National Institute for Health and Care Excellence

Guideline version (Consultation)

Chronic heart failure in adults: diagnosis and management

Evidence review for pharmacological therapy for heart failure with mildly reduced left ventricular ejection fraction

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.1 to 1.5.2 in the NICE guideline

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Draft for Consultation

This evidence review was developed by NICE

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ISBN:

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1 Chronic heart failure with mildly reduced left ventricular ejection fraction

1.1 Review question

Is it clinically- and cost-effective to use any of the following first-line pharmacological interventions, alone or in combination, in adults with chronic heart failure with mildly reduced left ventricular ejection fraction:

- Angiotension converting enzyme (ACE) inhibitor
- angiotensin-receptor blocker
- angiotensin receptor neprilysin inhibitor
- beta blocker
- mineralocorticoid receptor antagonist?

1.1.1 Introduction

Until 2014, there was a recurring question about the management of patients with heart failure whose left ventricular ejection fraction (LVEF) falls outside the classic definitions of heart failure with reduced ejection fraction (HFrEF) with LVEF ≤40%, and heart failure with preserved ejection fraction (HFpEF) with LVEF ≥50%. Those patients were not frequently included in randomised clinical trials of patients with heart failure. These patients were originally referred to as having heart failure with mid-range ejection fraction (HFmrEF). There was a call for developing an evidence-base for the management of these patients. A few years later, there was a move to modulate the name of HFmrEF to become heart failure with mildly reduced ejection fraction. Those with HFmrEF constitute the minority of patients with heart failure.

In the past 10-11 years, post hoc analyses of trials on patients with HFrEF and HFpEF which included patients with LVEF 41-49% have been conducted. In addition, trials were designed and conducted which, in the main, included patients with both HFmrEF and HFpEF. Therefore, to obtain evidence specifically related to patients with HFmrEF, post-hoc analyses were still needed.

The guidelines for treating these patients may remain at this stage reliant on the above types of what is ostensibly indirect evidence. There is a need to make sense of these analyses and appraise the clinical and cost effectiveness of these agents to enable the development of evidence-based guidelines.

1.1.2 Summary of the protocol

The protocol is summarised in Table 1. For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults diagnosed with chronic heart failure (CHF) due to left ventricular dysfunction with mildly reduced ejection fraction of 41-49% (HFmrEF)
Interventions	**Pharmacological agents:** • Angiotensin converting enzyme inhibitor (ACEI) • Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan) • Angiotensin receptor antagonist / blocker (ARB) • Beta-adrenergic antagonist/blocker (BB) • Mineralocorticoid receptor antagonist (MRA)

	• Combinations of the above (e.g. ACEI/ARB/ARNI + BB + MRA) **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-arrhythmics.
Comparisons	• Other active treatment alone or in combination • Placebo + usual CHF care or usual CHF care alone
Outcomes	• All-cause mortality [time-to-event (TTE)] • Cardiovascular mortality (TTE) • 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) (TTE; 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) • Withdrawal due to drug-related adverse events (dichotomous) • Acute kidney injury (AKI) – 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) Timepoint: 12 months (pool all times ≥3 months)
Study design	• RCTs • Published systematic reviews of RCTs • Published network meta-analyses (NMAs) and individual participant data meta-analyses (IPDs).

ACEI: Angiotensin converting enzyme inhibitor; AKI: acute kidney injury; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: beta-blocker; CHF: Chronic heart failure; HFmrEF: Chronic heart failure due to left ventricular dysfunction with mildly reduced ejection fraction of 41-49%; IPD: Individual participant data; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: Left ventricular ejection fraction; MLWHF: Minnesota Living With Heart Failure; MRA: Mineralocorticoid receptor antagonist; NMA: network meta-analysis; RCT: randomised controlled trial; TTE: Time-to-event.

Note: The thresholds for mildly reduced left ventricular ejection fraction were agreed with the committee during scoping of the guideline and confirmed at protocol development and are consistent with the published universal classification system (Bozkurt 2021).

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 and the methods document (report B).

