National Institute for Health and Care Excellence

Guideline version (Consultation)

Chronic heart failure in adults: diagnosis and management

Evidence review for mineralocorticoid receptor antagonist therapy for heart failure with preserved left ventricular ejection fraction

NICE guideline <number>

Evidence reviews underpinning recommendation 1.5.1 in the NICE guideline

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These evidence reviews were 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 (eplerenone, 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 ≤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 ≥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 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

Population	• Adults diagnosed with heart failure with preserved ejection fraction.
	• Preserved ejection fraction heart failure is defined as left ventricular ejection fraction (LVEF) ≥50%, 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:
	  ○ Left atrial volume >34 ml/m^2 in sinus rhythm, or >40 ml/m^2 in atrial fibrillation
	  ○ Ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E:e') >11
	  ○ Left ventricular hypertrophy (>12 mm wall thickness)
	  ○ Pulmonary arterial pressure >35 mmHg

	Diagnosis should be made by a heart failure specialist or heart failure specialist team. 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 ≥80% match the protocol criteria or there are subgroup data for the protocol population. Exclusion: • Children • Acute heart failure in hospital • Heart failure with reduced or mildly reduced ejection fraction • Heart failure due to right heart dysfunction (e.g., pre-capillary pulmonary hypertension and primary right ventricular cardiomyopathies) • High output heart failure • Adult congenital heart disease • Primary heart valve disease • Acute myocardial infarction (within 3 months of the event) • Treatment with chemotherapy
Intervention	• Mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone)
Comparison	Placebo + usual chronic heart failure care or usual chronic heart failure care alone

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	• All-cause mortality (time-to-event)
	• Cardiovascular mortality (time-to-event)
	• 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)
	• Unplanned hospitalisation or visits (heart failure-related) (time-to-event; including repeat events when reported)
	  ○ 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
	Adverse events (recorded as the number of people with at least one event, not the total number of events)
	• Withdrawal due to drug-related adverse events (dichotomous)
	• Acute Kidney Injury – serum creatinine rise of ≥50% over ≤7 days (dichotomous)
	• Hyponatraemia- serum sodium concentration <135 mmol/L (dichotomous)
	• Hyperkalaemia- serum potassium concentration ≥5.5 mmol/L (dichotomous)
	• Falls (dichotomous)
	• Gynaecomastia (dichotomous)
	Time points for analysis:
	  ○ 12 months (pool all times ≥3 months, taking the closest to 12 months follow-up time from each study if multiple time points are reported)
	Exclude if follow-up < 3 months

Study design	Inclusion: • Randomised controlled trials (RCTs) • Published systematic reviews of RCTs • Published network meta-analyses (NMAs) and individual participant data meta-analyses (IPDs).

	Exclusion: • 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.

Eight RCT studies (across 15 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 3 different MRA therapies – eplerenone, spironolactone, and finerenone (which have been combined as a class grouping in this review) – and compared these to placebo. Although finerenone was included in the review protocol, evidence on this intervention has been downgraded for indirectness as it is not currently licenced for use in chronic heart failure. 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 A2.

The TOPCAT trial included adults with LVEF ≥45%, but the full trial population was included in the analysis for this review because over 80% of participants had an LVEF ≥50%. A sensitivity analysis was undertaken using only the data from TOPCAT in those with an LVEF ≥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. Five of the studies (Docherty 2024, Deswaal 2011, Kurrelmeyer 2014, Mak 2009 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. Four studies (Edelmann, 2013; Kurrelmeyer, 2014; Mak, 2009; 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
Deswal, 2011 [RAAM-PEF]	25 mg of eplerenone per day for two weeks, followed by 50 mg daily for 22 weeks, if tolerated Placebo	Adults with HFpEF NYHA class II–III, with LVEF ≥50% and B-type natriuretic peptide levels ≥100pg/mL confirmed within 2 months of screening, with the ability to walk 50 meters and current use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, if tolerated for 4 weeks before enrolment. N=44	• All-cause mortality • Kansas City Cardiomyopathy Questionnaire • Heart failure-related hospitalisation • Serum creatinine • Hyperkalaemia Follow-up: 6 months
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	• All-cause mortality • Cardiovascular mortality • Kansas City Cardiomyopathy Questionnaire • Heart failure-related hospitalisation • Discontinuation due to drug-related events • Hyperkalaemia Follow-up: 12 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	• All-cause mortality • Minnesota Living with Heart Failure Questionnaire • SF-36 Physical Functioning Score • Cardiac hospitalisation • Hyperkalaemia • Gynaecomastia 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	• All-cause mortality • Kansas City Cardiomyopathy Questionnaire • Heart failure-related hospitalisation

Study	Intervention and comparison	Population	Outcomes
			• Transient and serious hyperkalaemia Follow-up: 6 months
Mak, 2009	25 mg of eplerenone per day with dose increased to 50 mg/day after 6 months Placebo	Patients with heart failure preserved systolic function, over 50% had prior NYHA class IV hospital admission, LVEF ≥45% (mean 63%), BNP >100 pg/mL N=44	• All-cause mortality • Minnesota Living with Heart Failure Questionnaire Follow-up: 12 months
Mottram, 2004	25 mg of spironolactone per day Placebo	Patients with diastolic heart failure with LVEF ≥50%, NYHA class II and hypertension requiring antihypertensive medication and reported exertional dyspnoea. N=30	• Gynaecomastia 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	• All-cause mortality • Cardiovascular mortality • Kansas City Cardiomyopathy Questionnaire • EQ-5D • Heart failure-related hospitalisation • Hyperkalaemia • Gynaecomastia 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	• Minnesota Living with Heart Failure Questionnaire • All-cause hospitalisation 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 Follow-up	№ 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: 1 to 3.3 years	7266 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	HR 0.89 (0.79 to 1.0)	Not estimable	Not estimable
All-cause mortality (dichotomous) Follow-up: 9 to 12 months	7802 (6 RCTs)	⨁◯◯◯ Very low[a,d]	RR 0.93 (0.84 to 1.03)	153 per 1,000	11 fewer per 1,000 (from 24 fewer to 5 more)
Cardiovascular mortality (time-to-event) Follow-up: 1 to 3.3 years	7266 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	HR 0.90 (0.77 to 1.06)	Not estimable	Not estimable
Cardiovascular mortality (dichotomous) Follow-up: 1 to 3.3 years	7266 (2 RCTs)	⨁⨁⨁◯ Moderate[e]	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	501 (3 RCTs)	⨁⨁⨁◯ Moderate[f]	-	The mean change in MLWHF was -0.3.	MD 1.14 lower (3.24 lower to 0.97 higher)
KCCQ overall summary score (OSS); change scores (score range: 0-100, higher scores are better) Follow-up: 6 to 12 months	3444 (2 RCTs) Follow-up: 6 months to 12 months	⨁⨁⨁⨁ High	-	The change from baseline was not reported	MD 1.32 higher (0.19 higher to 2.45 higher)
KCCQ clinical summary score (CSS); change scores (score range: 0-100, higher scores are better) Follow-up: 6 months	92 (2 RCT)	⨁⨁◯◯ Low[c,g]	-	The mean change in KCCQ CSS was 7.36	MD 3.84 lower (11.16 lower to 3.48 higher)
KCCQ total symptom score (TSS); change scores (score range 0-100, higher scores are better) Follow-up: 12 months	4221 (1 RCT)	⨁⨁◯◯ Low[b,h]	-	The mean change in KCCQ TSS was 7.31	MD 1.90 higher (0.7 higher to 3.09 higher)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MRA
SF-36 Physical functioning; final score (score range: 0-100, higher scores are better) Follow-up: 12 months	381 (1 RCT)	⨁⨁◯◯ Low[c,i]	-	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) Follow-up: 3.3 years	3395 (1 RCT)	⨁⨁⨁⨁ High	-	NR	MD 0.47 higher (0.27 lower to 1.21 higher)
Heart failure-related hospitalisation (time-to-event) Follow-up: 1 year to 3.3 years	7266 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	HR 0.77 (0.69 to 0.87)	Not estimable	Not estimable
Heart failure-related hospitalisation (total events) Follow-up: 1 year to 3.3 years	7266 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	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)[j]
Heart failure-related hospitalisation (dichotomous) Follow-up: 6 months to 3.3 years	7758 (5 RCTs)	⨁◯◯◯ Very low[c,e,i]	RR 0.87 (0.78 to 0.96)	159 per 1,000	21 fewer per 1,000 (from 35 fewer to 6 fewer)
All-cause hospitalisation (dichotomous) Follow-up: 9 months	71 (1 RCT)	⨁◯◯◯ Very low[a,c,d]	RR 0.71 (0.30 to 1.71)	265 per 1,000	77 fewer per 1,000 (185 fewer to 188 more)
Withdrawal due to drug-related events (dichotomous) Follow-up: 12 months	3808 (1 RCT)	⨁◯◯◯ Very low[c,e]	RR 1.22 (0.85 to 1.74)	28 per 1,000	6 more per 1,000 (from 4 fewer to 21 more)
AKI - Serum creatinine at ≥50% (dichotomous) Follow-up: 6 months to 3.3 years	3489 (2 RCTs)	⨁◯◯◯ Very low[b,c,h]	RR 1.46 (1.17 to 1.82)	70 per 1,000	32 more per 1,000 (from 12 more to 57 more)
Hyperkalaemia – Serum potassium concentration ≥5.5mmol/L (dichotomous) Follow-up: 6 months to 3.3 years	7619 (5 RCTs)	⨁⨁◯◯ Low[c,k]	RR 2.07 (1.81 to 2.36)	74 per 1,000	80 more per 1,000 (from 60 more to 101 more)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MRA
Gynaecomastia in men or breast tenderness/ enlargement in women (dichotomous) Follow-up: 6 months to 3.3 years	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)

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 as the majority of the evidence was indirect due to finerenone not being licensed for CHF.
c. 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.
d. Downgraded by 2 increment as the majority of the evidence was very indirect (due to reporting as number of events rather then time to event and using finerenone which is not licensed for CHF)
e. Downgraded by 1 increment as the majority of the evidence was indirect (due to reporting as number of events)
f. Downgraded by 1 increment for risk of bias due to some concerns for the majority of the evidence: no information provided regarding allocation concealment.
g. 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.
h. Downgraded by 1 increment for risk of bias due to unexplained deviations from the trial protocol (the FINEARTS-HF trial did not use the LVEF thresholds prespecified in the study protocol).
i. Downgraded by 1 increment for risk of bias due to no information regarding allocation concealment provided.
j. Absolute difference calculated based on difference in number of events per person-year reported in the papers.
k. Downgraded by 1 increment for indirectness due to the 50% increase not being within the acute time frame specified in the protocol.

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: 12 months to 3.4 years	⨁⨁⨁◯ Moderate[a]	HR 0.92 (0.81 to 1.04)	Not estimable	Not estimable
Cardiovascular mortality (time-to-event)	6745 (2 RCTs) Follow-up: 12 months to 3.4 years	⨁⨁⨁◯ Moderate[b]	HR 0.94 (0.79 to 1.12)	Not estimable	Not estimable
Heart failure-related hospitalisations (time-to-event)	6745 (2 RCTs)	⨁⨁◯◯ Low[a,b]	HR 0.78 (0.69 to 0.89)	Not estimable	Not estimable

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
	Follow-up: 12 months to 3.4 years				

HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial
a. Downgraded by 1 increment as the majority of the evidence was indirect due to finerenone not being licensed for CHF.
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.

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

Parameter	Value	Source
All-cause mortality – Hazard ratio (MRA vs no medicine) – all years	0.89	Guideline review – see **Table 3**
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 **Table 3**
Hospitalisation for heart failure – rate ratio – all years	0.79	Guideline review – see **Table 3**
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	£5,950	6.126	-	5.83
Spironalactone	£8,391	6.430		6.01
Increment	£2,441	0.303	£8,054	0.18

ICER: Incremental cos-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 (27th March 2025)

Class	Drug	Tablets/pack	Price/ pack	Tablets per day	Cost per year at max dose	Dose	Indication
MRA	Eplerenone	28	£3.96	1	£51.66	Initially 25mg daily, then increased to 50mg daily, increased within 4 weeks of initial treatment.	**[Off-label For HFpEF.]** Adjunct in stable patients with left ventricular ejection fraction ≤40% with evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event). Adjunct in chronic mild heart failure with left ventricular ejection fraction ≤30%
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	**[Off-label For HFpEF.]** 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 m2]
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	Eplerenone	£51.66	3 (2, 3)	£148 (£111, £148)	£200 (£163, £200)
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, indirectness due to finerenone not being licenced for CHF, and risk of bias due to limited allocation reporting, potential problems with the randomisation process, and unexplained deviations from the trial protocol.

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 ≥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 44 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.

All reported quality of life outcomes, including the Minnesota Living with Heart Failure measure, the Kansas City Cardiomyopathy Questionnaire, EQ-VAS, and SF-36, demonstrated no clinically important difference with the addition of MRAs.

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, eplerenone or finerenone could be considered as alternative options. However, finerenone is a more expensive alternative.

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 ≥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 ≥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.

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. While finerenone is expected to have a better side effect profile, its significantly higher acquisition cost combined with a lack of evidence of greater clinical effectiveness, makes its cost-effectiveness more uncertain.

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 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.

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 1.5.1.

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

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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

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

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. Journal of the American College of Cardiology 18(54): 1674-82

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

Upadhya, 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 (eplerenone, 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	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Date limitations – from date of searches in 2018 update; 6th December 2017 • English language studies • Human studies Other searches: Inclusion lists of relevant systematic reviews

Field	Content
	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. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details). Key paper: Solomon SD et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2024 Oct 24;391(16):1475-1485.
Condition or domain being studied	Chronic heart failure with preserved ejection fraction.
Population	**Inclusion**: Adults diagnosed with heart failure due to left ventricular dysfunction with preserved ejection fraction. Preserved ejection fraction CHF is defined as LVEF ≥50% plus a structural issue in the heart including two or more of the following: • Left atrial volume > 34 ml/m2 in sinus rhythm, or >40 ml/m2 in atrial fibrillation • Ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E:e') >11 • Left ventricular hypertrophy (>12 mm wall thickness), • Pulmonary arterial pressure >35 mmHg Diagnosis should be made by a heart failure specialist or heart failure specialist team. Studies including an indirect population (for example mixed HFmrEF and HFpEF) will only be included if ≥80% match the protocol criteria or there are subgroup data for the protocol population. **Exclusion**: • Children • Acute heart failure in hospital • Heart failure with reduced or mildly reduced EF • Heart failure due to right heart dysfunction (e.g., pre-capillary pulmonary hypertension and primary right ventricular cardiomyopathies) • High output heart failure

Field	Content
	• Adult congenital heart disease • Primary heart valve disease • Acute MI (within 3 months of the event) • Treatment with chemotherapy
Intervention	**Inclusion**: Mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone) **Mode of delivery**: oral **Analysis groupings**: a class effect will be assumed and all licenced agents and doses within a class will be pooled. 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.
Comparator	Placebo + usual CHF care or usual CHF care alone
Types of study to be included	**Inclusion**: • RCTs • Published systematic reviews of RCTs • Published individual participant data meta-analyses (IPDs). **Exclusion**: • Cross-over RCTs • Non-randomised studies 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

Field	Content
Context	This review will partially update NICE guideline NG106.
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause mortality (time-to-event) • Cardiovascular mortality (time-to-event) • 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) • Unplanned hospitalisation or visits (HF-related) (time-to-event; including repeat events when reported) • 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 Adverse events (recorded as the number of people with at least one event, not the total number of events) • Withdrawal due to drug-related adverse events (dichotomous) • Acute Kidney Injury – serum creatinine rise of ≥ 50% over ≤7 days (dichotomous) • Hyponatraemia – serum sodium concentration < 135 mmol/L (dichotomous) • Hyperkalaemia – serum potassium concentration ≥ 5.5 mmol/L (dichotomous) • Falls – (dichotomous) • Gynaecomastia (dichotomous) Time points for analysis: 12 months (pool all times ≥3 months, taking the closest to 12 months follow-up time from each study if multiple time points are reported) Exclude if follow-up < 3 months 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 (https://onlinelibrary.wiley.com/doi/epdf/10.1093/eurjhf/hft095). Indirect outcome definitions

Field	Content
	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. 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.
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. 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 Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior technical analyst. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments 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.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
Strategy for data synthesis	• 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. • 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

Field	Content	
	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. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 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. • 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. • 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 http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
Analysis of sub-groups	**Subgroups that will be investigated if heterogeneity is present:** • Renal function (eGFR <30mL/min; eGFR 30-60mL/min; eGFR >60mL/min) • Presence or absence of type 2 diabetes • MRA type (steroidal and non-steroidal)	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	

Field	Content		
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	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail chfiatreatment@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
Review team members	From NICE: Dr Sharon Swain		

Field	Content
	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 Developing NICE guidelines: the manual. 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: 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.

