis of paroxysmal atrial fibrillation or NT-proBNP <math>\geq 900</math> pg/mL (BNP <math>\geq 300</math> pg/mL) in atrial fibrillation (or if atrial fibrillation status is unknown or if patient has an ongoing diagnosis of paroxysmal atrial fibrillation) for participants obtained at the following time: • Within 90 days prior to randomization if patient had been hospitalized for HF requiring initiation or change in HF therapy or if patient had an urgent visit for HF requiring intravenous(IV) diuretic therapy, both within 90 days prior to randomization OR • Within 30 days prior to randomization if patient has not been hospitalized for HF nor had an urgent HF visit within the past 90 days</p> <p>Male or female. Women of childbearing potential can only be included in the study if a pregnancy test is negative at screening and baseline and if they agree to use adequate contraception which is consistent with local regulations regarding the methods for contraception for those participating in clinical trials</p> <p>Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.</p>
<b>Exclusion criteria</b>	<p>eGFR <math>&lt; 25</math> mL/min/1.73 m<sup>2</sup> at either screening or randomization visit.</p> <p>Serum/plasma potassium <math>&gt; 5.0</math> mmol/L at either screening or randomization visit. NOTE: one reassessment of potassium is allowed at the screening and randomization visit, respectively</p> <p>Acute inflammatory heart disease, e.g. acute myocarditis, within 90 days prior to randomization</p> <p>Myocardial infarction or any event which could have reduced the ejection fraction within 90 days prior to randomization</p> <p>Coronary artery bypass graft surgery in the 90 days prior to randomization</p> <p>Percutaneous coronary intervention in the 30 days prior to randomization</p> <p>Stroke or transient ischemic cerebral attack within 90 days prior to randomization</p>

Probable alternative cause of participants' HF symptoms that in the opinion of the investigator primarily accounts for patient's dyspnea such as significant pulmonary disease, anemia or obesity. Specifically, patients with the below are excluded:

Severe pulmonary disease requiring home oxygen, or chronic oral steroid therapy

History of primary pulmonary arterial hypertension • Hemoglobin <10 g/dl

Valvular heart disease considered by the investigator to be clinically significant

Body mass index (BMI) >50 kg/m<sup>2</sup> at screening

Systolic blood pressure (SBP) ≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments on 2 consecutive measurements at least 2-minute apart, at screening or at randomization

Life-threatening or uncontrolled arrhythmias at screening and/or randomization including but not limited to sustained ventricular tachycardia and atrial fibrillation, or atrial flutter with resting ventricular rate >110 bpm

Symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or at randomization

Any primary cause of HF scheduled for surgery, e.g. valve disease such as severe aortic stenosis or severe mitral regurgitation by the time of screening or randomization

History of peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, viral myocarditis, right heart failure in absence of left-sided structural disease, pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including amyloidosis • Presence of left ventricular assist device by the time of screening or randomization

History of hyperkalemia or acute renal failure during MRA treatment for >7 consecutive days, leading to permanent discontinuation of the MRA treatment

Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or serum test

Known hypersensitivity to the study intervention (active substance or excipients)

Hepatic insufficiency classified as Child-Pugh C at screening or randomization

Addison's disease

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	<p>Requirement of any IV vasodilating drug (e.g. nitrates, nitroprusside), any IV natriuretic peptide (e.g. nesiritide, carperitide), any IV positive inotropic agents, or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device) within 24 hours prior to randomization</p> <p>Participants who require treatment with more than one ACEI, ARB or angiotensin-receptor neprilysin inhibitor (ARNI), or two simultaneously at randomization</p> <p>Continuous (at least 90 days) treatment with an MRA (e.g. spironolactone, eplerenone, canrenone, esaxerenone) within 12 months prior to screening. Last intake at least 30 days before randomization. Treatment with MRA should not be interrupted with the purpose of enrolment into the study</p> <p>Concomitant treatment with any renin inhibitor or potassium-sparing diuretic that cannot be stopped prior to randomization and for the duration of the treatment period</p> <p>Concomitant systemic therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (e.g. itraconazole, ritonavir, indinavir, cobicistat, clarithromycin) or moderate or potent CYP3A4 inducers, that cannot be discontinued 7 days prior to randomization and for the duration of the treatment period</p> <p>Any other condition or therapy, which would make the participant unsuitable for this study and will not allow participation for the full planned study period (e.g. active malignancy or other condition limiting life expectancy to less than 12 months)</p> <p>Previous assignment to treatment during this study</p> <p>Participation in another interventional clinical study (e.g. Phase 1 to 3 clinical studies) or treatment with another investigational medicinal product within 30 days prior to randomization</p> <p>Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)</p> <p>Known current alcohol and/or illicit drug abuse that may interfere with the participant's safety and/or compliance at the discretion of the investigator</p> <p>Participant is in custody by order of an authority or a court of law</p>
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<b>Recruitment / selection of participants</b>	Not specified
<b>Intervention(s)</b>	Finerenone was administered at a maximum dose of 20 mg or 40 mg once daily, depending on the baseline estimated glomerular filtration rate (eGFR).
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	Not specified
<b>Number of participants</b>	6001
<b>Duration of follow-up</b>	Median follow-up was 32 months
<b>Indirectness</b>	None
<b>Method of analysis</b>	Intention-to-treat
<b>Additional comments</b>	This is the primary paper for FINEARTS-HF and outcome results are in the full population which included people LVEF $\geq 40$ . The present review focuses on the LVEF $>50$ subgroup analysis in this trial. Therefore, the data from this paper have not been used and risk of bias assessment has not been undertaken for this paper.

## Study arms

Finerenone (N = 3003)

Finerenone was administered at a maximum dose of 20 mg or 40 mg once daily, depending on the baseline estimated glomerular filtration rate (eGFR).

Placebo (N = 2998)

Placebo

## Characteristics

### Arm-level characteristics

<b>Characteristic</b>	<b>Finerenone (N = 3003)</b>	<b>Placebo (N = 2998)</b>
<b>% Female</b> Sample size	n = 1355 ; % = 45.1	n = 1377 ; % = 45.9
<b>Age</b> Mean (SD)	71.9 (9.6)	72 (9.7)
<b>Ethnicity</b> Sample size	n = NA ; % = NA	n = NA ; % = NA
<b>Ethnicity - Asian</b> Sample size	n = 497 ; % = 16.6	n = 499 ; % = 16.6
<b>Ethnicity - Black</b> Sample size	n = 49 ; % = 1.6	n = 39 ; % = 1.3
<b>Ethnicity - Other</b>	n = 91 ; % = 3	n = 91 ; % = 3

<b>Characteristic</b>	<b>Finerenone (N = 3003)</b>	<b>Placebo (N = 2998)</b>
Sample size		
<b>Ethnicity - white</b>	n = 2366 ; % = 78.8	n = 2369 ; % = 79
Sample size		
<b>NYHA class</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>NYHA class - NYHA class II</b>	n = 2081 ; % = 69.3	n = 2065 ; % = 68.9
Sample size		
<b>NYHA class - NYHA class III</b>	n = 903 ; % = 30.1	n = 910 ; % = 30.4
Sample size		
<b>NYHA class - NYHA class IV</b>	n = 18 ; % = 0.6	n = 23 ; % = 0.8
Sample size		
<b>LVEF</b>	52.6±7.8	52.5±7.8
Custom value		
<b>Type 2 diabetes</b>	n = 1217 ; % = 40.5	n = 1222 ; % = 40.8
Sample size		
<b>Atrial fibrillation</b>	n = 1165 ; % = 38.8	n = 1128 ; % = 37.6

<b>Characteristic</b>	<b>Finerenone (N = 3003)</b>	<b>Placebo (N = 2998)</b>
Sample size		
<b>Previous heart failure hospitalisation</b>	n = 1797 ; % = 59.8	n = 1822 ; % = 60.8
Sample size		
<b>Renal function (eGFR; mL/min/1.73m<sup>2</sup>)</b>	61.9±19.4	62.3±20.0
Custom value		
<b>Background (non-randomised) heart failure medications</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Background (non-randomised) heart failure medications - Beta-blocker</b>	n = 2541 ; % = 84.6	n = 2554 ; % = 85.2
Sample size		
<b>Background (non-randomised) heart failure medications - ACE inhibitor</b>	n = 1083 ; % = 36.1	n = 1072 ; % = 35.8
Sample size		
<b>Background (non-randomised) heart failure medications - ARB</b>	n = 1047 ; % = 34.9	n = 1055 ; % = 35.2
Sample size		
<b>Background (non-randomised) heart failure medications - Angiotensin receptor- neprilysin inhibitor</b>	n = 256 ; % = 8.5	n = 257 ; % = 8.6
Sample size		

Characteristic	Finerenone (N = 3003)	Placebo (N = 2998)
<b>Background (non-randomised) heart failure medications - Calcium channel blocker</b> Sample size	n = 958 ; % = 31.9	n = 1010 ; % = 33.7
<b>Background (non-randomised) heart failure medications - Sodium-glucose cotransporter-2 inhibitor</b> Sample size	n = 393 ; % = 13.1	n = 424 ; % = 14.1
<b>Background (non-randomised) heart failure medications - Loop diuretic</b> Sample size	n = 2618 ; % = 87.2	n = 2621 ; % = 87.4
<b>Background (non-randomised) heart failure medications - Thiazide diuretic</b> Sample size	n = 429 ; % = 14.3	n = 402 ; % = 13.4
<b>Background (non-randomised) heart failure medications - Potassium supplement</b> Sample size	n = 349 ; % = 11.6	n = 365 ; % = 12.2
<b>Background (non-randomised) heart failure medications - Glucagon-like peptide-1 receptor agonist</b> Sample size	n = 79 ; % = 2.6	n = 88 ; % = 2.9

## Outcomes

Study timepoints

Baseline

Chronic heart failure: evidence review for MRAs for heart failure with preserved ejection fraction (September 2025)

12 month

32 month

## Hazard ratios

<b>Outcome</b>	<b>Finerenone vs Placebo, Baseline, N2 = 2998, N1 = 3003</b>	<b>Finerenone vs Placebo, 12 month, N2 = 2998, N1 = 3003</b>	<b>Finerenone vs Placebo, 32 month, N2 = 2998, N1 = 3003</b>
<b>All-cause mortality</b> Hazard ratio/95% CI	NA (NA to NA)	NA (NA to NA)	0.93 (0.83 to 1.06)
<b>Death from cardiovascular causes</b> Hazard ratio/95% CI	NA (NA to NA)	NA (NA to NA)	0.93 (0.78 to 1.11)

## Continuous outcomes

<b>Outcome</b>	<b>Finerenone, Baseline, N = 3003</b>	<b>Finerenone, 12 month, N = 3003</b>	<b>Finerenone, 32 month, N = 3003</b>	<b>Placebo, Baseline, N = 2998</b>	<b>Placebo, 12 month, N = 2998</b>	<b>Placebo, 32 month, N = 2998</b>
<b>Kansas City Cardiomyopathy Questionnaire</b> Change from baseline Mean (SE)	NR (NR)	8 (0.3)	NR (NR)	NR (NR)	6.4 (0.3)	NR (NR)