Literature search methods

The searches for the effectiveness evidence were run on 11/02/2024 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.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

Included studies

One systematic review with an individual patient data (IPD) meta-analysis (Cleland 2018) and five randomised controlled trials (PEACE, CHARM, TOPCAT, FINEARTS-HF and PARAGON-HF) were included in the review; these are summarised in Table 2 below. Background information on the trials was provided by a further eight papers (Braunwald 2004, Pfeffer 1998, Pitt 2014, Swedberg 1999, Solomon 2019, Solomon 2024, Solomon 2024a and Vaduganathan 2024) and background information on the IPD meta-analysis was provided by Kotecha 2013.

Populations

Three of the studies (FINEARTS-HF, TOPCAT and PARAGON-HF) 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. Additionally, five of the studies limited to symptomatic heart failure, while one trial (Alzahrani 2018) was in people with ischemic cardiomyopathy and mildly reduced ejection fraction without clear evidence of symptomatic heart failure. This was included in the absence of any directly applicable data for ACEI versus placebo, but downgraded for population indirectness.

The FINEARTS-HF trial included adults with mildly reduced or preserved ejection fraction, but for this review only the data for the mildly reduced ejection fraction subgroup were analysed, in accordance with the review protocol. The preserved ejection fraction subgroup is included in review A4.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in 0.

Interventions and comparisons

One systematic review with IPD meta-analysis compared beta-blockers with placebo. The PEACE RCT (Alzaharani 2018) compared ACE inhibitor with placebo. The CHARM RCT compared ARB (Lund 2018) with placebo. The TOPCAT (Solomon 2016) and FINEARTS-HF (Docherty 2024) RCTs compared MRA with placebo. No relevant clinical studies comparing ARNI with placebo were identified. There was also no evidence identified on combinations of these active interventions.

The only pharmacological agent versus pharmacological agent comparison identified in the evidence was ARNI versus ARB in the PARAGON-HF trial (Solomon 2020).

The PEACE study (Alzaharani 2018) used trandolapril, which has been considered an indirect intervention because it is an ACE inhibitor licensed for hypertension and prophylaxis after myocardial infarction in patients with left ventricular dysfunction, rather than CHF. Similarly, finerenone (Docherty 2024) is an MRA currently unlicensed for CHF, so this has also been considered an indirect intervention.

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	Comments
Beta blocker versus placebo				
Cleland 2018 [Kotecha 2013] IPD meta-analysis	Beta-blockers Vs Placebo	11 placebo-controlled trials that recruited >300 patients, with a follow-up of >6 months and reported on mortality. N=716 participants for subgroup with LVEF 40-49%	• All-cause mortality (TTE) • Cardiovascular mortality (TTE) • Unplanned hospitalisation, heart failure-related (cardiovascular hospitalisation) (TTE) Follow-up: median 1.3 years.	Individual patient level meta-analysis Outcome indirectness for cardiovascular hospitalisation – broader than heart-failure hospitalisation. Subgroups with atrial fibrillation and sinus rhythm reported separately (but pooled in our analysis)
ACEI versus placebo				
Alzahrani 2018 [Braunwald 2004, Pfeffer 1998] PEACE trial	ACEI (2mg trandolapril per day, titrated to 4mg after 6 months if 2mg tolerated) Background treatment: Beta-blockers 59% Vs Placebo	Participants with LVEF 40-50%, aged 50 years or older (pre-specified subgroup) N=2512 Multicentre study	• All-cause mortality (events) • Cardiovascular mortality (events) • Unplanned hospitalisation or visits, heart failure-related (hospitalisation for non-fatal congestive heart failure) (events) Follow-up: mean 4.7 years	Outcome indirectness – not TTE as specified in protocol Intervention indirectness – ACEI not licensed for CHF Population indirectness – ischemic cardiomyopathy and mildly reduced ejection fraction without clear