Field	Content	
Keywords	Heart failure; pharmacological; mineralocorticoid receptor antagonists.	
Details of existing review of same topic by same authors	NA	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

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). 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.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.

	All questions – health economic evidence
Search strategy	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.
Review strategy	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. 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. 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} Inclusion and exclusion criteria 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. 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. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion 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 excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. Setting:

	All questions – health economic evidence
	UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. 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'. Studies published before 2010 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: 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.

1

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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 1st 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)	1st November 2024	Wiley	Issue 11 of 12, November 2024	3
Cochrane Central Register of Controlled Trials (CENTRAL)	1st November 2024	Wiley	Issue 10 of 12, October 2024	481
Embase	1st November 2024	Ovid	<1974 to 2024 October 31>	1981
MEDLINE	1st November 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to October 31, 2024>	600
Epistemonikos	1st November 2024	Epistemonikos	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)	9th January 2025	Wiley	Issue 1 of 12, January 2025	0
Cochrane Central Register of Controlled Trials (CENTRAL)	9th January 2025	Wiley	Issue 12 of 12, December 2024	14
Embase	9th January 2025	Ovid	<1974 to 2025 January 07>	78
MEDLINE	9th January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 06, 2025>	40
Epistemonikos	9th January 2025	Epistemonikos	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

Searches		
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

Searches		
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 psyclit 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

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

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

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

Database results – Quality of Life

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	25th July 2024	Ovid	Embase <1974 to 2024 July 24>	4213
MEDLINE	25th 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	4th December 2024	Ovid	Embase <1974 to 2024 December 03>	921
MEDLINE	4th December 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to December 02, 2024>	273
INAHTA	4th December 2024	INAHTA	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	13th January 2025	Ovid	Embase <1974 to 2025 January 10>	112
MEDLINE	13th January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 10, 2025>	56
INAHTA	13th January 2025	INAHTA	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	4th December 2024	Ovid	Embase <1974 to 2024 December 03>	187
MEDLINE	4th 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	13th January 2025	Ovid	Embase <1974 to 2025 January 10>	43
MEDLINE	13th 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 (HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).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

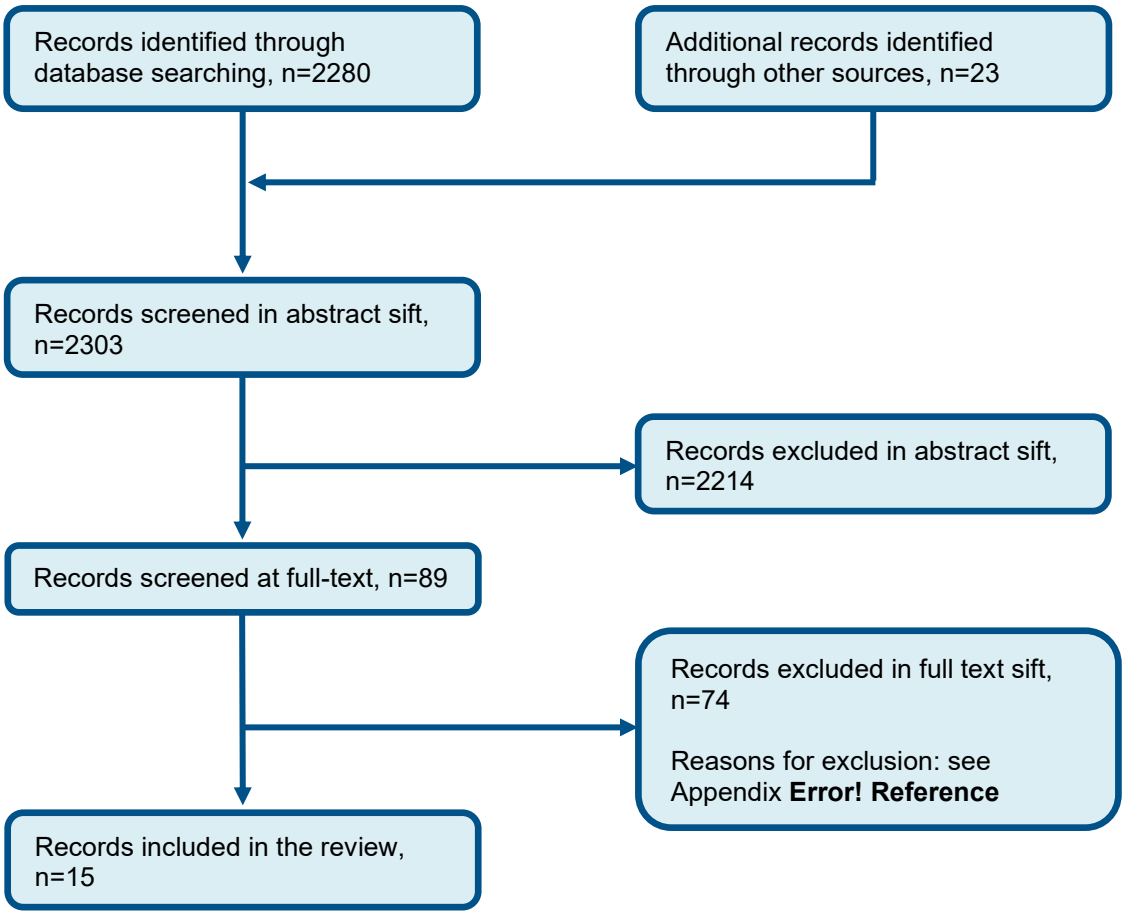
Database name: Medline Quality of Life

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	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).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

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

Sources of funding	the National Heart, Lung, and Blood Institute
Inclusion criteria	Aged ≥50 years Heart failure signs and symptoms LVEF ≥45% confirmed within 6 months before randomisation Systolic blood pressure <140 mm Hg or≤160 mm Hg and on treatment with ≥3 antihypertensive medications Serum potassium < 5.0 mmol/L 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≥ 100 pg/mL or NT-proBNP ≥360 pg/mL
Exclusion criteria	Severe systemic illness with life expectancy <3 years from randomisation Severe chronic obstructive pulmonary disease (ie requiring home oxygen or chronic oral steroid therapy) Known restrictive/ infiltrative cardiomyopathy, hypertrophic cardiomyopathy or constrictive pericarditis. Hemodynamically significant valvular heart disease (ie valvular disease anticipated to require surgical correction during the trial) Atrial fibrillation with a resting heart rate >90 beat/min Systolic blood pressure >160 mm Hg History of hyperkalaemia (≥5.5 mmol/L within the last 6 months or ≥5.0 mmol/L in the last 2 weeks) Severe renal dysfunction, defined as eGFR <30 mL/min per 1.73m2 or serum creatinine ≥2.5 mg/dL MI, coronary artery bypass graft surgery or stroke within 90 days before randomisation; percutaneous coronary intervention within 30 days before randomisation Use of aldosterone antagonist or potassium sparing diuretic within 14 days before randomisation

Recruitment / selection of participants	Recruitment based on screening eligibility based on review of medical records by study staff at or before the baseline visit.
Intervention(s)	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.
Comparator	Placebo
Population subgroups	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.
Number of participants	3168 (as of 2 September 2011)
Duration of follow-up	Projected follow-up 3.75 years
Indirectness	None
Method of analysis	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

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

Study arms

Spironolactone (N = 1722)

Placebo (N = 1723)

Outcomes

Dichotomous outcomes

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

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

Deswal A, Richardson P, Bozkurt B, 2011

Bibliographic Reference	Deswal A, Richardson P, Bozkurt B MD; Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF); Journal of Cardiac Failure; 2011; vol. 8 (no. 17); 634-642

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	RAAM-PEF/ NCT00108251
Study type	Randomised controlled trial (RCT)
Study location	United States
Study setting	Veterans Affairs Medical Center
Study dates	Not specified
Sources of funding	Not specified
Inclusion criteria	All patients had HFpEF (defined by clinical HF for ≥2 months before the screening visit with NYHA functional class II or III HF symptoms at enrolment, LVEF ≥50% within 2 months of screening and B-type natriuretic peptide levels ≥100pg/mL within 2 months of screening). Aged 18 years or older Systolic blood pressure ≤150 and diastolic ≤95 mm Hg for 4 weeks before and at enrollment

	Ability to walk 50m Current use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, if tolerated, for at least 4 weeks before enrolment.
Exclusion criteria	Need for eplerenone or spironolactone for treatment of other comorbid illnesses (e.g ascites) Hepatic impairment Serum creatinine > 2.5 mg/dL or serum potassium >5.0 mEq/L Prior intolerance to eplerenone or spironolactone Significant valvular heart disease, pericardial disease or severe chronic lung disease Patients with technically inadequate echocardiographic windows Patients with severe mitral annular calcification Unstable angina or acute myocardial infarction within 4 weeks before enrolment Severe peripheral vascular disease with claudication or other physical conditions limiting the distance walked Pregnant or lactating females History of active alcohol or substance abuse or history of repeated noncompliance History of cancer within 3 years (other than resected cutaneous basal or squamous cell carcinoma) Participation in any other drug trial within 30 days before enrolment.
Recruitment / selection of participants	Not specified
Intervention(s)	Eplerenone - Received 25mg/day for 2 weeks followed by 50mg daily for 22 weeks, if tolerated

Comparator	Placebo
Population subgroups	NA
Number of participants	44
Duration of follow-up	6 months
Indirectness	None
Method of analysis	T-test to examine differences between groups for normally distributed continuous variables and the Wilcoxon rank-sum test for nonparametrically distributed variables.
Additional comments	KCCQ standard deviation imputed.

Study arms

Eplerenone (N = 21)

Received 25mg/day for 2 weeks followed by 50mg daily for 22 weeks, if tolerated

Placebo (N = 23)

Placebo

Characteristics

Arm-level characteristics

Characteristic	Eplerenone (N = 21)	Placebo (N = 23)
Age Mean (SD)	72.2 (9.8)	68.7 (9.1)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class - NYHA class II Sample size	n = 14 ; % = 66.7	n = 12 ; % = 52.2
NYHA class - NYHA class III Sample size	n = 11 ; % = 47.8	n = 7 ; % = 33.3
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Heart failure aetiology - Hypertension Sample size	n = 21 ; % = 100	n = 23 ; % = 100
Heart failure aetiology - Coronary artery disease Sample size	n = 14 ; % = 66.7	n = 11 ; % = 47.8
LVEF	62.1 ±5.0%	62.5 ±7.5%

Characteristic	Eplerenone (N = 21)	Placebo (N = 23)
Custom value		
Type 2 diabetes Sample size	n = 13 ; % = 61.9	n = 14 ; % = 60.9
Atrial fibrillation Sample size	n = 3 ; % = 14.3	n = 3 ; % = 13
Previous heart failure hospitalisation Sample size	n = 9 ; % = 42.9	n = 14 ; % = 60.9
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Background (non-randomised) heart failure medications - ACE inhibitor or ARB Sample size	n = 20 ; % = 95.2	n = 23 ; % = 100
Background (non-randomised) heart failure medications - Diuretic Sample size	n = 20 ; % = 95.2	n = 23 ; % = 100
Background (non-randomised) heart failure medications - Beta-blocker Sample size	n = 16 ; % = 76.2	n = 19 ; % = 82.6
Background (non-randomised) heart failure medications - Calcium channel blockers Sample size	n = 11 ; % = 52.4	n = 11 ; % = 47.8

Outcomes

Study timepoints

Baseline

26 week

Dichotomous Outcomes

Outcome	Eplerenone, 26 week, N = 21	Placebo, 26 week, N = 23
Deaths No of events	n = 0	n = 0
Hospitalisation for heart failure No of events	n = 1	n = 2
Serum creatinine increase >50% No of events	n = 3	n = 1
Hyperkalaemia No of events	n = 3	n = 1
Gynaecomastia No of events	n = 0	n = 0

Continuous outcomes

Outcome	Eplerenone, Baseline, N = 21	Eplerenone, 26 week, N = 21	Placebo, Baseline, N = 23	Placebo, 26 week, N = 23
Kansas City Cardiomyopathy Questionnaire Overall summary score Mean (SD)	63.1 (22.8)	68.7 (22.8)	47.8 (25.1)	54.2 (22.8)
Kansas City Cardiomyopathy Questionnaire Clinical score Mean (SD)	61.5 (21.6)	66.3 (22)	46.9 (25.3)	54 (21.5)

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

Dichotomous Outcomes: Deaths: Eplerenone versus Placebo at 26 weeks

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: Kansas City Cardiomyopathy Questionnaire: Eplerenone versus Placebo at 26 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk for risk of bias due to noted differences between groups at baseline)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire: Clinical score: Eplerenone versus Placebo at 26 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk for risk of bias due to noted differences between groups at baseline)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes: Hospitalisation for heart failure: Eplerenone versus Placebo at 26 weeks

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.)*

Dichotomous Outcomes: Serum creatinine increase >50%: Eplerenone versus Placebo at 26 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: does not match protocol definition of AKI.)*

Dichotomous Outcomes: Hyperkalaemia Eplerenone versus Placebo at 26 weeks

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

Dichotomous Outcomes: Gynaecomastia: Eplerenone versus Placebo at 26 weeks

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

Secondary publication of another included study- see primary study for details	Solomon, 2024
Trial name / registration number	FINEARTS-HF/ NCT04435626.
Study location	Asia, Eastern Europe, Western Europe, Oceania, North America, and Latin America (37 countries total)
Study setting	Trial centre
Study dates	14 September 2020 to 10 January 2023
Sources of funding	Bayer
Inclusion criteria	Participants aged 40 years or older NYHA class II-IV Treatment with a diuretic for 30 days or longer before randomisation

	LVEF of ≥40% with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy) measured within 12 months of screening. Elevated natriuretic peptide levels s (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.
Exclusion criteria	eGFR <25 ml/min/1.73 m2, serum/plasma potassium >5.0 mmol/L at screening or randomization symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or randomization
Recruitment / selection of participants	Not specified
Intervention(s)	Finerenone was administered at a maximum dose of 20 mg or 40 mg once daily, depending on the baseline estimated glomerular filtration rate (eGFR).
Comparator	Placebo
Population subgroups	LVEF status
Number of participants	5993 participants with LVEF data available (3821 with relevant LVEF status ≥50% used)
Duration of follow-up	12 months
Method of analysis	Intention-to-treat