## Dichotomous outcomes

Outcome	Finerenone, 32 month, N = 3003	Placebo, 32 month, N = 2998
<b>Serum creatinine</b> >5.5 mmol/l No of events	n = 413 ; % = 14.3	n = 199 ; % = 6.9
<b>Hyperkalaemia</b> No of events	n = 289 ; % = 9.7	n = 125 ; % = 4.2

Upadhya, 2017

**Bibliographic Reference**

Upadhya, B; Hundley, WG; Brubaker, PH; Morgan, TM; Stewart, KP; Kitzman, DW; Effect of Spironolactone on Exercise Tolerance and Arterial Function in Older Adults with Heart Failure with Preserved Ejection Fraction; Journal of the American Geriatrics Society; 2017; vol. 65 (no. 11); 2374-2382

**Study details**

<b>Other publications associated with this study included in review</b>	NA
<b>Trial name / registration number</b>	NCT00123955

<b>Study location</b>	United States
<b>Study setting</b>	Wake Forest School of Medicine
<b>Study dates</b>	Not specified
<b>Sources of funding</b>	<p>NIH R01AG18915; The Claude D. Pepper Older Americans Independence Center of Wake Forest University NIH P30AG21332; Clinical and Translational Science Institute of Wake Forest School of Medicine NIH UL1TR001420; and the Kermit G. Phillips Chair in Cardiovascular Medicine of Wake Forest School of Medicine.</p> <p>This study was funded by R01AG18915 from the NIH; The Claude D. Pepper Older Americans Independence Center of Wake Forest University, P30AG21332; Clinical and Translational Science Institute of Wake Forest School of Medicine, NIH, UL1TR001420; and the Kermit G. Phillips Chair in Cardiovascular Medicine of Wake Forest School of Medicine.</p>
<b>Inclusion criteria</b>	Participants with confirmed HFpEF
<b>Exclusion criteria</b>	<p>Prior aldosterone antagonism use within the past 3 months.</p> <p>A known contraindication</p> <p>Concomitant therapy with a potassium sparing diuretic or potassium supplementation</p> <p>Baseline serum potassium &gt;5.0 meq/L</p> <p>Serum creatinine <math>\geq</math> 2.5 mg/dL</p>
<b>Recruitment / selection of participants</b>	Selected from chart review
<b>Intervention(s)</b>	Spironolactone 25mg/day

	The starting dose of spironolactone was 12.5 mg once daily in patients with baseline creatinine $\geq 2.0$ mg/dL or potassium $> 4.5$ meq/L; in all other patients the starting dose was 25 mg once daily. Among patients who initiated therapy with the 12.5-mg dose, the dose was increased to 25 mg daily as long as the creatinine remained $< 2.5$ mg/dl and potassium remained $\leq 5.0$ meq/L. Spironolactone was discontinued if 1-week creatinine was $\geq 2.5$ mg/dl or potassium $\geq 5.5$ meq/L.
<b>Comparator</b>	Placebo
<b>Population subgroups</b>	NA
<b>Number of participants</b>	80 participants randomised
<b>Duration of follow-up</b>	9 months
<b>Indirectness</b>	None
<b>Method of analysis</b>	Group comparisons of outcome measures between intervention groups were made by repeated measures analysis of covariance procedures.
<b>Additional comments</b>	1 patient death (attributed to a car accident)

## Study arms

Spironolactone (N = 42)

25 mg/day

Placebo (N = 38)

Placebo

## Characteristics

### Arm-level characteristics

<b>Characteristic</b>	<b>Spironolactone (N = 42)</b>	<b>Placebo (N = 38)</b>
<b>% Female</b>	n = 34 ; % = 81	n = 30 ; % = 79
Sample size		
<b>Age</b>	70 (1.1)	72 (1.2)
Mean (SD)		
<b>Ethnicity</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Ethnicity - African-American</b>	n = 9 ; % = 21	n = 14 ; % = 37
Sample size		
<b>NYHA class - NYHA class II</b>	n = 12 ; % = 29	n = 10 ; % = 26
Sample size		
<b>NYHA class - NYHA class III</b>	n = 27 ; % = 64	n = 24 ; % = 63
Sample size		
<b>LVEF</b>	62.6 ± 1.1	62.0 ± 1.1

Characteristic	Spirolactone (N = 42)	Placebo (N = 38)
Custom value		
<b>Type 2 diabetes</b>	n = 7 ; % = 17	n = 11 ; % = 29
Sample size		
<b>Background (non-randomised) heart failure medications</b>	n = NA ; % = NA	n = NA ; % = NA
Sample size		
<b>Background (non-randomised) heart failure medications - Beta-blockers</b>	n = 13 ; % = 31	n = 12 ; % = 32
Sample size		
<b>Background (non-randomised) heart failure medications - CA channel blockers</b>	n = 15 ; % = 36	n = 13 ; % = 34
Sample size		
<b>Background (non-randomised) heart failure medications - Digoxin</b>	n = 1 ; % = 2	n = 0 ; % = 0
Sample size		
<b>Background (non-randomised) heart failure medications - Diuretics</b>	n = 31 ; % = 74	n = 27 ; % = 71
Sample size		
<b>Background (non-randomised) heart failure medications - Nitrates</b>	n = 3 ; % = 7	n = 3 ; % = 8
Sample size		

## Outcomes

## Study timepoints

Baseline

9 month

## Dichotomous outcomes

Outcome	Spirolactone, 9 month, N = 37	Placebo, 9 month, N = 34
<b>All-cause hospitalisations</b>	n = 7 ; % = NR	n = 9 ; % = NR
No of events		

## Continuous outcomes

Outcome	Spirolactone, Baseline, N = 42	Spirolactone, 9 month, N = 37	Placebo, Baseline, N = 38	Placebo, 9 month, N = 34
<b>Minnesota Living with Heart Failure Questionnaire</b>				
Total	32 (21)	29 (18)	28 (19)	25 (18)
Mean (SD)				

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: All-cause hospitalisations: Spirolactone versus Placebo at 9 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable ( <i>Outcome indirectness: reported as dichotomous not time-to-event.</i> )

Continuous outcomes: Minnesota Living with Heart Failure Questionnaire: Total: Spironolactone versus Placebo at 9 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable



## Appendix E Forest plots

### E.1 Mineralocorticoid receptor antagonist versus placebo

#### Primary analysis: MRA versus placebo using full TOPCAT population

Figure 2: All-cause mortality (time-to-event)

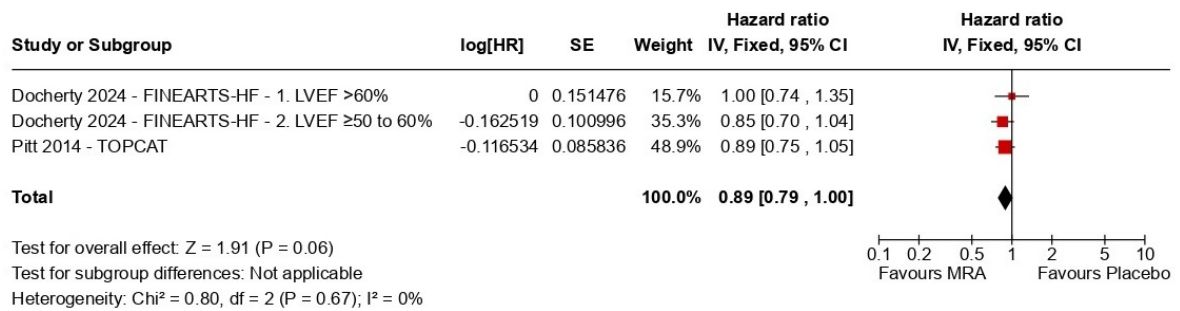


Figure 3: All-cause mortality (dichotomous)

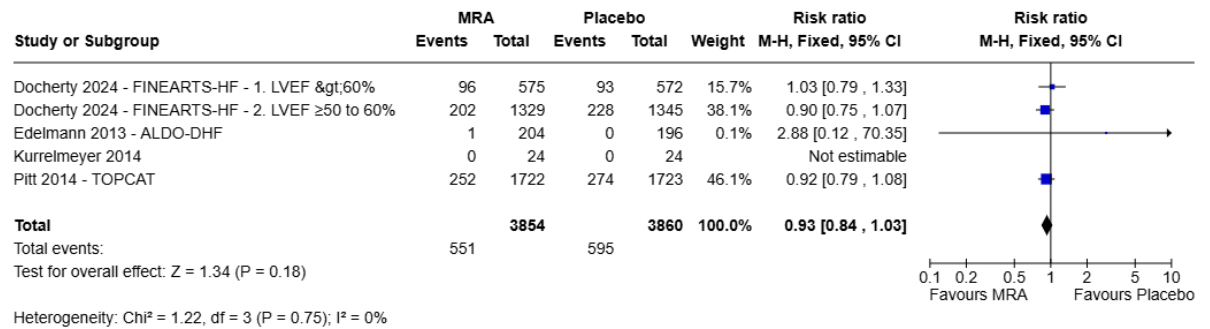
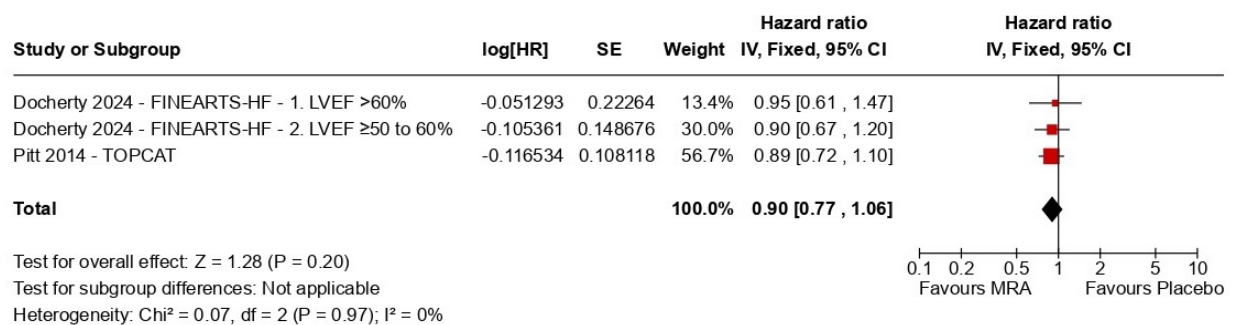
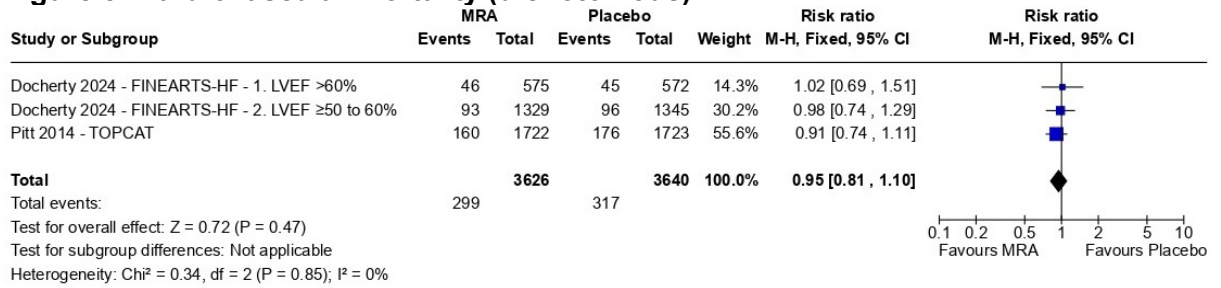