Study	Intervention and comparison	Population	Outcomes	Comments
	Background treatment: Beta-blockers 60% Run-in period: two weeks of 2mg trandolapril per day before randomisation.			evidence of symptomatic heart failure
ARB versus placebo				
Lund 2018 [Swedberg 1999] CHARM	ARB (candesartan, titrated from 4 to 8 mg/day up to the target dose of 32 mg) Vs Placebo Background treatment: ACEI 27%, beta-blocker 58% and MRA 11%	Men or women aged 18 years or older with symptomatic CHF according to NYHA class II-IV for ≥4 weeks before randomisation. N=1332 for subgroup of participants with LVEF 40-49% Multicentre study	• All-cause mortality (TTE, unadjusted) • Cardiovascular mortality (TTE, unadjusted) • Unplanned hospitalisation of visits, heart failure-related (heart failure hospitalisation, TTE) and recurrent heart failure hospitalisation) (rate ratio, unadjusted) Follow-up: mean 2.9 years	Original CHARM study considered spectrum of LVEF, with HFmrEF as subgroup.
MRA versus placebo				
Docherty 2024 [Solomon 2024, Solomon 2024a, Vaduganathan 2024]	MRA (finerenone maximum dose of 20 mg or 40 mg/day). Vs Placebo	Participants aged ≥40 years with CHF and LVEF ≥40%, NYHA II –IV, 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) N=2172 for subgroup with LVEF <50%	• All-cause mortality (TTE, adjusted and events) • Cardiovascular mortality (TTE, adjusted and events) • Health-related quality of life [KCCQ-total symptom score), change score, continuous] • Unplanned hospitalisation or visits, heart failure-related (first worsening	Subgroup analysis of FINEARTS-HF, split by categories of LVEF Intervention indirectness – finerenone not currently licensed for CHF

Study	Intervention and comparison	Population	Outcomes	Comments
FINEARTS-HF	Background treatment: Beta-blocker 88%, ACEI 40%, ARB 28%, ARNI 16%, SGLT2i 16%	Multi-centre study	heart failure events) (TTE, adjusted and events) • Total repeat unplanned hospitalisation or visits, heart failure-related (total worsening heart failure events) (rate ratio) • Withdrawal due to drug-related adverse events (treatment discontinuation due to adverse event) (events) • Hyperkalaemia (events) Follow-up: median 2.6 years	
Solomon 2016 [Pitt 2014] TOPCAT	MRA (spironolactone titrated to 45 mg/day). Vs Placebo Background treatment: ACEI/ARB 88%, and beta-blockers 78%	Participants aged ≥50 years with at least one sign or symptom of CHF and LVEF ≥45% and had a HF hospitalisation in last year or elevated BNP (BNP ≥100 pg/mL or NTproBNP ≥360 pg /mL). N=520 for subgroup with LVEF <50% from Solomon 2016 paper. Multi-centre study	• All-cause mortality (TTE, adjusted) • Cardiovascular mortality (TTE, adjusted) • Unplanned hospitalisation or visits, heart failure-related (heart failure hospitalisation) (TTE, adjusted) Follow-up: median 3.4 years	
ARNI versus ARB				
Solomon 2020 [Solomon 2019] PARAGON-HF	ARNI (97 mg sacubitril/103mg valsartan twice daily as target dose). Background treatment (of total n): MRA 24.6%; beta-blocker 79.9%.	Participants aged ≥50 years with symptoms of CHF (NYHA functional class II to IV) and LVEF ≥45%. Hospitalisation for HF within 9 months prior to enrolment or an elevated NT-proBNP (>300 pg/ml for patients not in AF or >900 pg/ml for patients in AF) N=4821 randomised	• Cardiovascular mortality (TTE) • Unplanned hospitalisation of visits, heart failure-related (heart failure hospitalisation) (TTE) Follow-up: median 35 months	Data from PARAGON-HF and PARADIGM-HF combined in this analysis. However, note that the eligibility criteria for PARADIGM-HF mean that this subgroup data must come from

Study	Intervention and comparison	Population	Outcomes	Comments
	Vs ARB (160mg valsartan twice daily) Background treatment (of total n): MRA 27.1%; beta-blocker 79.5%.	n=730 total for subgroup >40% to 50% LVEF (reported in Solomon 2020 paper) Multi-centre study		PARAGON-HF so ARNI vs ARB. Background treatment with ACEI or ARB (86%) before entry into the trial was discontinued before run-in period.

ACEI: Angiotensin converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BNP: B-type natriuretic peptides; CHF: Chronic heart failure; HFmrEF: Chronic heart failure due to left ventricular dysfunction with mildly reduced ejection fraction of 41-49%; IPD: Individual participant data; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: Left ventricular ejection fraction; MRA: Mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro-B-type natriuretic peptide level; NYHA: New York Health Association; SGLT2i: Sodium-glucose co-transporter 2 inhibitors; TTE: Time-to-event.

Note: Background treatment per arm for the relevant subgroup was not reported in most studies so background treatment for the total subgroup or total n (whole study) reported instead.