Additional comments	Patient totals: • LVEF 50-60% finerenone group = 1329 • 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 Sample size	n = NA ; % = NA
% Female - LVEF ≥50 to <60%	n = 1368 ; % = 51.2

Characteristic	Study (N = 3821)
Sample size	
% Female - LVEF >60% Sample size	n = 679 ; % = 59.2
Age Mean (SD)	NA (NA)
Age - LVEF ≥50 to <60% Mean (SD)	73.3 (9.1)
Age - LVEF >60% Mean (SD)	73.5 (9.2)
Ethnicity Sample size	n = NA ; % = NA
Ethnicity - Asian: LVEF ≥50 to <60%: Sample size	n = 359 ; % = 13.4
Ethnicity - Asian: LVEF>60% Sample size	n = 205 ; % = 17.9
Ethnicity - Black: LVEF ≥50 to <60% Sample size	n = 36 ; % = 1.3

Characteristic	Study (N = 3821)
Ethnicity - Black: LVEF >60% Sample size	n = 29 ; % = 2.5
Ethnicity - Other: LVEF ≥50 to <60% Sample size	n = 94 ; % = 3.5
Ethnicity - Other: LVEF >60% Sample size	n = 30 ; % = 2.6
Ethnicity - White: LVEF ≥50 to <60% Sample size	n = 2185 ; % = 81.7
Ethnicity - White: LVEF>60% Sample size	n = 883 ; % = 77
NYHA class Sample size	n = NA ; % = NA
NYHA class - Class II: LVEF ≥50 to <60% Sample size	n = 1828 ; % = 68.4
NYHA class - Class II: LVEF >60% Sample size	n = 815 ; % = 71.1
NYHA class - Class III/IV: LVEF ≥50 to <60%	n = 846 ; % = 31.6

Characteristic	Study (N = 3821)
Sample size	
NYHA class - Class III/IV: LVEF >60% Sample size	n = 331 ; % = 28.9
Type 2 diabetes Sample size	n = NA ; % = NA
Type 2 diabetes - LVEF ≥50 to <60% Sample size	n = 1097 ; % = 41
Type 2 diabetes - LVEF >60% Sample size	n = 472 ; % = 41.2
Atrial fibrillation Sample size	n = NA ; % = NA
Atrial fibrillation - LVEF ≥50 to <60% Sample size	n = 1099 ; % = 41.1
Atrial fibrillation - LVEF >60% Sample size	n = 421 ; % = 36.7
Previous heart failure hospitalisation Sample size	n = NA ; % = NA

Characteristic	Study (N = 3821)
Previous heart failure hospitalisation - LVEF ≥50 to <60% Sample size	n = 1582 ; % = 59.2
Previous heart failure hospitalisation - LVEF >60% Sample size	n = 583 ; % = 50.8
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	NA (NA)
Renal function (eGFR; mL/min/1.73m2) - LVEF ≥50 to <60% Mean (SD)	61 (19.3)
Renal function (eGFR; mL/min/1.73m2) - LVEF >60% Mean (SD)	59.6 (19.4)
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA
Background (non-randomised) heart failure medications - Beta blocker: LVEF ≥50 to <60% Sample size	n = 2242 ; % = 83.8
Background (non-randomised) heart failure medications - Beta-blocker: LVEF >60% Sample size	n = 927 ; % = 80.8
Background (non-randomised) heart failure medications - ACE inhibitor: LVEF ≥50 to <60%	n = 890 ; % = 33.3

Characteristic	Study (N = 3821)
Sample size	
Background (non-randomised) heart failure medications - ACE inhibitor: LVEF >60% Sample size	n = 392 ; % = 34.2
Background (non-randomised) heart failure medications - Angiotensin-receptor blockers: LVEF ≥50 to <60% Sample size	n = 1016 ; % = 38
Background (non-randomised) heart failure medications - Angiontensin-receptor blocker: LVEF >60% Sample size	n = 465 ; % = 40.5
Background (non-randomised) heart failure medications - ARNI: LVEF ≥50 to <60% Sample size	n = 145 ; % = 5.4
Background (non-randomised) heart failure medications - ARNI: LVEF >60% Sample size	n = 27 ; % = 2.4
Background (non-randomised) heart failure medications - SGLT2i: LVEF ≥50 to <60% Sample size	n = 366 ; % = 13.7
Background (non-randomised) heart failure medications - SGLT2i: LVEF>60% Sample size	n = 113 ; % = 9.9
Background (non-randomised) heart failure medications - Loop diuretic: LVEF ≥50 to <60% Sample size	n = 2318 ; % = 86.7

Characteristic	Study (N = 3821)
Background (non-randomised) heart failure medications - Loop diuretic: LVEF>60%	n = 943 ; % = 82.2
Sample size	

Outcomes

Study timepoints

Baseline

12 month

Hazard ratios and rate ratios

Outcome	Finerenone vs Placebo, 12 month, N2 = 1917, N1 = 1904
All-cause mortality - LVEF ≥50 to <60%	0.85 (0.7 to 1.04) [a]
Finerenone n = 1329, placebo n = 1345	
Hazard ratio/95% CI	
All-cause mortality - LVEF >60%	1.0 (0.74 to 1.34)[a]
Finerenone n = 575, placebo n = 572	
Hazard ratio/95% CI	
Cardiovascular death - LVEF ≥50 to <60%	0.9 (0.67 to 1.2) [a]

Outcome	Finerenone vs Placebo, 12 month, N2 = 1917, N1 = 1904
Finerenone n = 1329, placebo n = 1345 Hazard ratio/95% CI	
Cardiovascular death - LVEF >60% Finerenone n = 575, placebo n = 572 Hazard ratio/95% CI	0.95 (0.61 to 1.46) [a]
First worsening heart failure event - LVEF ≥50 to <60% Finerenone n = 1329, placebo n = 1345 Hazard ratio/95% CI	0.78 (0.65 to 0.94)[a]
First worsening heart failure event - LVEF >60% Finerenone n = 575, placebo n = 572 Hazard ratio/95% CI	0.69 (0.51 to 0.93)[a]
Heart failure-related hospitalisation (total events) - LVEF ≥50 to <60% Finerenone n = 1329, placebo n = 1345 Rate ratio/95% CI	0.73 (0.59 to 0.91)[a]
Heart failure-related hospitalisation (total events) – LVEF >60%	0.79 (0.57 to 1.09)[a]

Outcome	Finerenone vs Placebo, 12 month, N2 = 1917, N1 = 1904
Finerenone n = 575, placebo n = 572 Rate ratio/95% CI	

[a]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

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

Dichotomous outcomes

Outcome	Finerenone, 12 month, N = 1904	Placebo, 12 month, N = 1917
All-cause mortality - LVEF ≥50 to <60% Finerenone at 12 months, n=1329 Placebo at 12 months, n=1345 No of events	n = 202 ; % = 15.2	n = 228 ; % = 17
All-cause mortality - LVEF >60% Finerenone at 12 months, n=575 Placebo at 12 months, n=572 No of events	n = 96 ; % = 16.7	n = 93 ; % = 16.3
Cardiovascular mortality - LVEF ≥50 to <60% Finerenone at 12 months, n=1329 Placebo at 12 months, n=1345 No of events	n = 93 ; % = 7	n = 96 ; % = 7.1
Cardiovascular mortality - LVEF ≥60% Finerenone at 12 months, n=575 Placebo at 12 months, n=572 No of events	n = 46 ; % = 8	n = 45 ; % = 7.9
Discontinuation due to drug-related events - LVEF ≥50 to <60% Finerenone at 12 months, n=1323	n = 43 ; % = 3.3	n = 38 ; % = 2.8

Outcome	Finerenone, 12 month, N = 1904	Placebo, 12 month, N = 1917
Placebo at 12 months, n=1342 No of events		
Discontinuation due to drug-related events - LVEF >60% Finerenone at 12 months, n=572 Placebo at 12 months, n=571 No of events	n = 21 ; % = 3.7	n = 15 ; % = 2.6
Potassium (>5.5 mmol/l) - LVEF ≥50 to <60% Finerenone at 12 months, n=1275 Placebo at 12 months, n=1298 No of events	n = 182 ; % = 14.3	n = 87 ; % = 6.7
Potassium (>5.5 mmol/l) - LVEF >60% Finerenone at 12 months, n=558 Placebo at 12 months, n=551 No of events	n = 70 ; % = 12.5	n = 35 ; % = 6.4
Heart failure-related hospitalisation - LVEF ≥50 to <60% Finerenone at 12 months, n=1329 Placebo at 12 months, n=1345 No of events	n = 219; % = 16.5	n = 249; % = 18.5

Outcome	Finerenone, 12 month, N = 1904	Placebo, 12 month, N = 1917
Heart failure-related hospitalisation - LVEF >60% Finerenone at 12 months, n=575 Placebo at 12 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 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 (*Intervention indirectness: Finerenone not licensed for CHF)*

Hazard ratios: All-cause mortality: LVEF>60%: Finerenone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concerns

Section	Question	Answer
		(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Hazard ratios: Cardiovascular death: LVEF≥50to<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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Hazard ratios: Cardiovascular death: LVEF>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)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Hazard ratios: First worsening heart failure event: LVEF ≥50 to <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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Hazard ratios: First worsening heart failure event: LVEF>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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Hazard ratios: Heart failure-related hospitalisation (total events): LVEF≥50 to <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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Hazard ratios: Heart failure-related hospitalisation (total events): LVEF>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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire – total symptom score: LVEF≥50to<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 *(Intervention indirectness: Finerenone not licensed for CHF)*

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 *(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Dichotomous outcomes: Potassium (>5.5mmol/l): LVEF≥50to<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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Dichotomous outcomes: Potassium (>5.5mmol/l): LVEF>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)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness :Finerenone not licensed for CHF)*

Dichotomous outcomes: Discontinuation due to drug-related events: LVEF≥50to<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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Dichotomous outcomes: Discontinuation due to drug-related events: LVEF>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 *(Intervention indirectness: Finerenone not licensed for CHF)*

Dichotomous outcomes: All-cause mortality: LVEF≥50to<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 *(Intervention indirectness:* Finerenone not licensed for CHF; outcome indirectness: reported as dichotomous) not time-to-event.

Dichotomous outcomes: All-cause mortality: LVEF>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 *(Intervention indirectness:* Finerenone not licensed for CHF; outcome indirectness: reported as dichotomous)

Dichotomous outcomes: Cardiovascular mortality: Cardiovascular mortality: LVEF≥50to<60%: Finerenone versus Placebo at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some Concern*s* *(LVEF threshold used for categorisation of results different from that prespecified in the trial protocol)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness:* Finerenone not licensed for CHF; outcome indirectness: reported as dichotomous)

Dichotomous outcomes: Cardiovascular mortality: Cardiovascular mortality: LVEF≥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 *(Intervention indirectness:* Finerenone not licensed for CHF; outcome indirectness: reported as dichotomous)

Dichotomous outcomes: Heart failure-related hospitalisation: LVEF≥50to<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 *(Intervention indirectness:* Finerenone not licensed for CHF; outcome indirectness: reported as dichotomous)

Dichotomous outcomes: Heart failure-related hospitalisation: LVEF≥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 *(Intervention indirectness:* Finerenone not licensed for CHF; 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

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

Trial name / registration number	Aldo-DHF/ NCT00094302
Study location	Germany and Austria
Study setting	Study centres
Study dates	Not specified
Sources of funding	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).
Inclusion criteria	Current heart failure symptoms consistent with NYHA classes II or III Left ventricular ejection fraction (LVEF) ≥ 50% at rest Echocardiographic evidence of diastolic dysfunction (Grade ≥ I) or atrial fibrillation Peak VO2 ≤ 25mL/kg/min Males and females aged ≥ 50 years Written informed consent
Exclusion criteria	Prior documented systolic heart failure (LVEF ≤ 40%) Significant coronary artery disease (current angina pectoris or ischaemia on stress tests; untreated coronary stenosis .50%) Myocardial infarction or CABG within the last 3 months Definite or probable pulmonary disease (VC , 80% or FEV1 , 80% of reference values on spirometry) Severe obesity (BMI ≥ 36 kg/m2)

	Significant renal dysfunction (creatinine . 1.8 mg/dL) Significant hypotension (blood pressure , 90 mmHg systolic and/or ,50 mmHg diastolic) Mental disorders suspected to interact with study outcome 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 Significant laboratory abnormalities (potassium ≥ 5.1 mmol/L; haemoglobin ≤ 11g/dL, haematocrit ≤ 33%) Changes in concomitant medication within the last 2 weeks prior to screening visit Known contraindications for spironolactone or prior documented intolerance to an aldosterone receptor antagonist 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 Insulin-dependent diabetes mellitus with a history of ketoacidosis Suspected metabolic acidosis Pregnant or nursing women Women with child bearing potency without effective contraception (except for implants, hormonal depot injections, combined oral contraceptives, IUDs or vasectomized partner) Concomitant participation in other clinical trials Therapy with an aldosterone receptor antagonist within the last 3 months Participation in another clinical trial within the last 30 days
Recruitment / selection of participants	Recruitment noted, but described in detail.
Intervention(s)	Spironolactone 25 mg once daily

Comparator	Placebo
Population subgroups	Patients with diastolic heart failure
Number of participants	Aiming to recruit 420 participants
Duration of follow-up	6, 12, and 18 months
Indirectness	None
Method of analysis	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

Secondary publication of another included	NA

study- see primary study for details	
Other publications associated with this study included in review	NA
Trial name / registration number	Aldo-DHF/ ISRCTN94726526
Study type	Randomised controlled trial (RCT)
Study location	Germany and Austria
Study setting	Trial centres
Study dates	March 2007 to April 2012
Sources of funding	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.
Inclusion criteria	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 ≥1) or atrial fibrillation at presentation Maximum exercise capacity (peak VO2) of 25 mL/kg/min or less

Exclusion criteria	Prior documented reduced LVEF ≤40% Significant coronary artery disease (current angina pectoris or ischemia on stress tests, untreated coronary stenosis >50%) Myocardial infarction or coronary artery bypass graft surgery 3 months or less prior to enrollment Clinically relevant pulmonary disease (vital capacity <80% or forced expiratory volume in 1 second <80% of reference values on spirometry) Significant laboratory abnormalities (potassium ≥5.1 mmol/L; hemoglobin ≤11 g/dL; hematocrit ≤33%; serum creatinine >1.8 mg/dL; or estimated glomerular filtration rate [eGFR]<30 mL/min/1.73 m2 , calculated using the Modification of Diet in Renal Disease formula: 186x[serum creatinine {in micromoles per liter}/ 88.4]x1.154age [in years]-0.203 x1.21 [if patient is black]x0.742 [if patient is female]), k Known contraindications for spironolactone or known intolerance to or therapy with a mineralocorticoid receptor antagonist within the last 3 months Concomitant therapy with a potassium-sparing diuretic Potassium supplementation
Recruitment / selection of participants	Recruitment procedures were noted , but not described in detail.
Intervention(s)	Spironolactone 25mg/day
Comparator	Placebo
Population subgroups	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