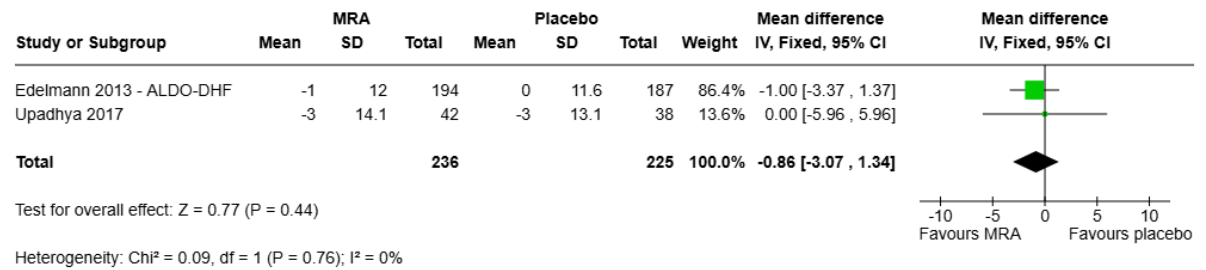
Figure 4: Cardiovascular mortality (time-to-event)



**Figure 5: Cardiovascular mortality (dichotomous)**

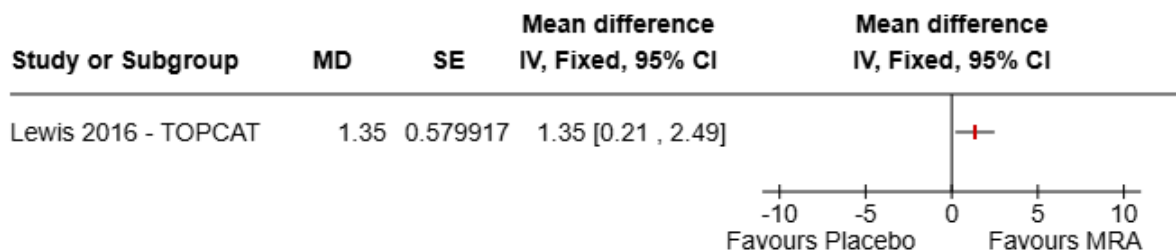


**Figure 6: Health-related quality of life: Minnesota Living with Heart Failure (score range 0-105, lower scores are better) (change scores)**



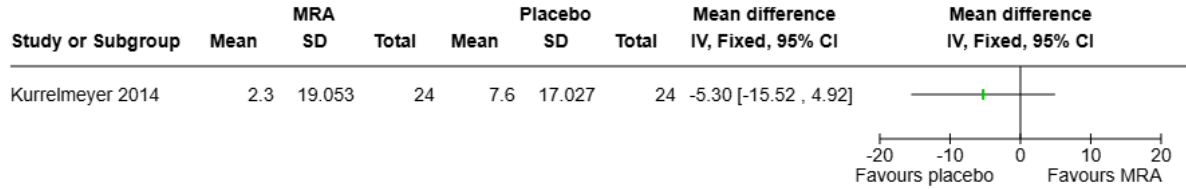
Change score was calculated from reported values.

**Figure 7: Health-related quality of life: Kansas City Cardiomyopathy Questionnaire (overall summary score) (score range 0-100, higher scores are better) (change scores)**



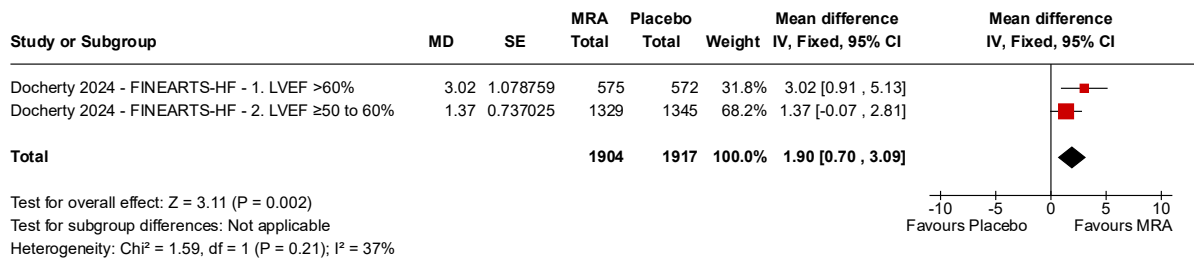
Source: Number analysed per group not available for Lewis 2016.

**Figure 8: Health-related quality of life: Kansas City Cardiomyopathy Questionnaire (clinical summary score) (score range 0-100, higher scores are better) (change scores)**

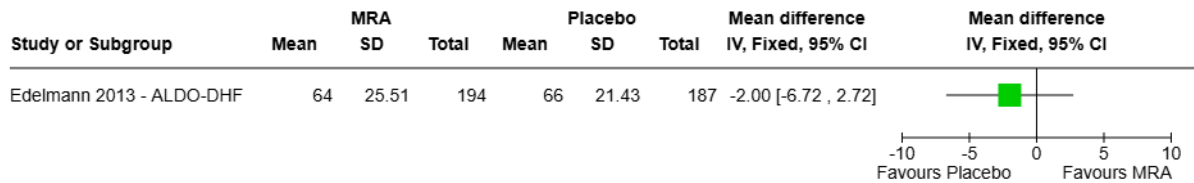


Change scores were calculated from reported values

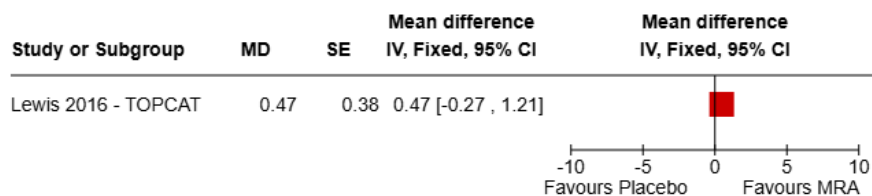
**Figure 9: Health-related quality of life: Kansas City Cardiomyopathy Questionnaire (total symptom score) (score range 0-100, higher scores are better) (change scores)**



**Figure 10: Health-related quality of life: SF-36: Physical Functioning (score range 0-100, higher scores are better) (final score)**

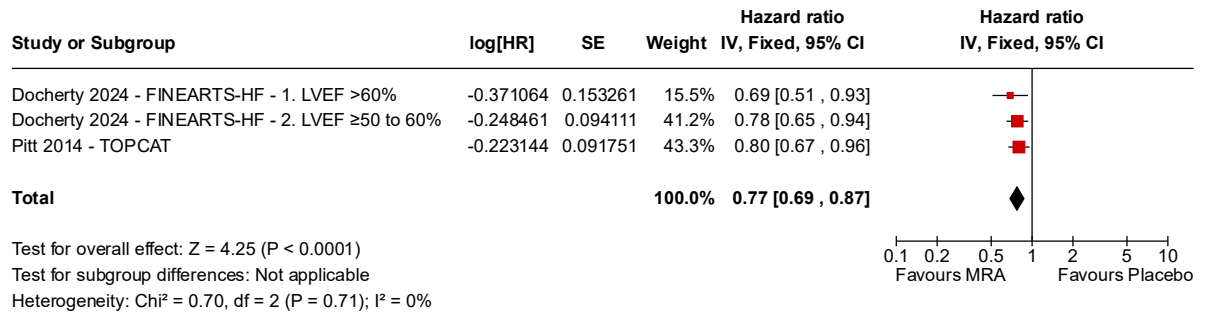


**Figure 11: Health-related quality of life: EQ-VAS (score range 0-100, higher scores are better) (change score)**

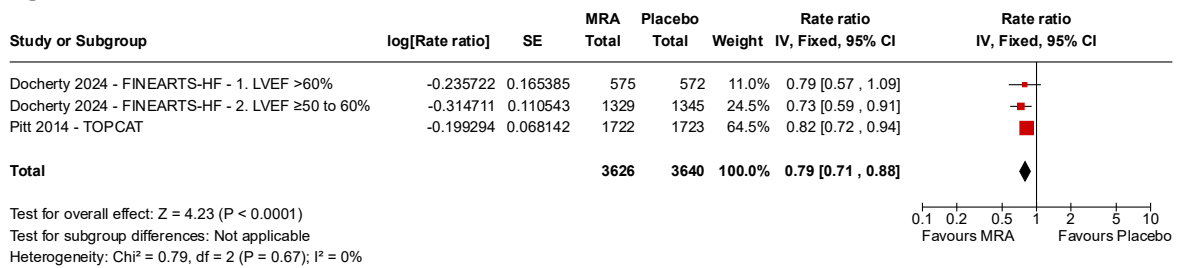


Number analysed per group not available.