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Beta-blockers versus placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blockers
All-cause mortality	716 (11 RCTs in an IPD meta-analysis) Follow-up: 1.3 years	⊕⊕◯◯ Low[a,b]	HR 0.79 (0.51 to 1.23)	Not estimable	
Cardiovascular mortality	716 (11 RCTs in an IPD meta-analysis) Follow-up: 1.3 years	⊕⊕◯◯ Low[a,b]	HR 0.60 (0.35 to 1.04)	Not estimable	
Unplanned hospitalisation, HF-related (cardiovascular hospitalisation)	709 (11 RCTs in an IPD meta-analysis) Follow-up: 1.3 years	⊕◯◯◯ Very low[a,b]	HR 0.98 (0.73 to 1.33)	Not estimable	

CI: confidence interval; HF: Heart failure; IPD: Individual participant data; HR: Hazard ratio; RCT: Randomised controlled trial
a. Downgraded by 1 increment for risk of bias because of some concerns about identification of all relevant trials (no clear search strategy reported or available, and no flowchart to show assessment of papers against inclusion criteria).
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).

Table 4: Clinical evidence summary: ACEI versus placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ACEI
All-cause mortality	2512 (1 RCT) Follow-up: mean 4.7 years	⊕◯◯◯ Very low[a,b]	RR 0.76 (0.60 to 0.98)	106 per 1,000	25 fewer per 1,000 (42 fewer to 2 fewer)
Cardiovascular mortality	2512 (1 RCT) Follow-up: mean 4.7 years	⊕◯◯◯ Very low[a,b]	RR 0.80 (0.56 to 1.14)	53 per 1,000	11 fewer per 1,000 (23 fewer to 7 more)
Unplanned hospitalisation or visits, HF-related (hospitalisation for nonfatal congestive heart failure)	2512 (1 RCT) Follow-up: mean 4.7 years	⊕◯◯◯ Very low[a,b]	RR 0.93 (0.63 to 1.38)	40 per 1,000	3 fewer per 1,000 (15 fewer to 15 more)

ACEI; Angiotensin converting enzyme inhibitor; CI: confidence interval; HF: Heart failure; IPD: Individual participant data; RCT: Randomised controlled trial; RR: Relative risk
a. Downgraded by 2 increments for indirectness: intervention indirectness due to the licenced indication being hypertension not CHF; outcome indirectness due to the outcome not being TTE as specified in the protocol;

population indirectness because the population included people with ischemic cardiomyopathy and mildly reduced ejection fraction without clear evidence of symptomatic heart failure.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).

Table 5: Clinical evidence summary: ARB versus placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (incidence rate)	
				Risk with Placebo	Risk difference with ARB
All-cause mortality	1332 (1 RCT) Follow-up: mean 2.9 years	⊕⊕◯◯ Low[a, b]	HR 0.79 (0.60–1.04)	60 per 1000 person years	12 fewer per 1000 person years[c]
Cardiovascular mortality	1332 (1 RCT) Follow-up: mean 2.9 years	⊕⊕◯◯ Low[a,b]	HR 0.81 (0.60–1.11)	48 per 1000 person years	9 fewer per 1000 person years[c]
Unplanned hospitalisation or visits, HF-related (heart failure hospitalisation)	1332 (1 RCT) Follow-up: mean 2.9 years	⊕⊕◯◯ Low[a,b]	HR 0.72 (0.55–0.95)	71 per 1000 person years	20 fewer per 1000 person years[c]
Repeat unplanned hospitalisation or visits, HF-related (recurrent heart failure hospitalisation)	1332 (1 RCT) Follow-up: mean 2.9 years	⊕⊕⊕◯ Moderate[a]	Rate ratio 0.48 (0.33–0.70)	141 per 1000 person years	64 fewer per 1000 person years[c]

ARB: Angiotensin receptor antagonist / blocker; CI: confidence interval; HF: Heart failure; HR: Hazard ratio; RCT: Randomised controlled trial
a. Downgraded by 1 increment for risk of bias because of some concerns about reporting of randomisation method and not able to assess baseline characteristics.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).
c. Absolute effect calculated from rate per 100 person years reported in the paper (not possible to estimate the variance).