Number of participants	422 patients
Duration of follow-up	12 months
Indirectness	None
Method of analysis	All analyses were based on the intention-to-treat principle.
Additional comments	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

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

Characteristic	Spironolactone (N = 213)	Placebo (N = 209)
Sample size		
LVEF Custom value	67 (8%)	67 (8%)
Type 2 diabetes Sample size	n = 36 ; % = 17	n = 34 ; % = 16
Atrial fibrillation Sample size	n = 13 ; % = 6	n = 9 ; % = 4
Previous heart failure hospitalisation Sample size	n = 111 ; % = 52	n = 110 ; % = 53
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	79 (19)	78 (18)
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Background (non-randomised) heart failure medications - Beta-blockers Sample size	n = 146 ; % = 69	n = 156 ; % = 75
Background (non-randomised) heart failure medications - Diuretics Sample size	n = 118 ; % = 55	n = 109 ; % = 52

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

Outcomes

Study timepoints

Baseline

12 month

Dichotomous outcomes

Outcome	Spironolactone, 12 month, N = 204	Placebo, 12 month, N = 196
All-cause mortality No of events	n = 1 ; % = 1	n = 0 ; % = 0
Cardiac hospitalisation	n = 21 ; % = 10	n = 15 ; % = 7

Outcome	Spironolactone, 12 month, N = 204	Placebo, 12 month, N = 196
No of events		
Potassium Ever increased >5.0mmol/L No of events	n = 44 ; % = 21	n = 22 ; % = 11
Gynaecomastia 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
Minnesota Living with Heart Failure Questionnaire Mean (95% CI)	NA (NA to NA)	21 (19 to 24)	NA (NA to NA)	21 (18 to 23)
SF-36 Physical Functioning score 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: Cardiac hospitalisation: 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 and cardiac not heart failure hospitalisation..)*

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

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00206232
Study location	US
Study setting	Methodist Hospital
Study dates	2004-2008
Sources of funding	Women’s Fund; Houston, Texas.
Inclusion criteria	≥18 years or older with a previous diagnosis of HFpEF

	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 Treatment with an ACEI, or ARB if ACEI intolerant, was required for ≥4 weeks before enrollment.
Exclusion criteria	Current treatment with spironolactone or eplerenone Previous intolerance to spironolactone Creatinine >2.5 mg/dL Serum potassium >5.0 mEq/L Significant valvular disease Pericardial disease Severe chronic lung disease with cor pulmonale Unstable angina or myocardial infarction ≤4 weeks before enrollment Severe peripheral vascular disease with claudication that limited walking distance Presence of other severe comorbid conditions with a life expectancy < 6 months Pregnant or lactating women
Recruitment / selection of participants	Not specified
Intervention(s)	Spironolactone (25mg/day)
Comparator	Placebo

Population subgroups	NA
Number of participants	48
Duration of follow-up	6 months
Indirectness	None
Method of analysis	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
Additional comments	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

Characteristic	Spironolactone (N = 24)	Placebo (N = 24)
% Female Sample size	n = 24 ; % = 100	n = 24 ; % = 100
Age Mean (SD)	66.3 (2.2)	76.4 (1.6)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class - NYHA class II Sample size	n = 8 ; % = 33	n = 16 ; % = 67
NYHA class - NYHA class III Sample size	n = 10 ; % = 42	n = 14 ; % = 58
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Heart failure aetiology - Coronary artery disease Sample size	n = 9 ; % = 37.5	n = 8 ; % = 33.3
Heart failure aetiology - Hypertension Sample size	n = 21 ; % = 87.5	n = 19 ; % = 79.2
LVEF	62.5 (1.2)	62.9 (1.2)

Characteristic	Spironolactone (N = 24)	Placebo (N = 24)
Mean (SD)		
Type 2 diabetes Sample size	n = 12 ; % = 50	n = 6 ; % = 25
Atrial fibrillation Sample size	n = 6 ; % = 25	n = 6 ; % = 25
Previous heart failure hospitalisation Sample size	n = 14 ; % = 58.3	n = 13 ; % = 54.2
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Background (non-randomised) heart failure medications - ACE-inhibitor Sample size	n = 17 ; % = 70.8	n = 16 ; % = 66.7
Background (non-randomised) heart failure medications - Angiotensin receptor blocker Sample size	n = 7 ; % = 29.2	n = 9 ; % = 37.5
Background (non-randomised) heart failure medications - Beta-blocker Sample size	n = 15 ; % = 62.5	n = 15 ; % = 62.5
Background (non-randomised) heart failure medications - Thiazide or loop diuretic Sample size	n = 20 ; % = 83.3	n = 18 ; % = 75

Characteristic	Spironolactone (N = 24)	Placebo (N = 24)
Background (non-randomised) heart failure medications - Digoxin Sample size	n = 3 ; % = 12.5	n = 2 ; % = 8.3
Background (non-randomised) heart failure medications - Calcium-antagonists Sample size	n = 6 ; % = 25	n = 7 ; % = 29.2
Background (non-randomised) heart failure medications - Nitrates Sample size	n = 13 ; % = 54.2	n = 8 ; % = 33.3
Background (non-randomised) heart failure medications - Oral anticoagulants Sample size	n = 5 ; % = 20.8	n = 5 ; % = 20.8
Background (non-randomised) heart failure medications - Aspirin Sample size	n = 6 ; % = 25	n = 8 ; % = 33.3
Background (non-randomised) heart failure medications - Lipid lowering drug Sample size	n = 13 ; % = 54.2	n = 14 ; % = 58.3

Outcomes

Study timepoints

Baseline

6 month

Dichotomous outcomes

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

Continuous outcomes

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

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 *(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)*
Overall bias and Directness	Overall Directness	Partially applicable *(*Outcome indirectness: *reported as dichotomous not time-to-event.)*

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 *(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)*
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 *(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)*
Overall bias and Directness	Overall Directness	Partially applicable *(*Outcome indirectness: *reported as dichotomous not time-to-event.)*

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 *(Some concerns for risk of bias due to differences between groups which could suggest a problem with the randomisation process)*
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

Secondary publication of another included study- see primary study for details	Pitt, 2014 is the primary study

Other publications associated with this study included in review	Solomon, 2016, Desai, 2018, Pfeffer, 2015, and Shah, 2013
Trial name / registration number	TOPCAT/ NCT00094302.
Indirectness	None

Study arms

Spironolactone (N = 1722)

15 to 45 mg/day

Placebo (N = 1723)

Placebo

Outcomes

Study timepoints

12 month

Contrast outcomes

Outcome	Spironolactone vs placebo , 12 month,
Kansas City Cardiomyopathy Questionnaire – overall summary score change from baseline Mean difference (SE) **N = 3400**	1.36 (0.44)
EQ-5D VAS change from baseline Mean difference (SE) **N = 3395**	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: 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: EQ-5D VAS: Spironolactone 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

Mak GJ, Ledwidge MT, Watson CJ, Phelan DM, Dawkins IR, 2009

Bibliographic Reference	Mak GJ, Ledwidge MT, Watson CJ, Phelan DM, Dawkins IR MNEA; Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone.; Journal of the American College of Cardiology; 2009; vol. 18 (no. 54); 1674-82

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT00505336
Study location	Ireland
Study setting	Community-based

Study dates	Not specified
Sources of funding	Grant support from the Irish Heart Foundation (The Noel Hickey Bursary) sponsored by Pfizer
Inclusion criteria	Patients with proven HFPSF (based on NYHA class IV heart failure admission or symptoms consistent with heart failure, B-type natriuretic peptide >100 pg/ml, LVEF >45% and evidence of diastolic dysfunction on Doppler-echocardiographic study)
Exclusion criteria	Clinically unstable as defined by any change in diuretic dose a month before enrollment or were already receiving eplerenone or spironolactone therapy Evidence of significant inflammatory disease, hepatic disease, or metabolic bone disease that may alter parameters of collagen metabolism, serum creatinine >200 micromol/litre Prior documented left ventricular ejection fraction <45% Hemodynamically significant valvular disease Corpulmonale, hypertrophic, restrictive, or constrictive cardiomyopathy Atrial fibrillation or flutter with resting ventricular rate >120 beats/min Severe anaemia Clinically significant pulmonary disease as evidenced by hospitalisations or use of oral corticosteroids for pulmonary decompensation within 12 months Patients who require home oxygen therapy
Recruitment / selection of participants	Recruited from community setting
Intervention(s)	Eplerenone 25 mg/day for 6 months followed by a dose increment to 50 mg/day until the 12-month time point
Comparator	Control group included usual heart failure care

Population subgroups	NA
Number of participants	44 participants randomised
Duration of follow-up	12 months
Indirectness	None
Method of analysis	Comparisons between eplerenone and control groups were made on changes over the study period using independent 2-sample t tests for continuous normally distributed data, Mann-Whitney tests for skewed continuous, and chi-square tests for categorical.
Additional comments	Creatinine reported as mean value, not as number of participants with AKI.

Study arms

Eplerenone (N = 24)

25mg/day of eplerenone. Dose increased to 50mg/day after 6 months to investigate any dose-response effects

Control group (N = 20)

Usual heart failure care

Characteristics

Arm-level characteristics

Characteristic	Eplerenone (N = 24)	Control group (N = 20)
Age Mean (SD)	80 (7.7)	79 (7.9)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class - NYHA class IV Sample size	n = 24 ; % = 100	n = 20 ; % = 100
Heart failure aetiology Sample size	n = NA	n = NA ; % = NA
Heart failure aetiology - Hypertension Sample size	n = 22 ; % = 92	n = 18 ; % = 90
Heart failure aetiology - Hyperlipidaemia Sample size	n = 9 ; % = 38	n = 4 ; % = 20
LVEF Custom value	63 ±9%	64 ±9.6%
Type 2 diabetes Sample size	n = 5 ; % = 21	n = 7 ; % = 35

Characteristic	Eplerenone (N = 24)	Control group (N = 20)
Atrial fibrillation Sample size	n = 14 ; % = 58	n = 12 ; % = 60
Previous heart failure hospitalisation Sample size	n = 12 ; % = 50	n = 11 ; % = 55
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Background (non-randomised) heart failure medications - Diuretic Sample size	n = 21 ; % = 88	n = 18 ; % = 90
Background (non-randomised) heart failure medications - ACE-inhibitor Sample size	n = 16 ; % = 67	n = 12 ; % = 60
Background (non-randomised) heart failure medications - ARB Sample size	n = 7 ; % = 29	n = 8 ; % = 40
Background (non-randomised) heart failure medications - Calcium-channel blocker Sample size	n = 4 ; % = 17	n = 5 ; % = 25
Background (non-randomised) heart failure medications - Statin Sample size	n = 15 ; % = 62	n = 12 ; % = 60
Background (non-randomised) heart failure medications - Beta-blocker	n = 15 ; % = 62	n = 15 ; % = 75

Characteristic	Eplerenone (N = 24)	Control group (N = 20)
Sample size		
Background (non-randomised) heart failure medications - Digoxin Sample size	n = 9 ; % = 38	n = 6 ; % = 30

Outcomes

Study timepoints

Baseline

6 month

12 month

Dichotomous outcomes

Outcome	Eplerenone, 12 month, N = 24	Control group, 12 month, N = 20
All-cause mortality No of events	n = 1	n = 1

Continuous outcomes

Outcome	Eplerenone, Baseline, N = 24	Eplerenone, 6 month, N = 24	Eplerenone, 12 month, N = 23	Control group, Baseline, N = 20	Control group, 6 month, N = 20	Control group, 12 month, N = 17
Minnesota Living with Heart Failure Questionnaire Mean (SD)	25 (19)	21 (17)	23 (20)	18 (13)	19 (12)	20 (13)

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

Dichotomous outcomes: All-cause mortality: Eplerenone versus Control group at 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about allocation concealment.)*
Overall bias and Directness	Overall Directness	Partially applicable *(*Outcome indirectness: *reported as dichotomous not time-to-event.)*

Dichotomous outcomes: All-cause mortality: Eplerenone versus Control group at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about allocation concealment.)*

Section	Question	Answer
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: Eplerenone versus Control group at 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information about allocation concealment and outcome assessors aware of the assigned intervention.)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Minnesota Living with Heart Failure Questionnaire: Eplerenone versus Control group at 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information about allocation concealment and outcome assessors aware of the assigned intervention.)*
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

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Not specified
Study location	Australia
Study setting	Community setting
Study dates	February 2002 to October 2002
Sources of funding	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.

Inclusion criteria	Patients had to have hypertension requiring antihypertensive medication and report exertional dyspnea (NYHA class II) but no history of angina or myocardial infarction
Exclusion criteria	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.
Recruitment / selection of participants	Participants were recruited from the community (non-hospital, ambulatory population in southeast Queensland).
Intervention(s)	Spironolactone (25mg/day)
Comparator	Placebo
Population subgroups	NA
Number of participants	30 patients
Duration of follow-up	6 months
Indirectness	Hypertensive diastolic heart disease population
Method of analysis	Linear regression was used to determine correlations between variables. In combination with respective t tests, multivariate analyses represented the primary endpoints.
Additional comments	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

Spironolactone (N = 15)

25mg/d

Placebo (N = 15)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Spironolactone (N = 15)	Placebo (N = 15)
% Female Sample size	n = 9 ; % = 60	n = 10 ; % = 66
Age Mean (SD)	61 (6)	62 (5)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA

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

Outcomes

Study timepoints

Baseline

6 month

Dichotomous outcomes

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

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

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Solomon 2016, Lewis 2016, Desai 2011, Desai 2018, Pfeffer 2015, and Shah 2013
Trial name / registration number	TOPCAT/NCT00094302
Study type	Randomised controlled trial (RCT)
Study location	United States, Canada, Brazil, Argentina, Russia, and Georgia
Study setting	Affiliated trial centre
Study dates	10 August 2006 to 31 January 2012
Sources of funding	National Heart, Lung, and Blood Institute
Inclusion criteria	Patients aged 50 years or older Had at least one sign and one symptom of heart failure on a prespecified list of clinically defined signs and symptoms LVEF of 45% or more Controlled systolic blood pressure

	Serum potassium level of less than 5.0 mmol per litre Had a history of hospitalisation within the past 12 months, with management of heart failure a major component of the care provided An elevated natriuretic peptide level within 60 days before randomization (a brain natriuretic peptide [BNP] level ≥100 pg per milliliter or an N-terminal pro-BNP [NT-proBNP] level ≥360 pg per ml
Exclusion criteria	Severe systemic illness with a life expectancy of less than 3 years Severe renal dysfunction
Recruitment / selection of participants	Not specified
Intervention(s)	Spironolactone Study drugs were initially administered at a dose of 15 mg once daily, which was increased to a maximum of 45 mg daily during the first 4 months after randomization. Subsequent dose adjustments were made as required.
Comparator	Placebo
Population subgroups	22 prespecified subgroups
Number of participants	3445 participants
Duration of follow-up	Mean follow-up was 3.3 years

Indirectness	None
Method of analysis	Intention-to-treat principle
Additional comments	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

Characteristic	Spironolactone (N = 1722)	Placebo (N = 1723)
% Female Sample size	n = 888 ; % = 51.6	n = 887 ; % = 51.5
Age Median (IQR)	68.7 (61 to 76.4)	68.7 (60.7 to 75.5)