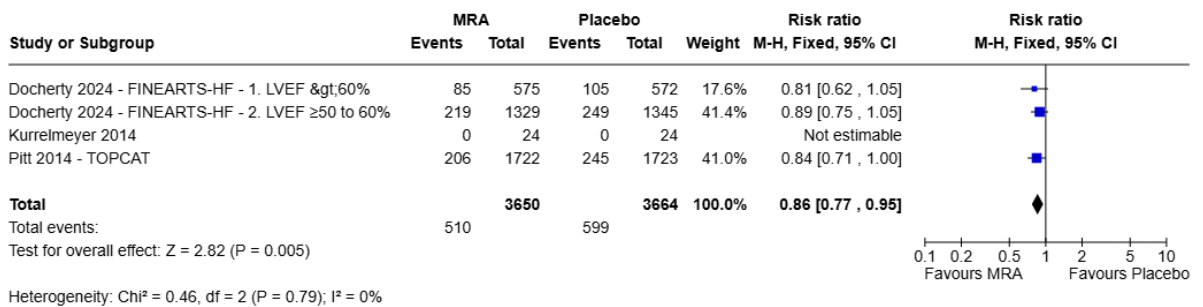
**Figure 12: Heart failure-related hospitalisation (time-to-event)**



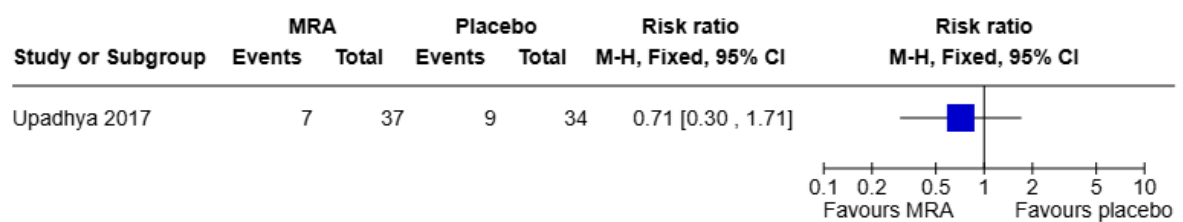
**Figure 13: Heart failure-related hospitalisation (total events; rate ratio)**



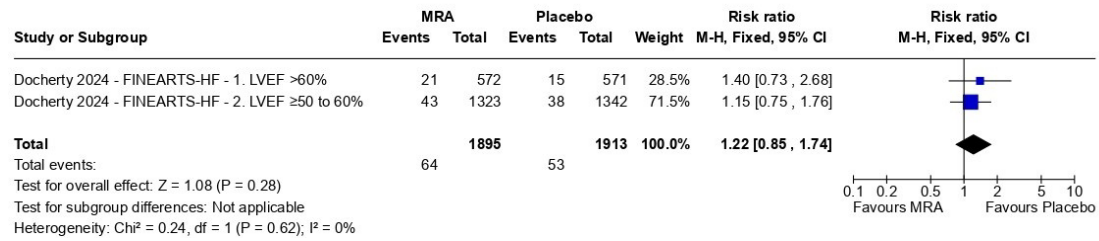
**Figure 14: Heart failure hospitalisation (dichotomous)**



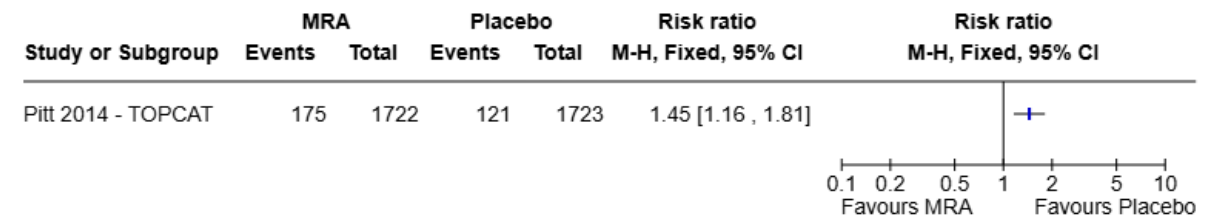
**Figure 15: All-cause hospitalisation (dichotomous)**



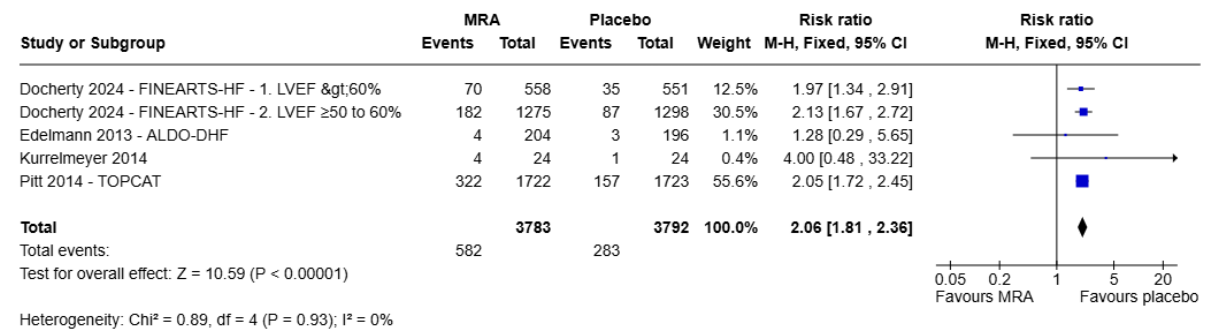
**Figure 16: Withdrawal due to drug-related events (dichotomous)**



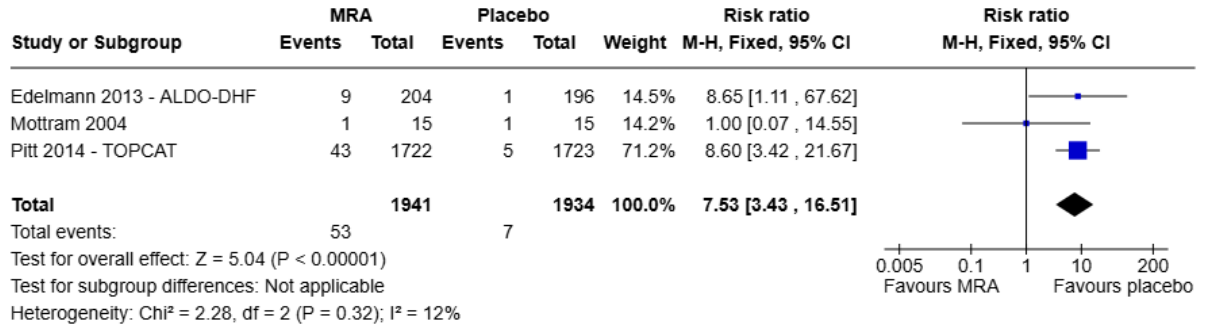
**Figure 17: Acute kidney injury (doubling of serum creatinine to a value beyond the upper reference limit) (dichotomous)**



**Figure 18: Hyperkalaemia – serum potassium concentration ≥5.5mmol/L (dichotomous)**

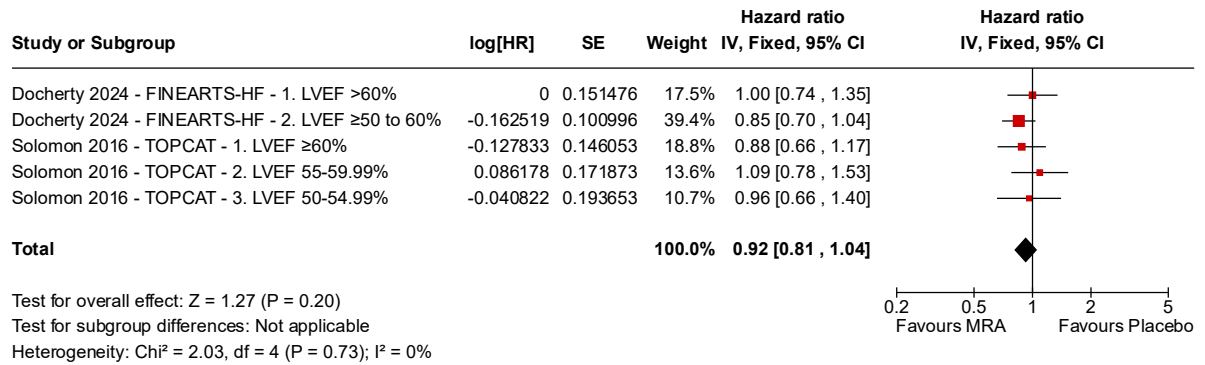


**Figure 19: Gynaecomastia in men and breast tenderness/enlargement in women (dichotomous)**

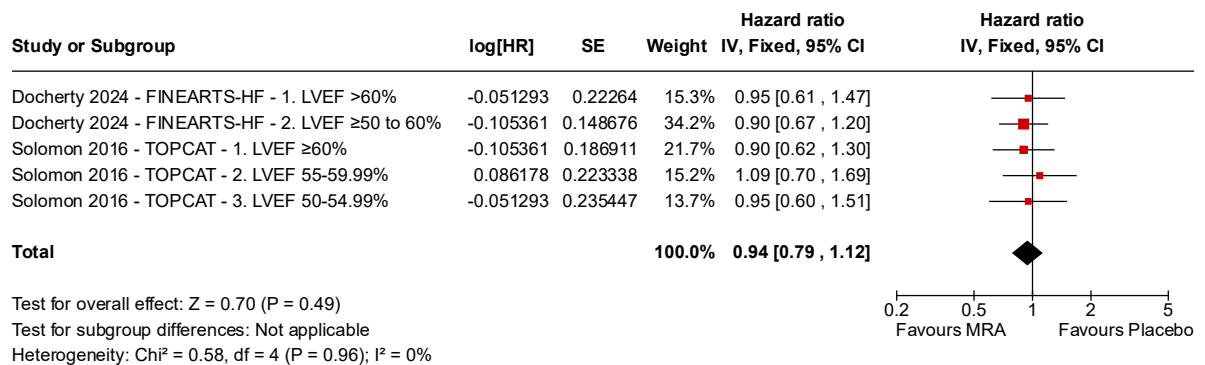


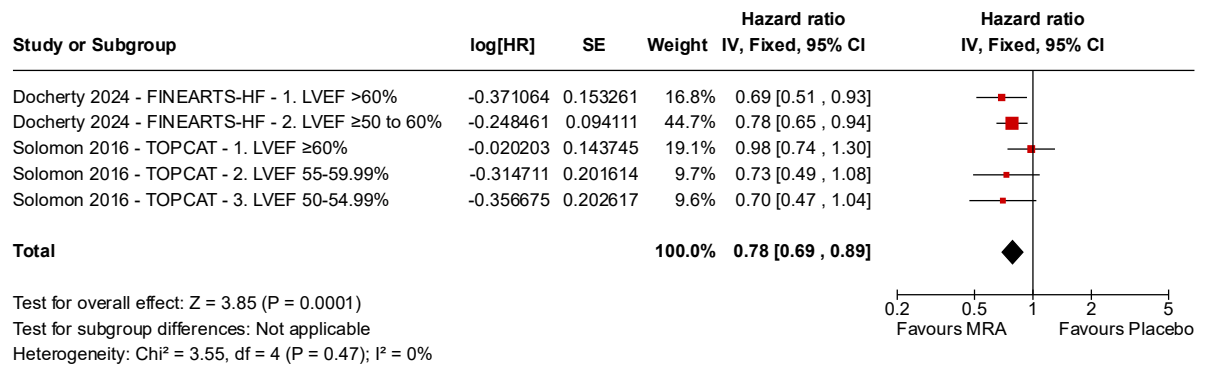
**Sensitivity analysis: MRA versus placebo using TOPCAT subgroup with LVEF ≥50%**