Table 6: Clinical evidence summary: MRA versus placebo

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 (HR)	2692 (2 RCTs) Follow-up: range 2.6 years to 3.4 years	⊕◯◯◯ Very low[a,b,c]	HR 0.91 (0.76 to 1.09)	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
All-cause mortality (dichotomous)	2172 (1 RCT) Follow-up: median 32 months	⊕◯◯◯ Very low[a,c,d]	RR 0.94 (0.79 to 1.13)	186 per 1,000	11 fewer per 1,000 (39 fewer to 24 more)
Cardiovascular mortality (HR)	2692 (2 RCTs) Follow-up: range 2.6 years to 3.4 years	⊕◯◯◯ Very low[a,b,c]	HR 0.81 (0.64 to 1.02)	Not estimable	
Cardiovascular mortality (dichotomous)	2172 (1 RCT) Follow-up: median 32 months	⊕◯◯◯ Very low[a,c,d]	RR 0.85 (0.67 to 1.10)	110 per 1,000	17 fewer per 1,000 (36 fewer to 11 more)
Health-related quality of life (KCCQ-TSS change score; adjusted) Scale: 0 to 100, higher scores better	2172 (1 RCT) Follow-up: mean 12 months	⊕⊕◯◯ Low[a,b]	-	The mean health-related quality of life (KCCQ-TSS change score; adjusted) was 6.78	MD 1.39 higher (0.19 lower to 2.97 higher)
Unplanned hospitalisation or visits, HF-related (first worsening heart failure events; HR)	2692 (2 RCTs) Follow-up: range 2.6 years to 3.4 years	⊕◯◯◯ Very low[a,b,c]	HR 0.77 (0.64 to 0.93)	Not estimable	
Unplanned hospitalisation or visits, HF-related (first unplanned hospitalisation or visit - HF related; dichotomous)	2172 (1 RCT) Follow-up: median 32 months	⊕◯◯◯ Very low[a,c,d]	RR 0.79 (0.66 to 0.94)	203 per 1,000	43 fewer per 1,000 (69 fewer to 12 fewer)
Repeat unplanned hospitalisation or visits, HF-related (total number of worsening heart failure events; rate ratio)	2172 (1 RCT) Follow-up: median 32 months	⊕◯◯◯ Very low[a,b,c]	Rate ratio 0.83 (0.65 to 1.05)	14.6 (12.5 to 17.0) per 100 person years[e]	2.8 less per 100 person years

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
Withdrawal due to drug-related adverse events (treatment discontinuation due to adverse event; dichotomous)	2170 (1 RCT) Follow-up: median 32 months	⨁◯◯◯ Very low[a,b,c]	RR 1.02 (0.62 to 1.67)	28 per 1,000	1 more per 1,000 (11 fewer to 19 more)
Hyperkalaemia (dichotomous)	2098 (1 RCT) Follow-up: median 32 months	⨁⨁◯◯ Low[a,b]	RR 2.05 (1.58 to 2.65)	74 per 1,000	78 more per 1,000 (43 more to 122 more)

CI: confidence interval; HF: Heart failure; HR: Hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire total symptom score*; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial; RR: Relative risk*
a. Downgraded by 1 increment because of some concerns about risk of bias (protocol deviations in subgroup definitions of LVEF categories)
b. Downgraded by 2 increments for indirectness of intervention (finerenone not licensed for CHF) and outcome (dichotomous, not time-to-event).
c. Downgraded by imprecision by 1 increment if the 95% confidence interval crosses one MID and 2 increments if the 95% confidence interval crosses both MIDs (0.8 and 1.25 for dichotomous and time-to-event outcomes; KCCQ TSS MID is 5).
d. Downgraded by 1 increment for intervention indirectness (finerenone not licensed for CHF).
e. Absolute effect calculated from rate per 100 person years reported in the paper (not possible to estimate the variance).

Table 7: Clinical evidence summary: ARNI versus ARB

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ARB	Risk difference with ARNI
Cardiovascular mortality	730 (1 RCT) Follow-up: median 35 months	⨁⨁◯◯ Low[a]	HR 0.98 (0.66 to 1.46)	Not estimable	
Unplanned hospitalisation or visits, HF-related (total heart failure hospitalisations)	730 (1 RCT) Follow-up: median 35 months	⨁⨁⨁◯ Moderate [a]	Rate ratio 0.73 (0.50 to 1.07)	Not estimable	

ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; CI: confidence interval; HF: Heart failure; HR: Hazard ratio; RCT: Randomised controlled
a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).