Characteristic	Spironolactone (N = 1722)	Placebo (N = 1723)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Ethnicity - white Sample size	n = 1525 ; % = 88.6	n = 1537 ; % = 89.2
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class - NYHA class I Sample size	n = 56 ; % = 3.3	n = 53 ; % = 3.1
NYHA class - NYHA class II Sample size	n = 1090 ; % = 63.3	n = 1104 ; % = 64.1
NYHA class - NYHA class III Sample size	n = 568 ; % = 33	n = 553 ; % = 32.1
NYHA class - NYHA class IV Sample size	n = 7 ; % = 0.4	n = 8 ; % = 0.5
LVEF Median (IQR)	56 (51 to 61)	56 (51 to 62)
Previous heart failure hospitalisation	n = 1232 ; % = 71.5	n = 1232 ; % = 71.5

Characteristic	Spironolactone (N = 1722)	Placebo (N = 1723)
Sample size		
Renal function (eGFR; mL/min/1.73m2) Median (IQR)	65.3 (53.9 to 79.2)	65.5 (53.5 to 79.1)

Outcomes

Study timepoints

Baseline

3.3 year

Hazard ratios

Outcome	Spironolactone vs Placebo, Baseline, N2 = 1723, N1 = 1722	Spironolactone vs Placebo, 3.3 year, N2 = 1723, N1 = 1722
All-cause mortality Hazard ratio/95% CI	NA (NA to NA)	0.89 (0.75 to 1.05)[a]
CV-related mortality Hazard ratio/95% CI	NA (NA to NA)	0.89 (0.72 to 1.1) [a]
Hospitalisation for heart failure	NA (NA to NA)	0.8 (0.67 to 0.96)[a]

Outcome	Spironolactone vs Placebo, Baseline, N2 = 1723, N1 = 1722	Spironolactone vs Placebo, 3.3 year, N2 = 1723, N1 = 1722
Hazard ratio/95% CI		

[a] 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

Outcome	Spironolactone, 3.3 year, N = 1722	Placebo, 3.3 year, N = 1723
All-cause mortality No of events	n = 252 ; % = 14.6	n = 274 ; % = 15.9
CV death No of events	n = 160 ; % = 9.3	n = 176 ; % = 10.2
Hospitalisation for heart failure No of events	n = 206 ; % = 12	n = 245 ; % = 14.2
Hyperkalaemia No of events	n = 322; % = 18.7	n = 157; % = 9.1
Serum creatinine >50% increase 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

Section	Question	Answer
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

Section	Question	Answer
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 *(Outcome indirectness: reported as dichotomous not time-to-event.)*

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 *(Outcome indirectness: reported as dichotomous not time-to-event.)*

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 *(Outcome indirectness: reported as dichotomous not time-to-event.)*

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

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

Characteristics

Study-level characteristics

Characteristic	**Study (N = 3445)**
% Female	n = 1775 ; % = 52

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

Characteristic	Study (N = 3445)
Ethnicity - Other Sample size	n = 70 ; % = 2
Type 2 diabetes Sample size	n = 1114 ; % = 32
Atrial fibrillation Sample size	n = 1213 ; % = 35
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	67.7 (20.1)
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA
Background (non-randomised) heart failure medications - Diuretic Sample size	n = 2817 ; % = 82
Background (non-randomised) heart failure medications - Angiotensin Converting Enzyme (ACE) inhibitors Sample size	n = 2251 ; % = 65
Background (non-randomised) heart failure medications - Angiotensin-receptor blockers Sample size	n = 688 ; % = 20
Background (non-randomised) heart failure medications - ACEi or ARB	n = 2889 ; % = 84

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

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

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

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

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

Recruitment / selection of participants	Not specified
Intervention(s)	Spironolactone Study drugs were initially administered at a dose of 15 mg once daily, which was increased to a maximum of 45 mg daily during the first 4 months after randomization. Subsequent dose adjustments were made as required.
Comparator	Placebo
Population subgroups	LVEF status and trial location (ie The Americas and Russia/ Georgia)
Number of participants	3444 participants
Duration of follow-up	3.4 years median
Indirectness	None
Method of analysis	Intention-to-treat principle
Additional comments	

Study arms

Spironolactone (N = 1722)

Placebo (N = 1723)

Characteristics

Study-level characteristics

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

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

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

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

Characteristic	Study (N = 3444)
Sample size	
Type 2 diabetes - LVEF >60% Sample size	n = 489 ; % = 36.7
Previous heart failure hospitalisation Sample size	n = NA ; % = NA
Previous heart failure hospitalisation - LVEF: 50-54.99% Sample size	n = 537 ; % = 75.4
Previous heart failure hospitalisation - LVEF: 55-59.99% Sample size	n = 662 ; % = 75.5
Previous heart failure hospitalisation - LVEF >60% Sample size	n = 916 ; % = 68.7
Renal function (eGFR; mL/min/1.73m2) LVEF 50-54.99% Mean (SD)	68 (21.4)
Renal function (eGFR; mL/min/1.73m2) - LVEF: 55-59.99% Mean (SD)	68 (19.9)
Renal function (eGFR; mL/min/1.73m2) - LVEF >60% Mean (SD)	66.5 (19.6)

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

Characteristic	Study (N = 3444)
Sample size	
Background (non-randomised) heart failure medications - Diuretics: LVEF ≥60%	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
All-cause mortality - LVEF: 50-54.99%	0.96 (0.66 to 1.41)
Hazard ratio/95% CI	total n = 712
All-cause mortality - LVEF: 55-59.99%	1.09 (0.78 to 1.53)
Hazard ratio/95% CI	total n = 879
All-cause mortality - LVEF >60%	0.88 (0.66 to 1.17)
Hazard ratio/95% CI	total n = 1333

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

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

Hazard ratios: All-cause mortality: 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: 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≥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; Goland, 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

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	FINEARTS-HF/ NCT04435626.
Study location	Asia, Eastern Europe, Western Europe, Oceania, North America, and Latin America (37 countries total)
Study setting	Trial centre
Study dates	14 September 2020 to 10 January 2023
Sources of funding	Bayer
Inclusion criteria	Participant must be aged 40 years and older, at the time of signing the informed consent. 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) On diuretic treatment for at least 30 days prior to randomization

	Documented LVEF of ≥40% 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 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 ≥3.8cm, LAA ≥20cm2 , LAVI >30 mL/m2 , LVMI ≥115 g/m2 (♂) / 95 g/m2 (♀), septal thickness or posterior wall thickness ≥1.1 cm NT-proBNP ≥300 pg/mL (BNP ≥100 pg/mL) in sinus rhythm and patient does not have an ongoing diagnosis of paroxysmal atrial fibrillation or NT-proBNP ≥900 pg/mL (BNP ≥300 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 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 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.
Exclusion criteria	eGFR <25 mL/min/1.73 m² at either screening or randomization visit. Serum/plasma potassium >5.0 mmol/L at either screening or randomization visit. NOTE: one reassessment of potassium is allowed at the screening and randomization visit, respectively Acute inflammatory heart disease, e.g. acute myocarditis, within 90 days prior to randomization Myocardial infarction or any event which could have reduced the ejection fraction within 90 days prior to randomization Coronary artery bypass graft surgery in the 90 days prior to randomization Percutaneous coronary intervention in the 30 days prior to randomization Stroke or transient ischemic cerebral attack within 90 days prior to randomization

	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/m2 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

	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
	Participants who require treatment with more than one ACEI, ARB or angiotensin-receptor neprilysin inhibitor (ARNI), or two simultaneously at randomization
	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
	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
	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
	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)
	Previous assignment to treatment during this study
	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
	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)
	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
	Participant is in custody by order of an authority or a court of law

Recruitment / selection of participants	Not specified
Intervention(s)	Finerenone was administered at a maximum dose of 20 mg or 40 mg once daily, depending on the baseline estimated glomerular filtration rate (eGFR).
Comparator	Placebo
Population subgroups	Not specified
Number of participants	6001
Duration of follow-up	Median follow-up was 32 months
Indirectness	None
Method of analysis	Intention-to-treat
Additional comments	This is the primary paper for FINEARTS-HF and outcome results are in the full population which included people LVEF >=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

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

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

Characteristic	Finerenone (N = 3003)	Placebo (N = 2998)
Sample size		
Previous heart failure hospitalisation Sample size	n = 1797 ; % = 59.8	n = 1822 ; % = 60.8
Renal function (eGFR; mL/min/1.73m2) Custom value	61.9±19.4	62.3±20.0
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Background (non-randomised) heart failure medications - Beta-blocker Sample size	n = 2541 ; % = 84.6	n = 2554 ; % = 85.2
Background (non-randomised) heart failure medications - ACE inhibitor Sample size	n = 1083 ; % = 36.1	n = 1072 ; % = 35.8
Background (non-randomised) heart failure medications - ARB Sample size	n = 1047 ; % = 34.9	n = 1055 ; % = 35.2
Background (non-randomised) heart failure medications - Angiotensin receptor- neprilysin inhibitor Sample size	n = 256 ; % = 8.5	n = 257 ; % = 8.6

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

Outcomes

Study timepoints

Baseline

12 month

32 month

Hazard ratios

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

Continuous outcomes

Outcome	Finerenone, Baseline, N = 3003	Finerenone, 12 month, N = 3003	Finerenone, 32 month, N = 3003	Placebo, Baseline, N = 2998	Placebo, 12 month, N = 2998	Placebo, 32 month, N = 2998
Kansas City Cardiomyopathy Questionnaire 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
Serum creatinine >5.5 mmol/l No of events	n = 413 ; % = 14.3	n = 199 ; % = 6.9
Hyperkalaemia 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

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

Study location	United States
Study setting	Wake Forest School of Medicine
Study dates	Not specified
Sources of funding	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. 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.
Inclusion criteria	Participants with confirmed HFpEF
Exclusion criteria	Prior aldosterone antagonism use within the past 3 months. A known contraindication Concomitant therapy with a potassium sparing diuretic or potassium supplementation Baseline serum potassium >5.0 meq/L Serum creatinine ≥ 2.5 mg/dL
Recruitment / selection of participants	Selected from chart review
Intervention(s)	Spironolactone 25mg/day

	The starting dose of spironolactone was 12.5 mg once daily in patients with baseline creatinine ≥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 ≤5.0 meq/L. Spironolactone was discontinued if 1-week creatinine was ≥2.5mg/dl or potassium ≥5.5 meq/L.
Comparator	Placebo
Population subgroups	NA
Number of participants	80 participants randomised
Duration of follow-up	9 months
Indirectness	None
Method of analysis	Group comparisons of outcome measures between intervention groups were made by repeated measures analysis of covariance procedures.
Additional comments	1 patient death (attributed to a car accident)

Study arms

Spironolactone (N = 42)

25 mg/day

Placebo (N = 38)

Placebo

Characteristics

Arm-level characteristics

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

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

Outcomes

Study timepoints

Baseline

9 month

Dichotomous outcomes

Outcome	Spironolactone, 9 month, N = 37	Placebo, 9 month, N = 34
All-cause hospitalisations No of events	n = 7 ; % = NR	n = 9 ; % = NR

Continuous outcomes

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

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

Dichotomous outcomes: All-cause hospitalisations: Spironolactone 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 *(Outcome indirectness: reported as dichotomous not time-to-event.)*

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)

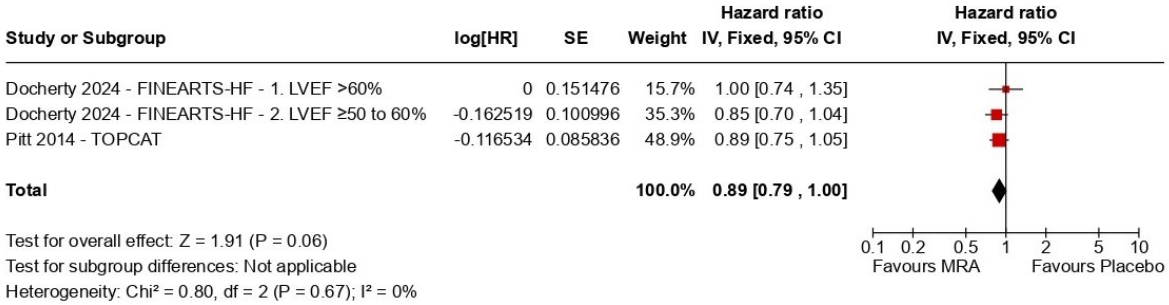


Figure 3: All-cause mortality (dichotomous)

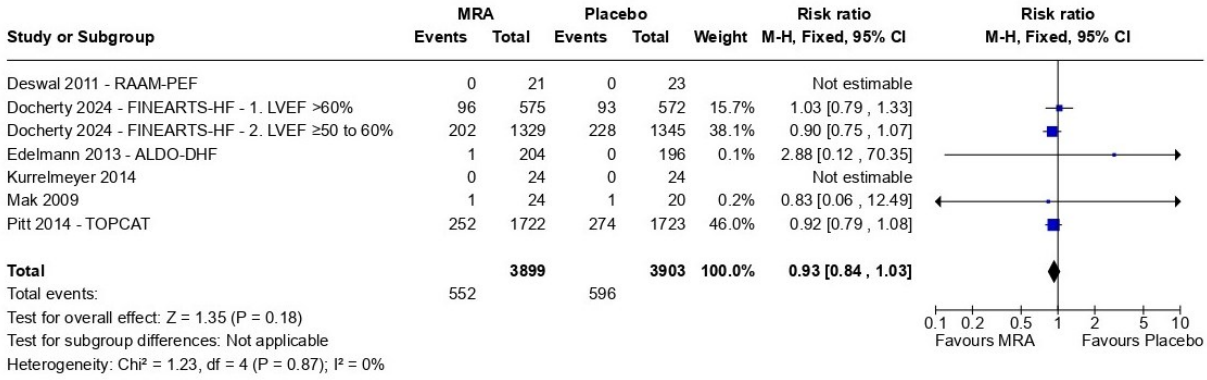


Figure 4: Cardiovascular mortality (time-to-event)

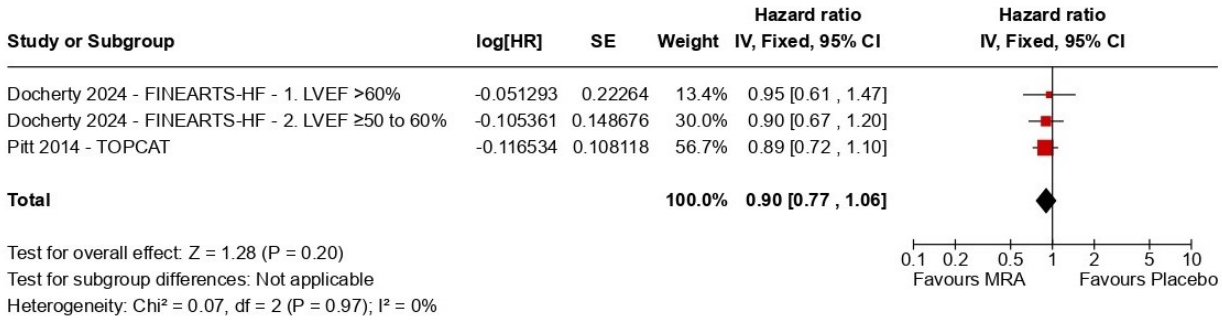


Figure 5: Cardiovascular mortality (dichotomous)