**Figure 20: All-cause mortality (time-to-event)**



**Figure 21: Cardiovascular mortality (time-to-event)**



**Figure 22: Heart failure-related hospitalisations (time-to-event)**

## Appendix F GRADE tables

### Primary analysis: using full TOPCAT population

**Table 9: Clinical evidence profile: MRAs vs. Placebo**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRAs	Placebo	Relative (95% CI)	Absolute (95% CI)		
<b>All-cause mortality (time-to-event) (follow-up: range 2.7 years to 3.3 years)</b>												
2	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	-/3626	-/3640	<b>HR 0.89</b> (0.79 to 1.00)	-	⊕⊕○○ Low <sup>a,b</sup>	CRITICAL
<b>All-cause mortality (dichotomous) (follow-up: range 1 to 3.3 years)</b>												
4	randomised trials	serious <sup>a</sup>	not serious	serious <sup>c</sup>	not serious	none	551/3854 (14.3%)	595/3860 (15.4%)	<b>RR 0.93</b> (0.84 to 1.03)	<b>11 fewer per 1,000</b> (from 25 fewer to 5 more)	⊕⊕○○ Low <sup>a,c</sup>	CRITICAL
<b>Cardiovascular mortality (time-to-event) (follow-up: range 2.7 to 3.3 years)</b>												
2	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	-/3626	-/3640	<b>HR 0.90</b> (0.77 to 1.06)	-	⊕⊕⊕○ Moderate <sup>b</sup>	CRITICAL
<b>Cardiovascular mortality (dichotomous) (follow-up: range 2.7 to 3.3 years)</b>												
2	randomised trials	not serious	not serious	serious <sup>c</sup>	not serious	none	299/3626 (8.2%)	317/3640 (8.7%)	<b>RR 0.95</b> (0.81 to 1.10)	<b>4 fewer per 1,000</b> (from 17 fewer to 9 more)	⊕⊕⊕○ Moderate <sup>c</sup>	CRITICAL

**Health-related quality of life: Minnesota Living with Heart Failure; change scores (score range: 0-105, lower scores are better) (follow-up: range 9 months to 12 months)**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRAs	Placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious <sup>d</sup>	not serious	not serious	not serious	none	236	225	-	MD 0.86 lower (3.07 lower to 1.34 higher)	⊕⊕⊕○ Moderate <sup>d</sup>	CRITICAL

Health-related quality of life: Kansas City Cardiomyopathy Questionnaire overall summary score; change scores (score range: 0-100, higher scores are better) (follow-up: 12 months)

1	randomised trials	not serious	not serious	not serious	not serious	none	1743	1746	-	MD 1.35 higher (0.21 higher to 2.49 higher)	⊕⊕⊕⊕ High	CRITICAL
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Health-related quality of life: Kansas City Cardiomyopathy Questionnaire clinical summary score; change scores (score range: 0-100, higher scores are better) (follow-up: mean 6 months)

1	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	24	24	-	MD 5.3 lower (15.25 lower to 4.92 higher)	⊕⊕○○ Low <sup>b,e</sup>	CRITICAL
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Health-related quality of life: Kansas City Cardiomyopathy Questionnaire total symptom score; change scores (score range 0-100, higher scores are better) (follow-up: mean 12 months)

1	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	1904	1917	-	MD 1.9 higher (0.7 higher to 3.09 higher)	⊕⊕⊕○ Moderate <sup>a</sup>	CRITICAL
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Health-related quality of life: SF-36 Physical functioning; final score (score range: 0-100, higher scores are better) (follow-up: mean 12 months)

1	randomised trials	serious <sup>d</sup>	not serious	not serious	serious <sup>b</sup>	none	194	187	-	MD 2 lower (6.72 lower to 2.72 higher)	⊕⊕○○ Low <sup>b,d</sup>	CRITICAL
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Health-related quality of life: EQ-VAS change score (score range: 0-100, higher scores are better) (follow-up: mean 3.3 years)

1	randomised trials	not serious	not serious	not serious	not serious	none			-	MD 0.47 higher (0.27 lower to 1.21 higher)	⊕⊕⊕⊕ High	CRITICAL
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRAs	Placebo	Relative (95% CI)	Absolute (95% CI)		

**Heart failure-related hospitalisation (time-to-event) (follow-up: range 2.7 to 3.3 years)**

2	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	3626	3640	<b>HR 0.77</b> (0.69 to 0.87)	-	Low <sup>a,b</sup>	CRITICAL
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**Heart failure-related hospitalisation (total events) (follow-up: range 2.7 to 3.3 years)**

2	randomised trials	not serious	not serious	not serious	serious <sup>b</sup>	none	3626 participants	3640 participants	<b>Rate ratio 0.79</b> (0.71 to 0.88)	<b>25 fewer per 1000 patient(s) per years</b> (from 35 fewer to 15 fewer) <sup>e</sup>	Moderate <sup>b</sup>	CRITICAL
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**Heart failure-related hospitalisation (dichotomous) (follow-up: range 6 months to 3.3 years)**

3	randomised trials	serious <sup>a</sup>	not serious	serious <sup>c</sup>	serious <sup>b</sup>	none	5101/3650 (14.0%)	599/3664 (16.3%)	<b>RR 0.86</b> (0.77 to 0.95)	<b>23 fewer per 1,000</b> (from 38 fewer to 8 fewer)	Very low <sup>a,b,c</sup>	CRITICAL
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**All-cause hospitalisation (dichotomous) (follow-up: mean 9 months)**

1	randomised trials	not serious	not serious	serious <sup>c</sup>	very serious <sup>b</sup>	none	7/37 (18.9%)	9/34 (26.5%)	<b>RR 0.71</b> (0.30 to 1.71)	<b>77 fewer per 1,000</b> (from 185 fewer to 188 more)	Very low <sup>a,b,c</sup>	CRITICAL
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**Withdrawal due to drug-related events (follow-up: mean 32 months)**

1	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	64/1895 (3.4%)	53/1913 (2.8%)	<b>RR 1.22</b> (0.85 to 1.74)	<b>6 more per 1,000</b> (from 4 fewer to 21 more)	Low <sup>a,b</sup>	CRITICAL
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**AKI – doubling of serum creatinine to a value beyond the upper reference limit (follow-up: 3.3 years)**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRAs	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious <sup>f</sup>	serious <sup>b</sup>	none	175/1722 (10.2%)	121/1723 (7.0%)	<b>RR 1.45</b> (1.16 to 1.81)	<b>32 more per 1,000</b> (from 11 more to 57 more)	⊕⊕○○ Low <sup>b,f</sup>	CRITICAL

**Hyperkalaemia (follow-up: range 6 months to 3.3 years)**

4	randomised trials	not serious	not serious	not serious	not serious	none	582/3783 (15.4%)	283/3792 (7.5%)	<b>RR 2.06</b> (1.81 to 2.36)	<b>79 more per 1,000</b> (from 60 more to 101 more)	⊕⊕⊕⊕ High	CRITICAL
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**Gynaecomastia in men or breast tenderness/ enlargement in women (follow-up: range 6 months to 3.3 years)**

3	randomised trials	not serious	not serious	not serious	not serious	none	53/1941 (2.7%)	7/1934 (0.4%)	<b>RR 7.53</b> (3.43 to 16.51)	<b>24 more per 1,000</b> (from 9 more to 56 more)	⊕⊕⊕⊕ High	CRITICAL
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EQ-VAS: EuroQoL visual analogue scale; HR: Hazard ratio; MD: Mean difference; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk; SF-36: Short Form-36 health survey

- a. Downgraded by 1 increment for risk of bias due to unexplained deviations from the trial protocol in the majority of the evidence (the FINEARTS-HF trial did not use the LVEF thresholds prespecified in the study protocol).
- b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes. KCCQ MID is 5; MLWHFQ MID is 5; SF36 physical summary score MID is 2; EQ5D VAS MID is 9.05.
- c. Downgraded by 1 increment as the majority of the evidence was indirect (due to reporting as number of events)
- d. Downgraded by 1 increment for risk of bias due to some concerns for the majority of the evidence: no information provided regarding allocation concealment.
- e. Downgraded by 1 increment for risk of bias due to some concerns for the majority of the evidence: differences between groups which could suggest a problem with the randomisation process and no information provided regarding allocation concealment.
- f. Downgraded by 1 increment for outcome indirectness due to the serum creatinine increase not being within the acute time frame specified in the protocol.
- g. Absolute difference calculated based on difference in number of events per person-year reported in the papers.

## Sensitivity analysis: using TOPCAT subgroup with LVEF $\geq 50\%$

**Table 10: Clinical evidence profile: MRA versus placebo using TOPCAT subgroup with LVEF  $\geq 50\%$**

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		

### All-cause mortality (time-to-event) (follow-up: range 2.7 to 3.3 years)

2	randomised trials	not serious	not serious	not serious	not serious	none	6745	<b>HR 0.92</b> (0.81 to 1.04)	-	⊕⊕⊕⊕ High	CRITICAL
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### Cardiovascular mortality (time-to-event) (follow-up: range 2.7 to 3.3 years)

2	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none	6745	<b>HR 0.94</b> (0.79 to 1.12)	-	⊕⊕⊕○ Moderate <sup>a</sup>	CRITICAL
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### Heart failure-related hospitalisation (follow-up: range 2.7 to 3.3 years)

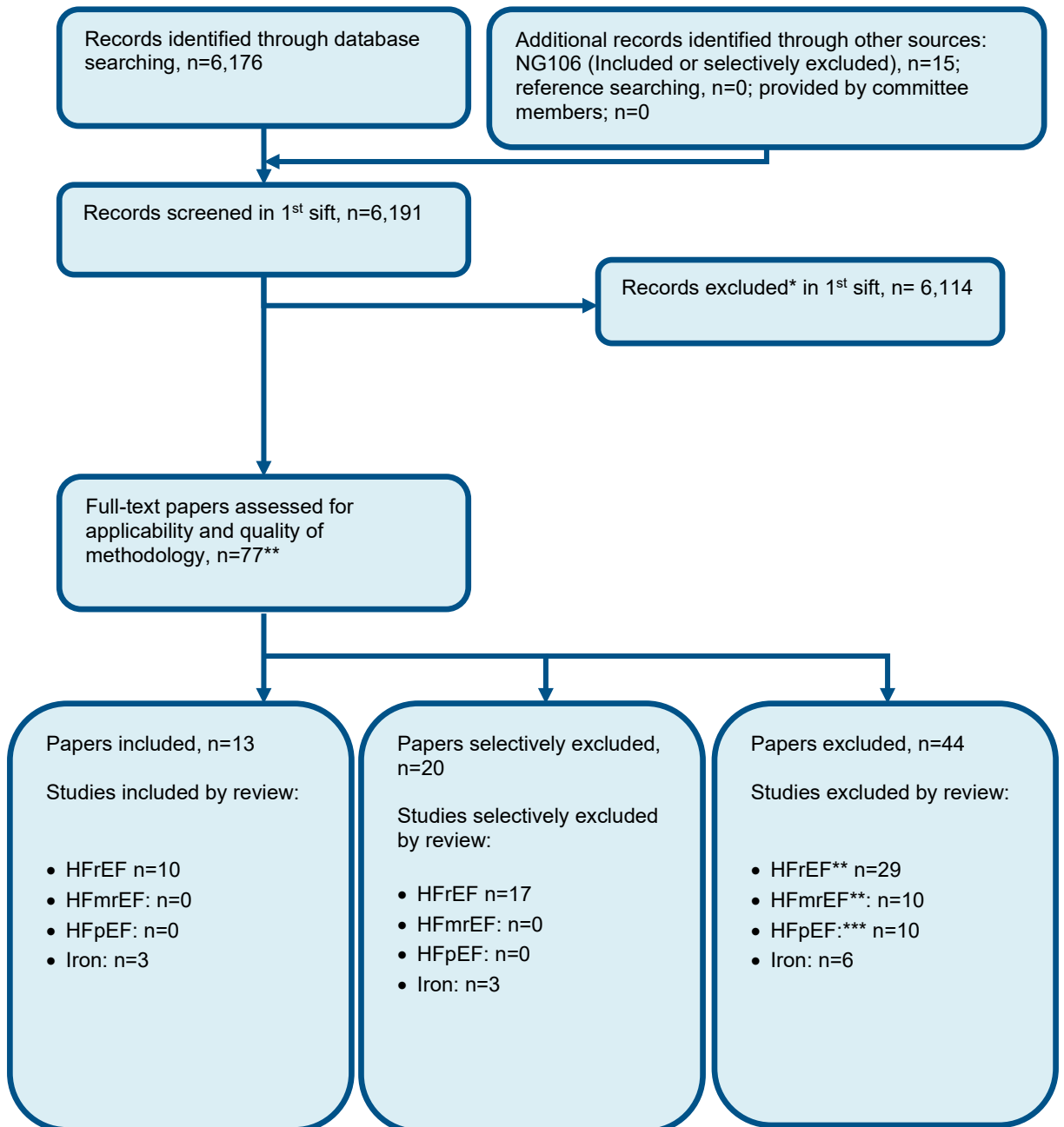
2	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none	6745	<b>HR 0.78</b> (0.69 to 0.89)	-	⊕⊕⊕○ Moderate <sup>a</sup>	CRITICAL
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HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25.