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. Further studies were sought through bibliography searching. A further 15 studies included previously in the guideline were re-assessed for applicability and quality.

Included studies

No health economic studies were included.

Excluded studies

Ten economic studies relating to this review question were identified but were excluded due to incorrect comparator and interventions. See Appendix JJ.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

ARNI compared with ARB

A simple economic model was developed for this review question comparing ARNI versus ARB in people with mildly reduced EF. Health outcomes were valued in terms of quality adjusted life years (QALYs) estimated by weighting the years of life with a quality of life (utility) score, and the results were presented using incremental cost-effectiveness ratios (ICERs) that express the cost per QALY gained.

The cohort Markov model was developed with a cycle length of 3 months and a 3-year time horizon based on the duration of the PARAGON-HF clinical trial. All parameters related to treatment effect were taken from the PARGAGON-HF trial, restricted to the mildly reduced population where possible. However, for the hospitalisation baseline rates, data from the entire trial population was used as a stratification was not possible. The hazard ratio (HR) associated with mortality for ARNI compared with ARB was very close to 1 (HR: 0.98 (0.66 to 1.46)), so the committee concluded that there was no statistically significant effect on mortality. For this reason, the committee agreed that a shorter time horizon, based on the PARAGON-HF clinical trial, was appropriate to capture the benefits associated with both treatments. The model includes two health states alive and dead and included costs associated with treatment, titration, monitoring, hospitalisations and management of adverse events. QALYs were accrued by weighting the time spent in the alive state by the corresponding utility value for that state adjusted for the utility losses (disutilities) due to hospitalisations and adverse events associated with treatment. An annual utility decrement was also assumed. The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) in England.

All costs and QALYs were discounted at a rate of 3.5% per year in line with the NICE reference case. See Table 8 for the full list of parameters included within the economic model.

Table 8: model parameters

Parameter	Value	Reference
Baseline rates		
Annual mortality rate with ARB	0.032	Solomon et al 2020
Annual HF hospitalisation rate with ARB	0.139	PARAGON-HF, Solomon et al 2019
Treatment effect		

Parameter	Value	Reference
ARNI treatment effect – all-cause mortality	HR: 1	Assumption based on Solomon et al 2020
ARNI treatment effect – HF hospitalisation	HR: 0.73	Solomon et al 2020
Adverse events		
ARB – Hyperkalaemia 3-montly rate	0.002	PARAGON-HF, Solomon et al 2019
ARB – Acute Kidney injury 3-montly rate	0.004	PARAGON-HF, Solomon et al 2019
ARB – Hypotension 3-montly rate	0.002	PARAGON-HF, Solomon et al 2019
ARB – UTI rate 3-montly rate	0.002	PARAGON-HF, Solomon et al 2019
ARNI – Hyperkalaemia 3-montly rate	0.001	PARAGON-HF, Solomon et al 2019
ARNI – Acute Kidney injury 3-montly rate	0.003	PARAGON-HF, Solomon et al 2019
ARNI – Hypotension 3-montly rate	0.002	PARAGON-HF, Solomon et al 2019
ARNI – UTI rate 3-montly rate	0.002	PARAGON-HF, Solomon et al 2019
Unit costs		
ARB treatment	£5.17	NHS drug tariff and prescription cost analysis 2023/24
ARNI treatment	£298.59	NHS drug tariff and prescription cost analysis 2023/24
ARB initiation and titration	£270.76	PSSRU 2023, assuming GP initiation and 5 further titration visits with a Band 7 nurse, a blood test for renal function is assumed at every titration visit (NHS cost collection 2023/2024 weighted average of clinical biochemistry DAPS PATH04)
ARNI initiation and titration	£265.98	PSSRU 2023, assuming specialist initiation and two further visits with a band 7 nurse, a blood test for renal function is assumed at every titration visit (NHS cost collection 2023/2024 weighted average of clinical biochemistry DAPS PATH04)
Heart failure hospitalisation	£2,889	NHS cost collection 2023/2024. EB30A-E weighted average of long and short stay heart failure hospitalisation with and without complications
Hyperkalaemia	£151.24	PSSRU 2023, McMurray et al 2018 two additional GP visits and a blood test