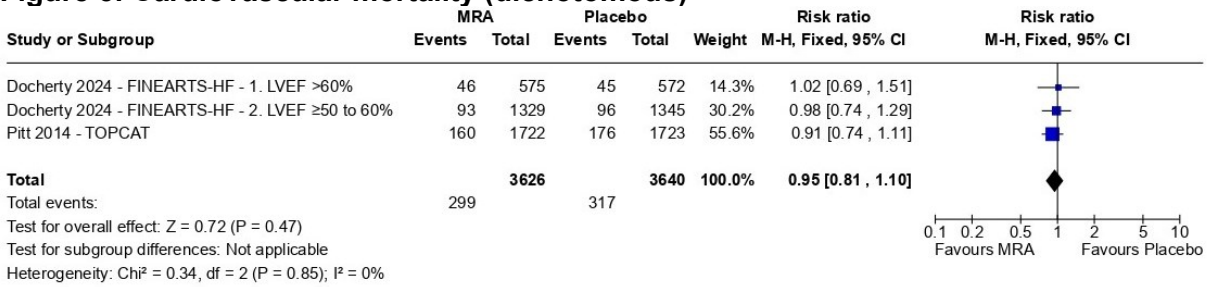
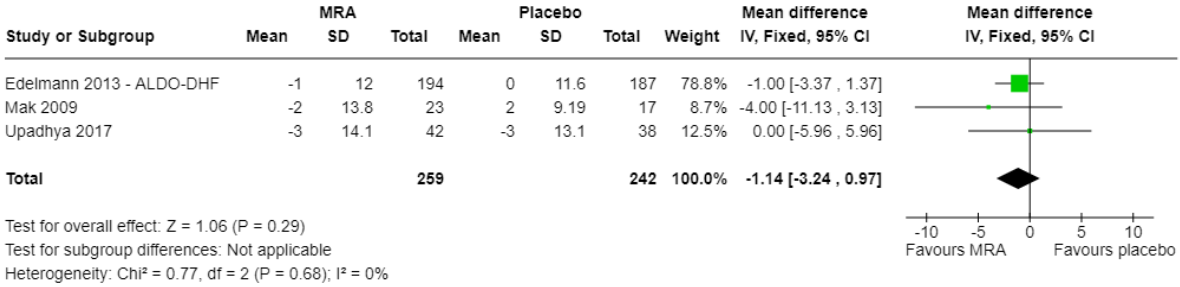
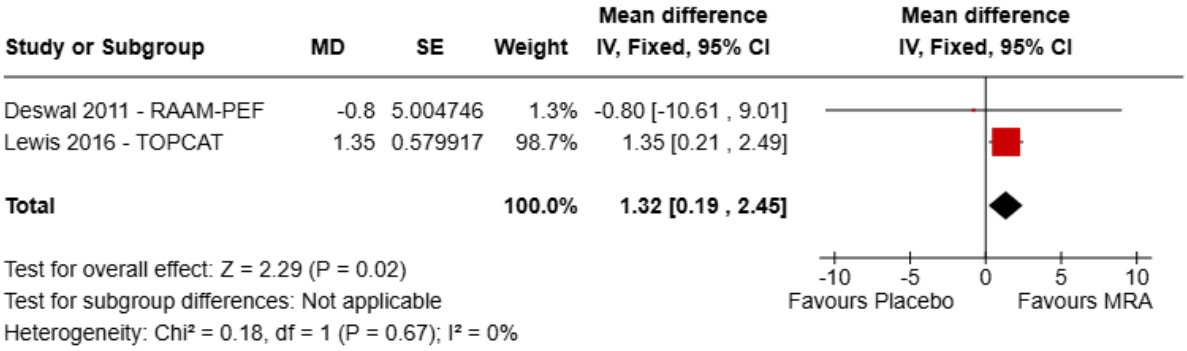


Figure 6: Health-related quality of life: Minnesota Living with Heart Failure (score range 0-105, lower scores are better) (change scores)[1]



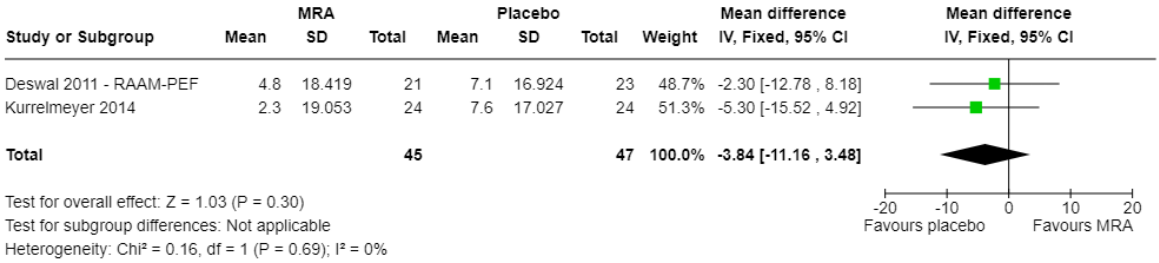
1. *Change score was calculated from reported values.*

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



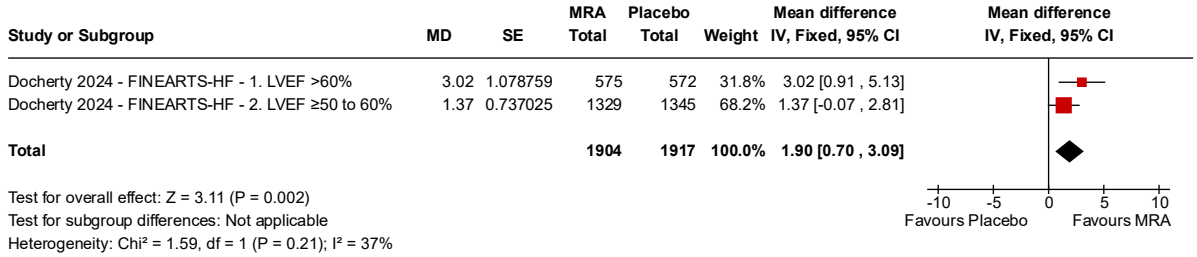
Number analysed per group not available for Lewis 2016.

Figure 8: Health-related quality of life: Kansas City Cardiomyopathy Questionnaire (clinical summary score) (score range 0-100, higher scores are better) (change scores)[1]



1. 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)



Test for overall effect: Z = 3.11 (P = 0.002)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%

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

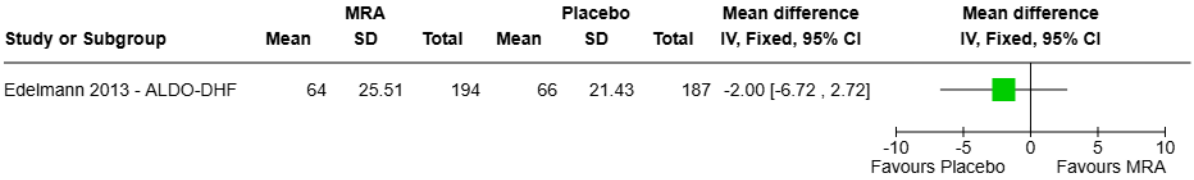
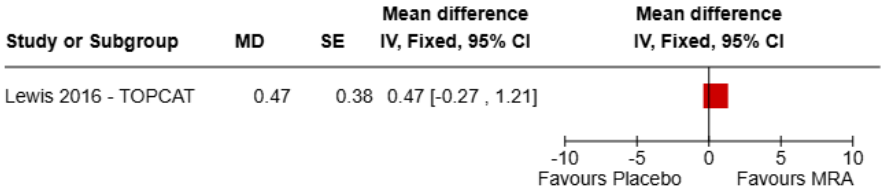
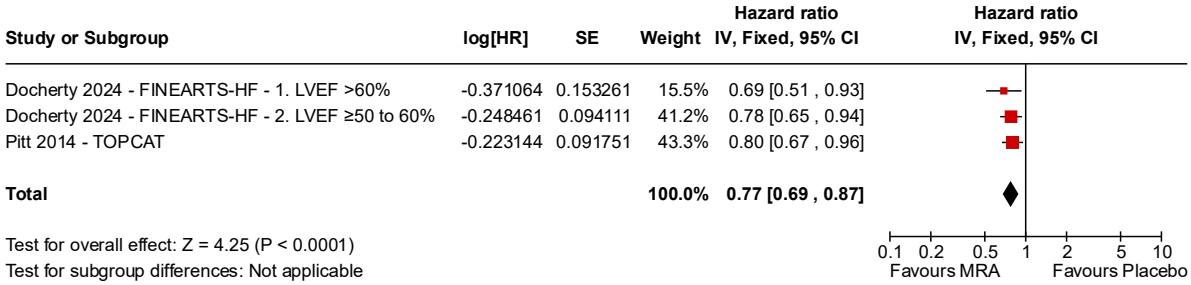


Figure 11: Health-related quality of life: EQ-VAS (score range 0-100, higher scores are better) (change score)



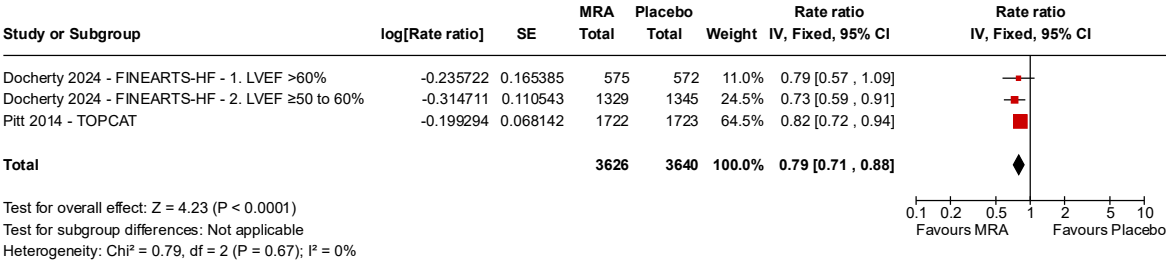
Number analysed per group not available.

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



Test for overall effect: Z = 4.25 (P < 0.0001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.70, df = 2 (P = 0.71); I² = 0%

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



Test for overall effect: Z = 4.23 (P < 0.0001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0%

Figure 14: Heart failure-related hospitalisation (dichotomous)

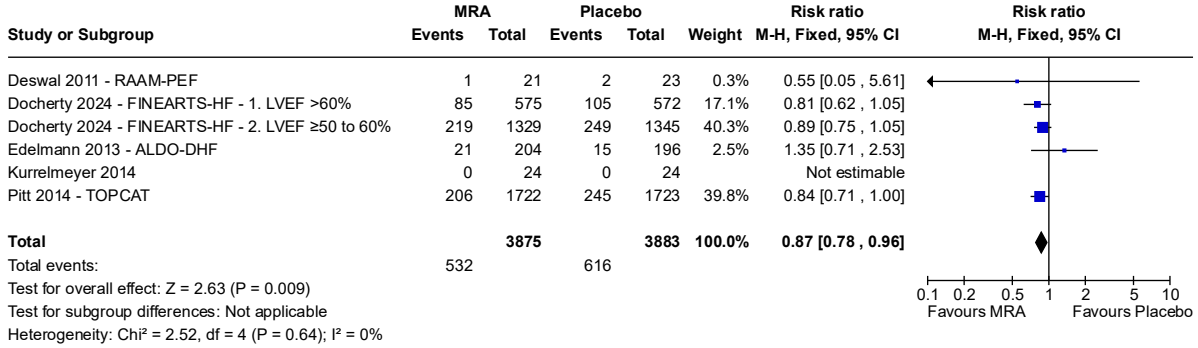


Figure 15: All-cause hospitalisation (dichotomous)

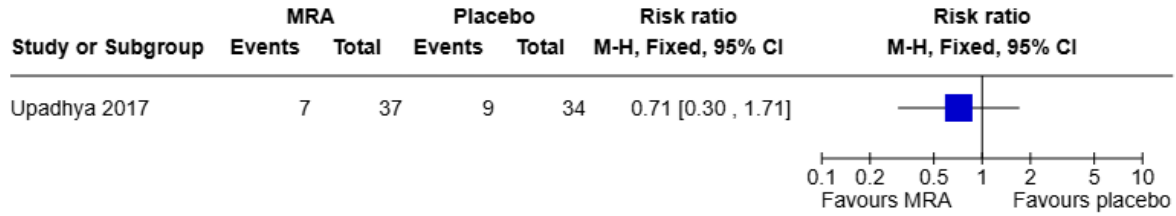


Figure 16: Withdrawal due to drug-related events (dichotomous)

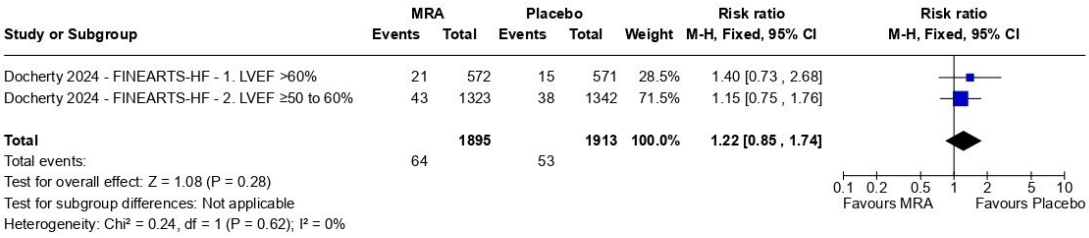


Figure 17: AKI - Serum creatinine rise at 50% (dichotomous)

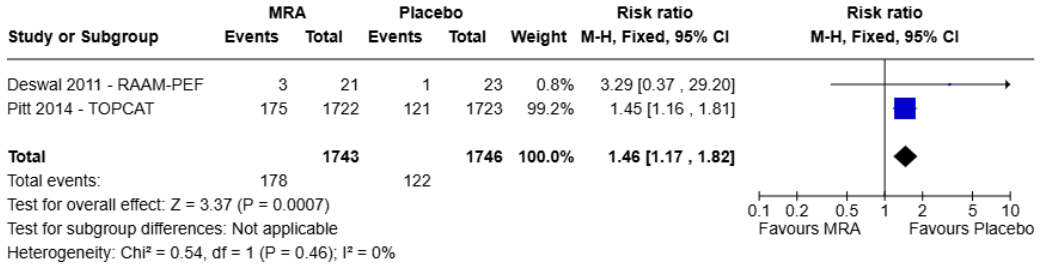


Figure 18: Hyperkalaemia - Serum potassium concentration ≥5.5mmol/L (dichotomous)