## Appendix G Economic evidence study selection

Figure 23: Flow chart of health economic study selection for the guideline update



\* Non-relevant population, intervention, comparison, design or setting; non-English language

\*\*1 study was identified that met both the HFrEF and HFmrEF population criteria

\*\*\* the same 10 studies were reviewed for both the HFmrEF and HFpEF populations

## **Appendix H Economic evidence tables**

No economic studies were included for this review question.

## **Appendix I Health economic model**

This review question was not prioritised for health economic modelling.

## Appendix J Excluded studies

### J.1 Clinical evidence studies

**Table 11: Studies excluded from the clinical review**

Study	Exclusion reason
<a href="#">Agarwal, R., Filippatos, G., Pitt, B. et al. (2022) Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: The FIDELITY pooled analysis.</a> <i>European Heart Journal</i> 43(6): 474-484a	- Population not relevant to this review protocol <i>Population focused on participants with type 2 diabetes and chronic kidney disease which was not in line with the protocol.</i>
<a href="#">Agarwal, Rajiv, Kolkhof, Peter, Bakris, George et al. (2021) Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine.</a> <i>European heart journal</i> 42(2): 152-161	- Review article but not a systematic review
Agostoni P EA (2005) Spironolactone improves lung diffusion in chronic heart failure. <i>European Heart Journal</i> 2(26): 159-164	- Population not relevant to this review protocol <i>Population focused on participants with chronic heart failure with lung diffusion which was not in line with the protocol.</i>
<a href="#">Beldhuis, Iris E, Myhre, Peder L, Claggett, Brian et al. (2019) Efficacy and Safety of Spironolactone in Patients With HFpEF and Chronic Kidney Disease.</a> <i>JACC. Heart failure</i> 7(1): 25-32	- Secondary publication of an included study that does not provide any additional relevant information
<a href="#">Beldhuis, Iris E, Myhre, Peder L, Bristow, Michael et al. (2021) Spironolactone in Patients With Heart Failure, Preserved Ejection Fraction, and Worsening Renal Function.</a> <i>Journal of the American College of Cardiology</i> 77(9): 1211-1221	- Population not relevant to this review protocol <i>Population stratified by renal function, but this was defined by creatinine levels, which was not in line with the protocol.</i>
<a href="#">Bonsu, Kwadwo Osei; Arunmanakul, Poukwan; Chaiyakunapruk, Nathorn (2018) Pharmacological treatments for heart failure with preserved ejection fraction-a systematic review and indirect comparison.</a> <i>Heart failure reviews</i> 23(2): 147-156	- Systematic review used as source of primary studies <i>Does not include all relevant studies due to the recent publication of the FINEARTS trial</i>
<a href="#">Chimura, Misato, Petrie, Mark C, Schou, Morten et al. (2024) Finerenone Improves Outcomes in Patients with Heart Failure with Mildly Reduced or Preserved Ejection Fraction Irrespective of Age: A Prespecified Analysis of FINEARTS-HF.</a> <i>Circulation. Heart failure</i>	- Secondary publication of an included study that does not provide any additional relevant information <i>Results stratified by age</i>
<a href="#">Chimura, Misato, Wang, Xiaowen, Jhund, Pardeep S et al. (2024) Finerenone in Women and Men With Heart Failure With Mildly Reduced or Preserved Ejection Fraction: A Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial.</a> <i>JAMA cardiology</i>	- Population not relevant to this review protocol <i>Mixed population of participants with mildly reduced and preserved ejection fractions.</i>

Study	Exclusion reason
<a href="#">Desai, Akshay S, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Finerenone in Patients With a Recent Worsening Heart Failure Event: The FINEARTS-HF Trial.</a> Journal of the American College of Cardiology	- Secondary publication of an included study that does not provide any additional relevant information
Deswal A, Richardson P, Bozkurt B MD (2011) Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). Journal of Cardiac Failure 8(17): 634-642	- Study does not contain an intervention relevant to this review protocol  <i>Intervention is eplerenone, which is unlicensed for CHF with preserved ejection fraction.</i>
<a href="#">Doggrell, S (2003) Should the aldosterone-receptor antagonist - eplerenone - be used after acute myocardial infarction with left ventricular dysfunction?.</a> Expert opinion on pharmacotherapy 4(9): 1605-1607	- Not a peer-reviewed publication
<a href="#">Elshahat, Ahmed, Mansour, Ahmed, Ellabban, Mohamed et al. (2024) Comparative effectiveness and safety of eplerenone and spironolactone in patients with heart failure: a systematic review and meta-analysis.</a> BMC cardiovascular disorders 24(1): 489	- Systematic review used as source of primary studies  <i>Indirect population; Mixed LVEF</i>
<a href="#">Fernandes, Barbara Pereira, Conceicao, Lino Sergio Rocha, Martins-Filho, Paulo Ricardo Saquete et al. (2018) Effect of Mineralocorticoid Receptor Antagonists in Individuals With Heart Failure With Preserved Ejection Fraction: A Systematic Review.</a> Journal of cardiac failure 24(9): 618-621	- Systematic review used as source of primary studies  <i>Does not include all relevant studies due to the recent publication of the FINEARTS trial</i>
<a href="#">Ferreira, Joao Pedro, Cleland, John G, Girerd, Nicolas et al. (2023) Spironolactone effect on cardiac structure and function of patients with heart failure and preserved ejection fraction: a pooled analysis of three randomized trials.</a> European journal of heart failure 25(1): 108-113	- Study does not contain any outcomes relevant to this review protocol
<a href="#">Ferreira, Joao Pedro, Rossello, Xavier, Eschaliier, Romain et al. (2019) MRAs in Elderly HF Patients: Individual Patient-Data Meta-Analysis of RALES, EMPHASIS-HF, and TOPCAT.</a> JACC. Heart failure 7(12): 1012-1021	- Secondary publication of an included study that does not provide any additional relevant information  <i>Data stratified by age. Not a subgroup of interest.</i>
<a href="#">Ferreira, Joao Pedro, Rossello, Xavier, Pocock, Stuart J et al. (2020) Spironolactone dose in heart failure with preserved ejection fraction: findings from TOPCAT.</a> European journal of heart failure 22(9): 1615-1624	- Secondary publication of an included study that does not provide any additional relevant information
<a href="#">Frankenstein, Lutz, Seide, Svenja, Tager, Tobias et al. (2020) Relative Efficacy of Spironolactone, Eplerenone, and cAnRenone in patients with Chronic Heart failure</a>	- Population not relevant to this review protocol  <i>Population included HFrEF</i>

Study	Exclusion reason
<p><a href="#">(RESEARCH): a systematic review and network meta-analysis of randomized controlled trials.</a> Heart failure reviews 25(2): 161-171</p>	
<p><a href="#">Fukuta, Hidekatsu, Goto, Toshihiko, Wakami, Kazuaki et al. (2019) Effects of mineralocorticoid receptor antagonists on left ventricular diastolic function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials.</a> Heart and vessels 34(4): 597-606</p>	<p>- Systematic review used as source of primary studies</p> <p><i>Does not include all relevant studies due to the publication of the FINEARTS trial</i></p>
<p><a href="#">Japp, Deepa, Shah, Anoop, Fiskens, Sheila et al. (2017) Mineralocorticoid receptor antagonists in elderly patients with heart failure: a systematic review and meta-analysis.</a> Age and ageing 46(1): 18-25</p>	<p>- Systematic review used as source of primary studies</p> <p><i>Does not include all relevant studies due to the publication of the FINEARTS trial</i></p>
<p><a href="#">Jha, V.; Aymanom, C.D.; Tiwari, S. (2022) Randomized, Placebo-Controlled Study to Investigate the Effects of Eplerenone in Patients with Heart Failure of Different Etiologies.</a> International Journal of Pharmaceutical and Clinical Research 14(1): 289-294</p>	<p>- Population not relevant to this review protocol</p> <p><i>Population not specific to HFpEF</i></p>
<p><a href="#">Jhund, Pardeep S, Talebi, Atefeh, Henderson, Alasdair D et al. (2024) Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis.</a> Lancet (London, England) 404(10458): 1119-1131</p>	<p>- Meta-analysis of already included trials</p>
<p><a href="#">Kapelios, Chris J, Murrow, Jonathan R, Nuhrenberg, Thomas G et al. (2019) Effect of mineralocorticoid receptor antagonists on cardiac function in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials.</a> Heart failure reviews 24(3): 367-377</p>	<p>- Systematic review used as source of primary studies</p> <p><i>No relevant outcomes reported</i></p>
<p>Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S STEA (2002) Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with congestive heart failure. Journal of Nuclear Medicine 10(43): 1279-1285</p>	<p>- Population not relevant to this review protocol</p> <p><i>Reduced LVEF</i></p>
<p>Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H EA (2013) Fibrosis and cardiac function in obesity: a randomised controlled trial of aldosterone blockade. Heart: 320-6</p>	<p>- Population not relevant to this review protocol</p> <p><i>Population focused on obese patients, not specifically HFpEF</i></p>
<p>Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H EA (2011) A randomized study of the beneficial effects of aldosterone antagonism on lv function, structure, and fibrosis markers in metabolic syndrome. JACC: Cardiovascular Imaging: 1239-49</p>	<p>- Population not relevant to this review protocol</p> <p><i>Population focused on those with metabolic syndrome.</i></p>