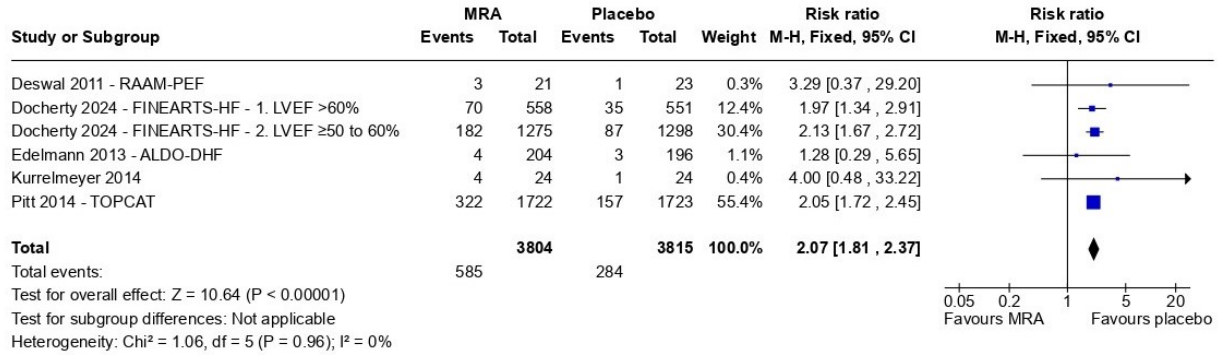
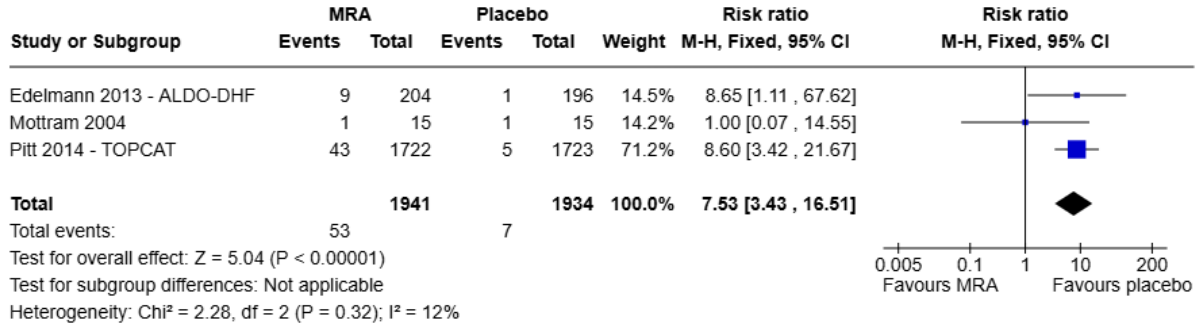


Figure 19: Gynaecomastia in men and breast tenderness/enlargement in women (dichotomous)



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

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

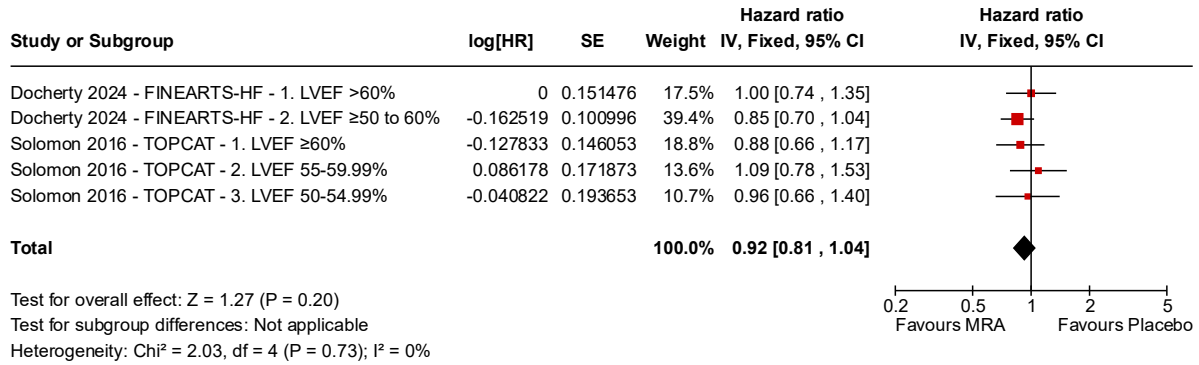
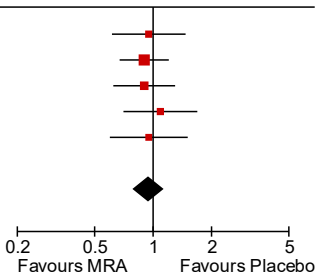


Figure 21: Cardiovascular mortality (time-to-event)

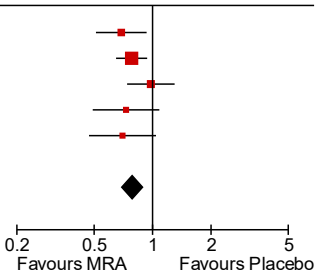
Study or Subgroup	log[HR]	SE	Weight	Hazard ratio IV, Fixed, 95% CI
Docherty 2024 - FINEARTS-HF - 1. LVEF >60%	-0.051293	0.22264	15.3%	0.95 [0.61 , 1.47]
Docherty 2024 - FINEARTS-HF - 2. LVEF ≥50 to 60%	-0.105361	0.148676	34.2%	0.90 [0.67 , 1.20]
Solomon 2016 - TOPCAT - 1. LVEF ≥60%	-0.105361	0.186911	21.7%	0.90 [0.62 , 1.30]
Solomon 2016 - TOPCAT - 2. LVEF 55-59.99%	0.086178	0.223338	15.2%	1.09 [0.70 , 1.69]
Solomon 2016 - TOPCAT - 3. LVEF 50-54.99%	-0.051293	0.235447	13.7%	0.95 [0.60 , 1.51]
Total			**100.0%**	**0.94 [0.79 , 1.12]**



Test for overall effect: Z = 0.70 (P = 0.49)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.58, df = 4 (P = 0.96); I² = 0%

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

Study or Subgroup	log[HR]	SE	Weight	Hazard ratio IV, Fixed, 95% CI
Docherty 2024 - FINEARTS-HF - 1. LVEF >60%	-0.371064	0.153261	16.8%	0.69 [0.51 , 0.93]
Docherty 2024 - FINEARTS-HF - 2. LVEF ≥50 to 60%	-0.248461	0.094111	44.7%	0.78 [0.65 , 0.94]
Solomon 2016 - TOPCAT - 1. LVEF ≥60%	-0.020203	0.143745	19.1%	0.98 [0.74 , 1.30]
Solomon 2016 - TOPCAT - 2. LVEF 55-59.99%	-0.314711	0.201614	9.7%	0.73 [0.49 , 1.08]
Solomon 2016 - TOPCAT - 3. LVEF 50-54.99%	-0.356675	0.202617	9.6%	0.70 [0.47 , 1.04]
Total			**100.0%**	**0.78 [0.69 , 0.89]**



Test for overall effect: Z = 3.85 (P = 0.0001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 3.55, df = 4 (P = 0.47); I² = 0%

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)		
All-cause mortality (time-to-event) (follow-up: range 1 years to 3.3 years)												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/3626	-/3640	**HR 0.89** (0.79 to 1.00)	-	⨁◯◯◯ Very low[a,b,c]	CRITICAL
All-cause mortality (dichotomous) (follow-up: range 9 months to 12 months)												
6	randomised trials	serious[a]	not serious	very serious[d]	not serious	none	552/3899 (14.2%)	596/3903 (15.3%)	**RR 0.93** (0.84 to 1.03)	**11 fewer per 1,000** (from 24 fewer to 5 more)	⨁◯◯◯ Very low[a,d]	CRITICAL
Cardiovascular mortality (time-to-event) (follow-up: range 1 years to 3.3 years)												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	-/3626	-/3640	**HR 0.90** (0.77 to 1.06)	-	⨁⨁⨁◯ Moderate[c]	CRITICAL
Cardiovascular mortality (dichotomous) (follow-up: range 1 years to 3.3 years)												
2	randomised trials	not serious	not serious	serious[e]	not serious	none	299/3626 (8.2%)	317/3640 (8.7%)	**RR 0.95** (0.81 to 1.10)	**4 fewer per 1,000** (from 17 fewer to 9 more)	⨁⨁⨁◯ Moderate[e]	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)		
3	randomised trials	serious[f]	not serious	not serious	not serious	none	259	242	-	MD **1.14 lower** (3.24 lower to 0.97 higher)	⨁⨁⨁◯ Moderate[f]	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: range 6 months to 12 months)												
2	randomised trials	not serious	not serious	not serious	not serious	none	1743	1746	-	MD **1.32 higher** (0.19 higher to 2.45 higher)	⨁⨁⨁⨁ High	CRITICAL
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)												
2	randomised trials	serious[g]	not serious	not serious	serious[c]	none	45	47	-	MD **3.84 lower** (11.16 lower to 3.48 higher)	⨁⨁◯◯ Low[c,g]	CRITICAL
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[h]	not serious	serious[b]	not serious	none	2304	1917	-	MD **1.9 higher** (0.7 higher to 3.09 higher)	⨁⨁◯◯ Low[b,h]	CRITICAL
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[i]	not serious	not serious	serious[c]	none	194	187	-	MD **2 lower** (6.72 lower to 2.72 higher)	⨁⨁◯◯ Low[c,i]	CRITICAL
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

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 1 years to 3.3 years)												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	3626	3640	**HR 0.77** (0.69 to 0.87)	-	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Heart failure-related hospitalisation (total events) (follow-up: range 1 to 3.3 years)												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	3626 participants	3640 participants	**Rate ratio 0.79** (0.71 to 0.88)	**25 fewer per 1000 patient(s) per years** (from 35 fewer to 15 fewer)	⨁⨁⨁◯ Moderate[c]	CRITICAL
Heart failure-related hospitalisation (dichotomous) (follow-up: range 6 months to 3.3 years)												
5	randomised trials	serious[a]	not serious	very serious[d]	serious[c]	none	532/3875 (13.7%)	616/3883 (15.9%)	**RR 0.87** (0.78 to 0.96)	**21 fewer per 1,000** (from 35 fewer to 6 fewer)	⨁◯◯◯ Very low[a,c,d]	CRITICAL
All-cause hospitalisation (dichotomous) (follow-up: mean 9 months)												
1	randomised trials	not serious	not serious	serious[e]	very serious[c]	none	7/37 (18.9%)	9/34 (26.5%)	**RR 0.71** (0.30 to 1.71)	**77 fewer per 1,000** (from 185 fewer to 188 more)	⨁◯◯◯ Very low[c,e]	CRITICAL
Withdrawal due to drug-related events (follow-up: mean 12 months)												
1	randomised trials	serious[h]	not serious	serious[b]	serious[c]	none	64/1895 (3.4%)	53/1913 (2.8%)	**RR 1.22** (0.85 to 1.74)	**6 more per 1,000** (from 4 fewer to 21 more)	⨁◯◯◯ Very low[b,c,h]	CRITICAL
Serum creatinine rise of 50% or greater (follow-up: range 6 months to 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)		
2	randomised trials	not serious	not serious	serious[i]	serious[c]	none	178/1743 (10.2%)	122/1746 (7.0%)	**RR 1.46** (1.17 to 1.82)	**32 more per 1,000** (from 12 more to 57 more)	⨁⨁◯◯ Low[c,i]	CRITICAL
Hyperkalaemia (follow-up: range 6 months to 3.3 years)												
5	randomised trials	not serious	not serious	not serious	not serious	none	585/3804 (15.4%)	284/3815 (7.4%)	**RR 2.07** (1.81 to 2.36)	**80 more per 1,000** (from 60 more to 101 more)	⨁⨁⨁⨁ High	CRITICAL
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%)	**RR 7.53** (3.43 to 16.51)	**24 more per 1,000** (from 9 more to 56 more)	⨁⨁⨁⨁ High	CRITICAL

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 as the majority of the evidence was indirect due to finerenone not being licensed for CHF.

c. 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..

d. Downgraded by 2 increment as the majority of the evidence was very indirect (due to reporting as number of events rather then time to event and using finerenone which is not licensed for CHF)

e. Downgraded by 1 increment as the majority of the evidence was indirect (due to reporting as number of events)

f. Downgraded by 1 increment for risk of bias due to some concerns for the majority of the evidence: no information provided regarding allocation concealment.

g. 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.

h. Downgraded by 1 increment for risk of bias due to unexplained deviations from the trial protocol (the FINEARTS-HF trial did not use the LVEF thresholds prespecified in the study protocol).

i. Downgraded by 1 increment for risk of bias due to no information regarding allocation concealment provided.

j. Downgraded by 1 increment for indirectness due to the 50% increase not being within the acute time frame specified in the protocol.

Sensitivity analysis: using TOPCAT subgroup with LVEF ≥50%

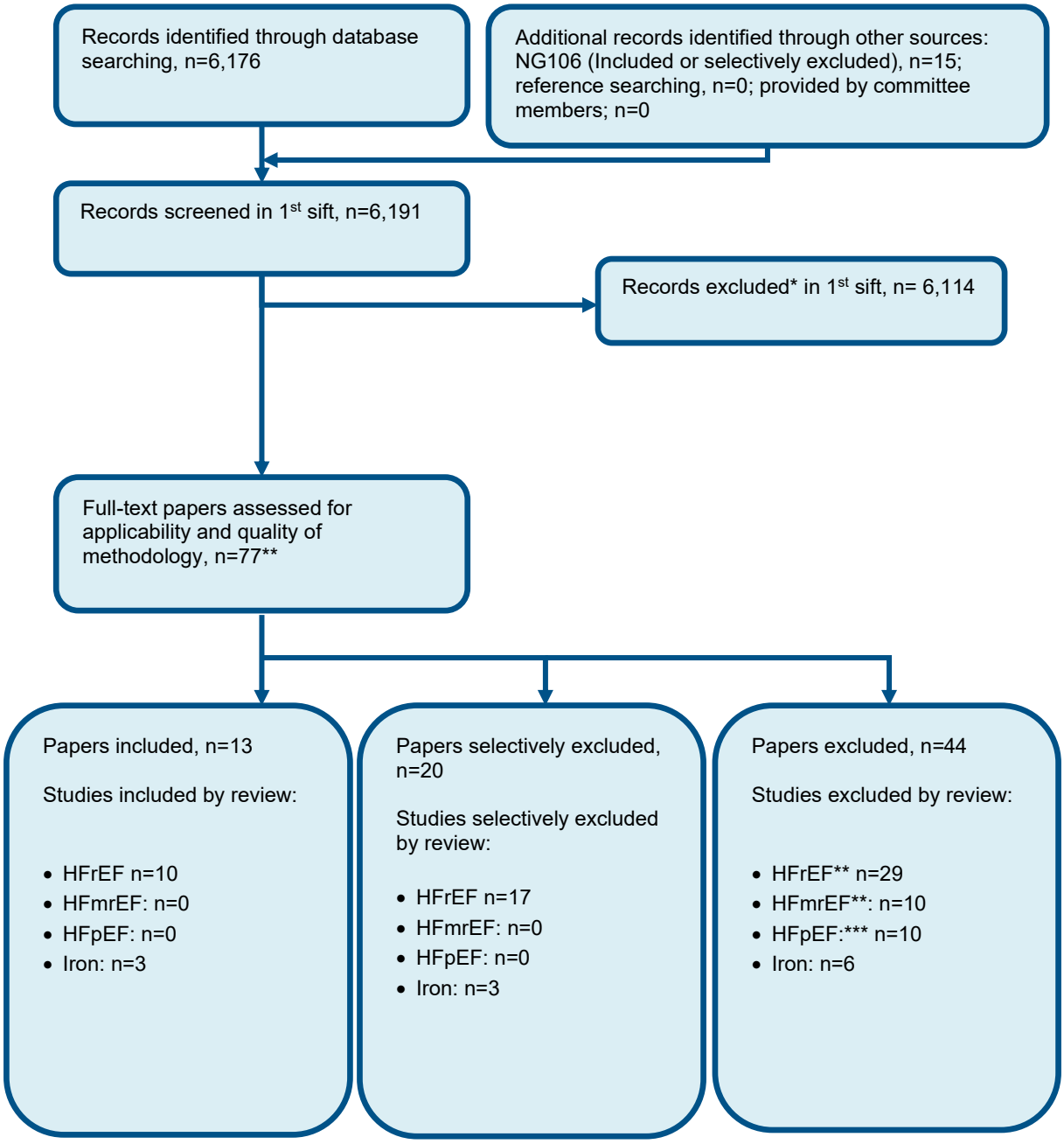
Table 10: Clinical evidence profile: MRA versus placebo using TOPCAT subgroup with LVEF ≥50%

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 12 months to 3.4 years)											
2	randomised trials	not serious	not serious	serious[a]	not serious	none	6745	**HR 0.92** (0.81 to 1.04)	-	⊕⊕⊕◯ Moderate[a]	CRITICAL
Cardiovascular mortality (time-to-event) (follow-up: range 12 months to 3.4 years)											
2	randomised trials	not serious	not serious	not serious	serious[b]	none	6745	**HR 0.94** (0.79 to 1.12)	-	⊕⊕⊕◯ Moderate[b]	CRITICAL
Heart failure-related hospitalisation (follow-up: range 12 months to 3.4 years)											
2	randomised trials	not serious	not serious	serious[a]	serious[b]	none	6745	**HR 0.78** (0.69 to 0.89)	-	⊕⊕◯◯ Low[a,b]	CRITICAL

HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist
a. Downgraded by 1 increment as the majority of the evidence was indirect due to finerenone not being licensed for CHF.
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.

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
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. European Heart Journal 43(6): 474-484a	- Population not relevant to this review protocol *Population focused on participants with type 2 diabetes and chronic kidney disease which was not in line with the protocol.*
Agarwal, Rajiv, Kolkhof, Peter, Bakris, George et al. (2021) Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. European heart journal 42(2): 152-161	- Review article but not a systematic review
Agostoni P EA (2005) Spironolactone improves lung diffusion in chronic heart failure. European Heart Journal 2(26): 159-164	- Population not relevant to this review protocol *Population focused on participants with chronic heart failure with lung diffusion which was not in line with the protocol.*
Beldhuis, Iris E, Myhre, Peder L, Claggett, Brian et al. (2019) Efficacy and Safety of Spironolactone in Patients With HFpEF and Chronic Kidney Disease. JACC. Heart failure 7(1): 25-32	- Secondary publication of an included study that does not provide any additional relevant information
Beldhuis, Iris E, Myhre, Peder L, Bristow, Michael et al. (2021) Spironolactone in Patients With Heart Failure, Preserved Ejection Fraction, and Worsening Renal Function. Journal of the American College of Cardiology 77(9): 1211-1221	- Population not relevant to this review protocol *Population stratified by renal function, but this was defined by creatinine levels, which was not in line with the protocol.*
Bonsu, Kwadwo Osei; Arunmanakul, Poukwan; Chaiyakunapruk, Nathorn (2018) Pharmacological treatments for heart failure with preserved ejection fraction-a systematic review and indirect comparison. Heart failure reviews 23(2): 147-156	- Systematic review used as source of primary studies *Does not include all relevant studies due to the recent publication of the FINEARTS trial*
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. Circulation. Heart failure	- Secondary publication of an included study that does not provide any additional relevant information *Results stratified by age*
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. JAMA cardiology	- Population not relevant to this review protocol *Mixed population of participants with mildly reduced and preserved ejection fractions.*

Study	Exclusion reason
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. Journal of the American College of Cardiology	- Secondary publication of an included study that does not provide any additional relevant information
Doggrell, S (2003) Should the aldosterone-receptor antagonist - eplerenone - be used after acute myocardial infarction with left ventricular dysfunction?. Expert opinion on pharmacotherapy 4(9): 1605-1607	- Not a peer-reviewed publication
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. BMC cardiovascular disorders 24(1): 489	- Systematic review used as source of primary studies *Indirect population; Mixed LVEF*
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. Journal of cardiac failure 24(9): 618-621	- Systematic review used as source of primary studies *Does not include all relevant studies due to the recent publication of the FINEARTS trial*
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. European journal of heart failure 25(1): 108-113	- Study does not contain any outcomes relevant to this review protocol
Ferreira, Joao Pedro, Rossello, Xavier, Eschalier, Romain et al. (2019) MRAs in Elderly HF Patients: Individual Patient-Data Meta-Analysis of RALES, EMPHASIS-HF, and TOPCAT. JACC. Heart failure 7(12): 1012-1021	- Secondary publication of an included study that does not provide any additional relevant information *Data stratified by age. Not a subgroup of interest.*
Ferreira, Joao Pedro, Rossello, Xavier, Pocock, Stuart J et al. (2020) Spironolactone dose in heart failure with preserved ejection fraction: findings from TOPCAT. European journal of heart failure 22(9): 1615-1624	- Secondary publication of an included study that does not provide any additional relevant information
Frankenstein, Lutz, Seide, Svenja, Tager, Tobias et al. (2020) Relative Efficacy of Spironolactone, Eplerenone, and cAnRenone in patients with Chronic Heart failure (RESEARCH): a systematic review and network meta-analysis of randomized controlled trials. Heart failure reviews 25(2): 161-171	- Population not relevant to this review protocol *Population included HFrEF*
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	- Systematic review used as source of primary studies

Study	Exclusion reason
heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Heart and vessels 34(4): 597-606	*Does not include all relevant studies due to the publication of the FINEARTS trial*
Japp, Deepa, Shah, Anoop, Fisken, Sheila et al. (2017) Mineralocorticoid receptor antagonists in elderly patients with heart failure: a systematic review and meta-analysis. Age and ageing 46(1): 18-25	- Systematic review used as source of primary studies *Does not include all relevant studies due to the publication of the FINEARTS trial*
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. International Journal of Pharmaceutical and Clinical Research 14(1): 289-294	- Population not relevant to this review protocol *Population not specific to HFpEF*
Jhund, Pardeep S, Talebi, Atefeh, Henderson, Alasdair D et al. (2024) Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. Lancet (London, England) 404(10458): 1119-1131	- Meta-analysis of already included trials
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. Heart failure reviews 24(3): 367-377	- Systematic review used as source of primary studies *No relevant outcomes reported*
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	- Population not relevant to this review protocol *Reduced LVEF*
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	- Population not relevant to this review protocol *Population focused on obese patients, not specifically HFpEF*
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	- Population not relevant to this review protocol *Population focused on those with metabolic syndrome.*
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. Circulation. Heart failure 11(3): e004457	- Secondary publication of an included study that does not provide any additional relevant information *Results stratified by race*

Study	Exclusion reason
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. Frontiers in pharmacology 14: 1084442	- Study design not relevant to this review protocol *Retrospective cohort study design*
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. Medicine 97(35): e11942	- Systematic review used as source of primary studies *No relevant outcomes reported*
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. Blood pressure 30(3): 145-153	- Population not relevant to this review protocol *Population comprised of patients with hypertension and diabetes*
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. Cardiovascular Diabetology 21(1): 237	- Systematic review used as source of primary studies *Does not include all relevant trials due to the recent publication of the FINEARTS trial.*
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. Frontiers in Pharmacology 12: 707777	- Systematic review used as source of primary studies *Does not include all relevant studies due to the recent publication of the FINEARTS trial.*
Liu (2006) Effects of spironolactone in treatment of elderly hypertension patients with diastolic heart failure. Chin J New Drugs Clin Rem: 567-70	- Study not reported in English *Study reported in Chinese*
Mc Causland, Finnian R, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Finerenone and Kidney Outcomes in Patients with Heart Failure: The FINEARTS-HF Trial. Journal of the American College of Cardiology	- Population not relevant to this review protocol *Population comprised of a mix of participants with mildly reduced and preserved ejection fractions.*
McDiarmid, Adam K, Swoboda, Peter P, Erhayiem, Bara et al. (2020) Myocardial Effects of Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction. Journal of the American Heart Association 9(1): e011521	- Study does not contain any outcomes relevant to this review protocol
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. Circulation. Heart failure 13(1): e006638	- Study design not relevant to this review protocol *Short communications piece*

Study	Exclusion reason
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. Heart, lung & circulation 30(9): 1292-1301	- Study does not include a comparison relevant to this review protocol *Within-class comparison*
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. 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 *Data reported based on presence of atrial fibrillation*
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. Journal of the American Heart Association 7(21): e009664	- Secondary publication of an included study that does not provide any additional relevant information *Data reported based on participant BMI or natriuretic peptides*
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. Medicine 97(16): e0254	- Population not relevant to this review protocol *Population focused on HFrEF*
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. European journal of heart failure 22(3): 559-561	- Secondary publication of an included study that does not provide any additional relevant information
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	- Secondary publication of an included study that does not provide any additional relevant information
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	- Study does not contain any outcomes relevant to this review protocol
Rujic, D., Schou, M., Madsen, P.L. et al. (2023) Echocardiographic Evaluation of Spironolactone on Myocardial Remodeling in Atrial Fibrillation	- Study does not contain any outcomes relevant to this review protocol *focused on myocardial remodelling*

Study	Exclusion reason
with Preserved Ejection Fraction: the INSPIRE-AF randomized controlled trial. medRxiv	
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	- Systematic review does not report any outcomes of relevance to this protocol
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)	- Secondary publication of an included study that does not provide any additional relevant information
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	- Study does not contain any outcomes relevant to this review protocol *Focuses on prognostic value of longitudinal strain.*
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	- Secondary publication of an included study that does not provide any additional relevant information *Data reported based on event vs. non-event*
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	- Secondary publication of an included study that does not provide any additional relevant information
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. Circulation. Heart failure 7(1): 104-15	- Secondary publication of an included study that does not provide any additional relevant information
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. BMJ open 6(10): e012241	- Population not relevant to this review protocol *<80% with CHF*
Shantsila, Eduard, Shahid, Farhan, Sun, Yongzhong et al. (2020) Spironolactone to improve exercise tolerance in people with	- Population not relevant to this review protocol *<80% with CHF*

Study	Exclusion reason
permanent atrial fibrillation and preserved ejection fraction: the IMPRESS-AF RCT.	
Shantsila, Eduard, Shahid, Farhan, Sun, Yongzhong et al. (2020) Spironolactone in Atrial Fibrillation With Preserved Cardiac Fraction: The IMPRESS-AF Trial. Journal of the American Heart Association 9(18): e016239	- Population not relevant to this review protocol *<80% with CHF*
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. European journal of heart failure 26(6): 1334-1346	- Secondary publication of an included study that does not provide any additional relevant information
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. JACC. Heart failure 9(11): 795-802	- Secondary publication of an included study that does not provide any additional relevant information *Information focuses on patients with cardiac amyloidosis*
Sperry, BW, Tang, Y, Jones, PG et al. (2021) Cumulative events in the TOPCAT trial. European journal of heart failure 23(3): 491-492	- Study design not relevant to this review protocol *Research letter*
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. Clinical and translational science 15(10): 2493-2504	- Comparator in study does not match that specified in this review protocol *Comparator is AZD9977*
Sreenivasan, Jayakumar, Malik, Aaqib, Khan, Muhammad Shahzeb et al. (2024) Pharmacotherapies in Heart Failure With Preserved Ejection Fraction: A Systematic Review and Network Meta-Analysis. Cardiology in review 32(2): 114-123	- Systematic review used as source of primary studies *Does not include all relevant studies*
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. American heart journal 271: 136-147	- Secondary publication of an included study that does not provide any additional relevant information *Data stratified by prior hospitalisation for heart failure*
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	- Population not relevant to this review protocol *Population focused on congestive heart failure patients who were also receiving continuous peritoneal dialysis*

Study	Exclusion reason
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	- Population not relevant to this review protocol *Population focused on haemodialysis patients*
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. JACC. Heart failure 10(2): 73-84	- Population not relevant to this review protocol *Population focused on HFrEF*
Tsujimoto, Tetsuro and Kajio, Hiroshi (2020) Spironolactone Use and Improved Outcomes in Patients With Heart Failure With Preserved Ejection Fraction With Resistant Hypertension. Journal of the American Heart Association 9(23): e018827	- Secondary publication of an included study that does not provide any additional relevant information
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). Circulation journal : official journal of the Japanese Circulation Society 82(1): 148-158	- Population not relevant to this review protocol *Population focused on HFrEF*
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. JAMA cardiology	- Secondary publication of an included study that does not provide any additional relevant information
Vaduganathan, Muthiah, Claggett, Brian L, Lam, Carolyn S P et al. (2024) Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial. European journal of heart failure 26(6): 1324-1333	- Secondary publication of an included study that does not provide any additional relevant information
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. Nature medicine	- Population not relevant to this review protocol *<80% of participants in the pooled analysis had CHF*
Vardeny, Orly, Claggett, Brian, Vaduganathan, Muthiah et al. (2019) Influence of Age on Efficacy and Safety of Spironolactone in Heart Failure. JACC. Heart failure 7(12): 1022-1028	- Secondary publication of an included study that does not provide any additional relevant information
Vardeny, Orly, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Finerenone, Serum Potassium, and Clinical Outcomes in	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
Heart Failure With Mildly Reduced or Preserved Ejection Fraction. JAMA cardiology	
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. ESC heart failure 11(1): 475-482	- Secondary publication of an included study that does not provide any additional relevant information
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. JAMA network open 5(9): e2231963	- Systematic review does not contain an intervention relevant to this review protocol *Intervention of focus was SGLT2 inhibitors*
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. Medicine 98(13): e14967	- Systematic review used as source of primary studies *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).*
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. Journal of the American College of Cardiology	- Secondary publication of an included study that does not provide any additional relevant information *Relevant information already presented in an included record (Docherty, 2024)*
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. Heart failure reviews 24(5): 637-646	- Population not relevant to this review protocol *Population with LVEF <45%*
Zafeiropoulos, Stefanos, Farmakis, Ioannis T, Milioglou, Ioannis et al. (2024) Pharmacological Treatments in Heart Failure With Mildly Reduced and Preserved Ejection Fraction: Systematic Review and Network Meta-Analysis. JACC. Heart failure 12(4): 616-627	- Systematic review used as source of primary studies *NMA that does not include all of the relevant studies due to recent publication of the FINEARTS trial*
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. Heart (British Cardiac Society) 104(5): 407-415	- Systematic review used as source of primary studies *Does not include all relevant studies due to the recent publication of the FINEARTS trial.*

J.2 Health economic studies

Table 12: Studies excluded from the health economic review

Study	Exclusion reason
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. European journal of heart failure 25(8): 1386-1395	- Wrong intervention/comparator – SGLT2 inhibitor
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. PharmacoEconomics 37(8): 1071	- Wrong intervention/comparator
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. Hospital practice (1995) 46(4): 197-202	- Wrong intervention/comparator
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. PharmacoEconomics - open 8(1): 19-30	- Wrong intervention/comparator – SGLT2 inhibitor
Kolovos, Spyros, Bellanca, Leana, Groyer, Harinala et al. (2023) Multinational cost-effectiveness analysis of empagliflozin for heart failure patients with ejection fraction >40. ESC heart failure 10(6): 3385-3397	- Wrong intervention/comparator – SGLT2 inhibitor
Kolovos, Spyros, Bellanca, Leana, Groyer, Harinala et al. (2023) Cost-effectiveness of empagliflozin in heart failure patients irrespective of ejection fraction in England. Journal of cardiovascular medicine (Hagerstown, Md.) 24(10): 758-764	- Wrong intervention/comparator – SGLT2 inhibitor
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. ESC heart failure 11(1): 261-270	- Wrong intervention/comparator – SGLT2 inhibitor
Zhou, Jennifer, Liew, Danny, Kaye, David M et al. (2022) Cost-Effectiveness of Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction. Circulation. Cardiovascular quality and outcomes 15(10): e008638	- Wrong intervention/comparator – SGLT2 inhibitor