Study	Exclusion reason
<a href="#">Lewis, Eldrin F, Claggett, Brian, Shah, Amil M et al. (2018) Racial Differences in Characteristics and Outcomes of Patients With Heart Failure and Preserved Ejection Fraction in the Treatment of Preserved Cardiac Function Heart Failure Trial.</a> <i>Circulation</i> . Heart failure 11(3): e004457	<p>- Secondary publication of an included study that does not provide any additional relevant information</p> <p><i>Results stratified by race</i></p>
<a href="#">Li, Jun-Feng, Qu, Xiang, Gao, Zhan et al. (2023) Association between dosing of spironolactone and outcomes in heart failure with preserved ejection fraction patients combined with chronic kidney disease-----Balance of efficacy and risk.</a> <i>Frontiers in pharmacology</i> 14: 1084442	<p>- Study design not relevant to this review protocol</p> <p><i>Retrospective cohort study design</i></p>
<a href="#">Li, Shuai, Zhang, Xinling, Dong, Mei et al. (2018) Effects of spironolactone in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials.</a> <i>Medicine</i> 97(35): e11942	<p>- Systematic review used as source of primary studies</p> <p><i>No relevant outcomes reported</i></p>
<a href="#">Lin, M, Heizati, M, Wang, L et al. (2021) A systematic review and meta-analysis of effects of spironolactone on blood pressure, glucose, lipids, renal function, fibrosis and inflammation in patients with hypertension and diabetes.</a> <i>Blood pressure</i> 30(3): 145-153	<p>- Population not relevant to this review protocol</p> <p><i>Population comprised of patients with hypertension and diabetes</i></p>
<a href="#">Lin, Y., Cai, Z., Yuan, J. et al. (2022) Effect of pharmacological treatment on outcomes of heart failure with preserved ejection fraction: an updated systematic review and network meta-analysis of randomized controlled trials.</a> <i>Cardiovascular Diabetology</i> 21(1): 237	<p>- Systematic review used as source of primary studies</p> <p><i>Does not include all relevant trials due to the recent publication of the FINEARTS trial.</i></p>
<a href="#">Lin, Y., Wu, M., Liao, B. et al. (2021) Comparison of Pharmacological Treatment Effects on Long-Time Outcomes in Heart Failure With Preserved Ejection Fraction: A Network Meta-analysis of Randomized Controlled Trials.</a> <i>Frontiers in Pharmacology</i> 12: 707777	<p>- Systematic review used as source of primary studies</p> <p><i>Does not include all relevant studies due to the recent publication of the FINEARTS trial.</i></p>
Liu (2006) Effects of spironolactone in treatment of elderly hypertension patients with diastolic heart failure. <i>Chin J New Drugs Clin Rem</i> : 567-70	<p>- Study not reported in English</p> <p><i>Study reported in Chinese</i></p>
Mak GJ, Ledwidge MT, Watson CJ, Phelan DM, Dawkins IR MNEA (2009) Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. <i>Journal of the American College of Cardiology</i> 18(54): 1674-82	<p>- Study does not contain an intervention relevant to this review protocol</p> <p><i>Intervention is eplerenone, which is unlicensed for CHF with preserved ejection fraction.</i></p>
<a href="#">Mc Causland, Finnian R, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Finerenone and Kidney Outcomes in Patients</a>	<p>- Population not relevant to this review protocol</p>

Study	Exclusion reason
<a href="#">with Heart Failure: The FINEARTS-HF Trial.</a> Journal of the American College of Cardiology	<i>Population comprised of a mix of participants with mildly reduced and preserved ejection fractions.</i>
<a href="#">McDiarmid, Adam K, Swoboda, Peter P, Erhayiem, Bara et al. (2020) Myocardial Effects of Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction.</a> Journal of the American Heart Association 9(1): e011521	- Study does not contain any outcomes relevant to this review protocol
<a href="#">Myhre, Peder L, Vaduganathan, Muthiah, O'Meara, Eileen et al. (2020) Mechanistic Effects of Spironolactone on Cardiovascular and Renal Biomarkers in Heart Failure With Preserved Ejection Fraction: A TOPCAT Biorepository Study.</a> Circulation. Heart failure 13(1): e006638	- Study design not relevant to this review protocol  <i>Short communications piece</i>
<a href="#">Nabati, Maryam, Tabiban, Sasan, Khani, Afshin et al. (2021) The Effects of Spironolactone and Eplerenone on Left Ventricular Function Using Echocardiography in Symptomatic Patients With New-Onset Systolic Heart Failure: A Comparative Randomised Controlled Trial.</a> Heart, lung & circulation 30(9): 1292-1301	- Study does not include a comparison relevant to this review protocol  <i>Within-class comparison</i>
<a href="#">Neefs, Jolien, van den Berg, Nicoline W E, Krul, Sebastien P J et al. (2020) Effect of Spironolactone on Atrial Fibrillation in Patients with Heart Failure with Preserved Ejection Fraction: Post-Hoc Analysis of the Randomized, Placebo-Controlled TOPCAT Trial.</a> American journal of cardiovascular drugs : drugs, devices, and other interventions 20(1): 73-80	- Secondary publication of an included study that does not provide any additional relevant information  <i>Data reported based on presence of atrial fibrillation</i>
<a href="#">Pandey, Ambarish, Berry, Jarett D, Drazner, Mark H et al. (2018) Body Mass Index, Natriuretic Peptides, and Risk of Adverse Outcomes in Patients With Heart Failure and Preserved Ejection Fraction: Analysis From the TOPCAT Trial.</a> Journal of the American Heart Association 7(21): e009664	- Secondary publication of an included study that does not provide any additional relevant information  <i>Data reported based on participant BMI or natriuretic peptides</i>
<a href="#">Pei, Hui, Wang, Wei, Zhao, Di et al. (2018) The use of a novel non-steroidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure: A systematic review and meta-analysis.</a> Medicine 97(16): e0254	- Population not relevant to this review protocol  <i>Population focused on HFrEF</i>
<a href="#">Petutschnigg, J, Ferreira, JP, Holzendorf, V et al. (2020) Body fat phenotypes and treatment response to spironolactone in ambulatory patients with heart failure and preserved ejection fraction: a post-hoc analysis of the Aldo-DHF trial.</a> European journal of heart failure 22(3): 559-561	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
<p><a href="#">Pfeffer, Marc A, Claggett, Brian, Assmann, Susan F et al. (2015) Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 131(1): 34-42</a></p>	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>
<p><a href="#">Przewlocka-Kosmala, Monika, Marwick, Thomas H, Mysiak, Andrzej et al. (2019) Usefulness of myocardial work measurement in the assessment of left ventricular systolic reserve response to spironolactone in heart failure with preserved ejection fraction. European heart journal. Cardiovascular Imaging 20(10): 1138-1146</a></p>	<p>- Study does not contain any outcomes relevant to this review protocol</p>
<p><a href="#">Rujic, D., Schou, M., Madsen, P.L. et al. (2023) Echocardiographic Evaluation of Spironolactone on Myocardial Remodeling in Atrial Fibrillation with Preserved Ejection Fraction: the INSPIRE-AF randomized controlled trial. medRxiv</a></p>	<p>- Study does not contain any outcomes relevant to this review protocol <i>focused on myocardial remodelling</i></p>
<p><a href="#">Sampaio Rodrigues, Thalys, Garcia Quarto, Levindo Jose, Nogueira, Savio Carvalho et al. (2024) Incidence and progression of atrial fibrillation in patients with and without heart failure using mineralocorticoid receptor antagonists: a meta-analysis. Clinical research in cardiology : official journal of the German Cardiac Society 113(6): 884-897</a></p>	<p>- Systematic review does not report any outcomes of relevance to this protocol</p>
<p><a href="#">Schnelle, Moritz, Leha, Andreas, Eidizadeh, Abass et al. (2021) Plasma Biomarker Profiling in Heart Failure Patients with Preserved Ejection Fraction before and after Spironolactone Treatment: Results from the Aldo-DHF Trial. Cells 10(10)</a></p>	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>
<p><a href="#">Shah, Amil M, Claggett, Brian, Sweitzer, Nancy K et al. (2015) Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. Circulation 132(5): 402-14</a></p>	<p>- Study does not contain any outcomes relevant to this review protocol <i>Focuses on prognostic value of longitudinal strain.</i></p>
<p><a href="#">Shah, Amil M, Claggett, Brian, Sweitzer, Nancy K et al. (2014) Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circulation. Heart failure 7(5): 740-51</a></p>	<p>- Secondary publication of an included study that does not provide any additional relevant information <i>Data reported based on event vs. non-event</i></p>
<p><a href="#">Shah, Amil M, Claggett, Brian, Sweitzer, Nancy K et al. (2015) Prognostic Importance of Changes in Cardiac Structure and Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. Circulation. Heart failure 8(6): 1052-8</a></p>	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>

Study	Exclusion reason
<p><a href="#">Shah, Amil M, Shah, Sanjiv J, Anand, Inder S et al. (2014) Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial.</a> <i>Circulation. Heart failure</i> 7(1): 104-15</p>	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>
<p><a href="#">Shantsila, Eduard, Haynes, Ronnie, Calvert, Melanie et al. (2016) IMproved exercise tolerance in patients with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation rationale and design of the IMPRESS-AF randomised controlled trial.</a> <i>BMJ open</i> 6(10): e012241</p>	<p>- Population not relevant to this review protocol &lt;80% with CHF</p>
<p><a href="#">Shantsila, Eduard, Shahid, Farhan, Sun, Yongzhong et al. (2020) Spironolactone to improve exercise tolerance in people with permanent atrial fibrillation and preserved ejection fraction: the IMPRESS-AF RCT.</a></p>	<p>- Population not relevant to this review protocol &lt;80% with CHF</p>
<p><a href="#">Shantsila, Eduard, Shahid, Farhan, Sun, Yongzhong et al. (2020) Spironolactone in Atrial Fibrillation With Preserved Cardiac Fraction: The IMPRESS-AF Trial.</a> <i>Journal of the American Heart Association</i> 9(18): e016239</p>	<p>- Population not relevant to this review protocol &lt;80% with CHF</p>
<p><a href="#">Solomon, Scott D, Ostrominski, John W, Vaduganathan, Muthiah et al. (2024) Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: The FINEARTS-HF trial.</a> <i>European journal of heart failure</i> 26(6): 1334-1346</p>	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>
<p><a href="#">Sperry, Brett W, Hanna, Mazen, Shah, Sanjiv J et al. (2021) Spironolactone in Patients With an Echocardiographic HFpEF Phenotype Suggestive of Cardiac Amyloidosis: Results From TOPCAT.</a> <i>JACC. Heart failure</i> 9(11): 795-802</p>	<p>- Secondary publication of an included study that does not provide any additional relevant information <i>Information focuses on patients with cardiac amyloidosis</i></p>
<p><a href="#">Sperry, BW, Tang, Y, Jones, PG et al. (2021) Cumulative events in the TOPCAT trial.</a> <i>European journal of heart failure</i> 23(3): 491-492</p>	<p>- Study design not relevant to this review protocol <i>Research letter</i></p>
<p><a href="#">Squire, Iain B, Gabrielsen, Anders, Greasley, Peter J et al. (2022) Effect of AZD9977 and spironolactone on serum potassium in heart failure with preserved or mildly reduced ejection fraction, and renal impairment: A randomized trial.</a> <i>Clinical and translational science</i> 15(10): 2493-2504</p>	<p>- Comparator in study does not match that specified in this review protocol <i>Comparator is AZD9977</i></p>
<p><a href="#">Sreenivasan, Jayakumar, Malik, Aaqib, Khan, Muhammad Shahzeb et al. (2024) Pharmacotherapies in Heart Failure With Preserved Ejection Fraction: A Systematic</a></p>	<p>- Systematic review used as source of primary studies <i>Does not include all relevant studies</i></p>

Study	Exclusion reason
<a href="#">Review and Network Meta-Analysis</a> . Cardiology in review 32(2): 114-123	
<a href="#">Szabo, Barna, Benson, Lina, Savarese, Gianluigi et al. (2024) Previous heart failure hospitalization, spironolactone, and outcomes in heart failure with preserved ejection fraction - a secondary analysis of TOPCAT</a> . American heart journal 271: 136-147	<p>- Secondary publication of an included study that does not provide any additional relevant information</p> <p><i>Data stratified by prior hospitalisation for heart failure</i></p>
Taheri S, Mortazavi M, Pourmoghadas A, Seyrafian S, Alipour Z KS (2012) A prospective double-blind randomized placebo-controlled clinical trial to evaluate the safety and efficacy of spironolactone in patients with advanced congestive heart failure on continuous ambulatory peritoneal dialysis. Saudi Journal of Kidney Diseases and Transplantation 3(23): 507-512	<p>- Population not relevant to this review protocol</p> <p><i>Population focused on congestive heart failure patients who were also receiving continuous peritoneal dialysis</i></p>
Taheri S, Mortazavi M, Shahidi S, Pourmoghadas A, Garakyaraghi M SSEA (2009) Spironolactone in chronic hemodialysis patients improves cardiac function. Saudi Journal of Kidney Diseases and Transplantation 3(20): 392-7	<p>- Population not relevant to this review protocol</p> <p><i>Population focused on haemodialysis patients</i></p>
<a href="#">Tromp, Jasper, Ouwerkerk, Wouter, van Veldhuisen, Dirk J et al. (2022) A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction</a> . JACC. Heart failure 10(2): 73-84	<p>- Population not relevant to this review protocol</p> <p><i>Population focused on HFrEF</i></p>
<a href="#">Tsujiimoto, Tetsuro and Kajio, Hiroshi (2020) Spironolactone Use and Improved Outcomes in Patients With Heart Failure With Preserved Ejection Fraction With Resistant Hypertension</a> . Journal of the American Heart Association 9(23): e018827	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>
<a href="#">Tsutsui, Hiroyuki, Ito, Hiroshi, Kitakaze, Masafumi et al. (2017) Double-Blind, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Eplerenone in Japanese Patients With Chronic Heart Failure (J-EMPHASIS-HF)</a> . Circulation journal : official journal of the Japanese Circulation Society 82(1): 148-158	<p>- Population not relevant to this review protocol</p> <p><i>Population focused on HFrEF</i></p>
<a href="#">Vaduganathan, Muthiah, Claggett, Brian L, Desai, Akshay S et al. (2024) Estimated Long-Term Benefits of Finerenone in Heart Failure: A Prespecified Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial</a> . JAMA cardiology	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>
<a href="#">Vaduganathan, Muthiah, Claggett, Brian L, Lam, Carolyn S P et al. (2024) Finerenone in patients with heart failure with mildly reduced or</a>	<p>- Secondary publication of an included study that does not provide any additional relevant information</p>

Study	Exclusion reason
<a href="#">preserved ejection fraction: Rationale and design of the FINEARTS-HF trial.</a> European journal of heart failure 26(6): 1324-1333	
<a href="#">Vaduganathan, Muthiah, Filippatos, Gerasimos, Claggett, Brian L et al. (2024) Finerenone in heart failure and chronic kidney disease with type 2 diabetes: FINE-HEART pooled analysis of cardiovascular, kidney and mortality outcomes.</a> Nature medicine	- Population not relevant to this review protocol  <i>&lt;80% of participants in the pooled analysis had CHF</i>
<a href="#">Vardeny, Orly, Claggett, Brian, Vaduganathan, Muthiah et al. (2019) Influence of Age on Efficacy and Safety of Spironolactone in Heart Failure.</a> JACC. Heart failure 7(12): 1022-1028	- Secondary publication of an included study that does not provide any additional relevant information
<a href="#">Vardeny, Orly, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Finerenone, Serum Potassium, and Clinical Outcomes in Heart Failure With Mildly Reduced or Preserved Ejection Fraction.</a> JAMA cardiology	- Secondary publication of an included study that does not provide any additional relevant information
<a href="#">Wang, Qi, Yu, Fei, Su, Hao et al. (2024) Recurrent heart failure hospitalizations in heart failure with preserved ejection fraction: an analysis of TOPCAT trial.</a> ESC heart failure 11(1): 475-482	- Secondary publication of an included study that does not provide any additional relevant information
<a href="#">Xiang, Boyang, Zhang, Ruiqi, Wu, Xiaoguang et al. (2022) Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis.</a> JAMA network open 5(9): e2231963	- Systematic review does not contain an intervention relevant to this review protocol  <i>Intervention of focus was SGLT2 inhibitors</i>
<a href="#">Xiang, Yajie, Shi, Wenhai, Li, Zhuolin et al. (2019) Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction: A meta-analysis of randomized clinical trials.</a> Medicine 98(13): e14967	- Systematic review used as source of primary studies  <i>Does not include all relevant studies due to the recent publication of the FINEARTS trial. Does not match protocol population due to including mixed preserved and mildly reduced LVEF).</i>
<a href="#">Yang, Mingming, Henderson, Alasdair D, Talebi, Atefeh et al. (2024) Effect of Finerenone on the KCCQ in Patients With HFmrEF/HFpEF: A Prespecified Analysis of FINEARTS-HF.</a> Journal of the American College of Cardiology	- Secondary publication of an included study that does not provide any additional relevant information  <i>Relevant information already presented in an included record (Docherty, 2024)</i>
<a href="#">Yang, Pingping, Shen, Wen, Chen, Xi et al. (2019) Comparative efficacy and safety of mineralocorticoid receptor antagonists in heart failure: a network meta-analysis of randomized controlled trials.</a> Heart failure reviews 24(5): 637-646	- Population not relevant to this review protocol  <i>Population with LVEF &lt;45%</i>
<a href="#">Zafeiropoulos, Stefanos, Farmakis, Ioannis T, Milioglou, Ioannis et al. (2024) Pharmacological Treatments in Heart Failure With Mildly Reduced and Preserved Ejection Fraction: Systematic</a>	- Systematic review used as source of primary studies

Study	Exclusion reason
<a href="#">Review and Network Meta-Analysis</a> . JACC. Heart failure 12(4): 616-627	<i>NMA that does not include all of the relevant studies due to recent publication of the FINEARTS trial</i>
<a href="#">Zheng, Sean Lee, Chan, Fiona T, Nabeebaccus, Adam A et al. (2018) Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis</a> . Heart (British Cardiac Society) 104(5): 407-415	- Systematic review used as source of primary studies  <i>Does not include all relevant studies due to the recent publication of the FINEARTS trial.</i>

## J.2 Health economic studies

**Table 12: Studies excluded from the health economic review**

Study	Exclusion reason
<a href="#">Booth, David, Davis, Jason A, McEwan, Phil et al. (2023) The cost-effectiveness of dapagliflozin in heart failure with preserved or mildly reduced ejection fraction: A European health-economic analysis of the DELIVER trial</a> . European journal of heart failure 25(8): 1386-1395	- Wrong intervention/comparator – SGLT2 inhibitor
<a href="#">Bounthavong, Mark, Butler, Javed, Dolan, Chantal M et al. (2019) Correction to: Cost-Effectiveness Analysis of Patiromer and Spironolactone Therapy in Heart Failure Patients with Hyperkalemia</a> . PharmacoEconomics 37(8): 1071	- Wrong intervention/comparator
<a href="#">Dasta, Joseph F, Sundar, Shirin, Chase, Sandra et al. (2018) Economic impact of tolvaptan treatment vs. fluid restriction based on real-world data among hospitalized patients with heart failure and hyponatremia</a> . Hospital practice (1995) 46(4): 197-202	- Wrong intervention/comparator
<a href="#">Fauchier, Laurent, Lamblin, Nicolas, Tardu, Jean et al. (2024) Public Health Impact and Cost-Effectiveness of Empagliflozin (JARDIANCE R) in the Treatment of Patients with Heart Failure with Preserved Ejection Fraction in France, Based on the EMPEROR-Preserved Clinical Trial</a> . PharmacoEconomics - open 8(1): 19-30	- Wrong intervention/comparator – SGLT2 inhibitor
<a href="#">Kolovos, Spyros, Bellanca, Leana, Groyer, Harinala et al. (2023) Multinational cost-effectiveness analysis of empagliflozin for heart failure patients with ejection fraction &gt;40</a> . ESC heart failure 10(6): 3385-3397	- Wrong intervention/comparator – SGLT2 inhibitor

Study	Exclusion reason
<p><a href="#">Kolovos, Spyros, Bellanca, Leana, Groyer, Harinala et al. (2023) Cost-effectiveness of empagliflozin in heart failure patients irrespective of ejection fraction in England.</a> Journal of cardiovascular medicine (Hagerstown, Md.) 24(10): 758-764</p>	<p>- Wrong intervention/comparator – SGLT2 inhibitor</p>
<p><a href="#">Tsutsui, Hiroyuki, Sakamaki, Hiroyuki, Momomura, Shin-Ichi et al. (2024) Empagliflozin cost-effectiveness analysis in Japanese heart failure with mildly reduced and preserved ejection fraction.</a> ESC heart failure 11(1): 261-270</p>	<p>- Wrong intervention/comparator – SGLT2 inhibitor</p>
<p><a href="#">Zhou, Jennifer, Liew, Danny, Kaye, David M et al. (2022) Cost-Effectiveness of Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction.</a> Circulation. Cardiovascular quality and outcomes 15(10): e008638</p>	<p>- Wrong intervention/comparator – SGLT2 inhibitor</p>