Parameter	Value	Reference
Acute Kidney injury	£3,080.83	NHS cost collection 2023/2024, Tafazolli et al 2023 weighted average of long and short stay LA07H, LA07J-N, LA07P acute kidney injury
Hypotension	£176.20	NHS cost collection 2023/2024 McMurray et al 2018 (UK clinical opinion)
UTI	£74.10	PSSRU 2023, Committee feedback 15 minutes GP appointment
Quality of life		
ARB – EQ-5D at 8 months	-0.014	PARAGON-HF, Chandra et al 2022
ARNI – EQ-5D at 8 months	-0.005	PARAGON-HF, Chandra et al 2022
Annual utility decrement	0.008	NICE TA388 PARADIGM-HF
Hyperkalaemia utility decrement	0	Assumed aligns with Tafazolli et al 2023
Acute Kidney injury utility decrement	0.010	Tafazolli et al 2023, Emperor reduced clinical trial
Hypotension utility decrement	0.025	Tafazolli et al 2023, Emperor reduced clinical trial
UTI utility decrement	0	Tafazolli et al 2023, Sullivan et al 2016
Hospitalisation utility decrement	0.019	NICE TA773

ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; EQ-5D: EuroQol-5 dimensions GP: General practitioner, HF: Heart failure; UTI: Urinary tract infection

The results found ARNI compared with ARB to have an ICER of £119,451 per QALY which is not considered cost effective at NICE's £20,000 per QALY gained threshold (Table 9). The committee anticipated that it was unlikely that ARNI could become cost effective even if further scenarios were tested or the time horizon increased.

Table 9: HFmrEF model results

Strategy	Mean cost per person	Mean QALYs per person	Incremental cost	Incremental QALYs	Incremental cost per QALY (i.e. ICER)	NHB at £20,000/QALY
ARB	£1,749	1.898	-	-	-	1.811
ARNI	£4,386	1.921	£2,637	0.022	£119,191	1.701

QALY: quality adjusted life year; ICER: incremental cost effectiveness ration, NHB: net health benefit

1 ACE inhibitors, ARB, beta-blockers and MRAs compared with no treatment

2 This area was not prioritised for new cost-effectiveness analysis. However, the guideline model used to evaluate medicines for heart failure with
3 reduced ejection fraction was adapted to inform this question as sensitivity analyses. Model parameters unique to mildly reduced ejection fraction
4 analysis can be found in Table 10. For other methods and parameters see Supplement D1: Economic analysis report for chronic heart failure with
5 reduced ejection fraction.

6 **Table 10: Key model parameters**

Parameter	Value	Source
All-cause mortality – Baseline rate per year –0-5 years	0.060	Guideline review (ARB vs placebo) – See Table 5
All-cause mortality – Hazard ratio (BB vs no medicine) – all years	0.79	Guideline review – see Table 3
All-cause mortality – Risk ratio (ACEI vs no medicine) – all years	0.76	Guideline review – see Table 4
All-cause mortality – Hazard ratio (ARB vs no medicine) – all years	0.79	Guideline review – see Table 5
All-cause mortality – Hazard ratio (MRA vs no medicine) – all years	0.91	Guideline review – see Table 6
Utility gain	Zero	Assumed for simplicity but likely to be some improvement
Hospitalisation for heart failure – Baseline rate - 0-5 years	0.071	Guideline review (ARB vs placebo) – See Table 5
Hospitalisation for heart failure - Hazard ratio (BB vs no medicine) – all years	0.98	Guideline review – see Table 3
Hospitalisation for heart failure – Risk ratio ACEI vs no medicine) – all years	0.93	Guideline review – see Table 4
Hospitalisation for heart failure - Hazard ratio (ARB vs no medicine) – all years	0.72	Guideline review – see Table 5
Hospitalisation for heart failure - Hazard ratio (MRA vs no medicine) – all years	0.79	Guideline review – see Table 6
Cost per year (BB)	£12.50	NHS drug tariff – see Table 15
Cost per year (ACEI)	£21.86	NHS drug tariff – see Table 15
Cost per year (ARB)	£20.69	NHS drug tariff – see Table 15

Parameter	Value	Source
Cost per year (spironolactone)	£38.35	NHS drug tariff – see Table 15
Visits for initiation and titration BB	1 GP visit 4 GP nurse visits	Expert opinion – see Table 15
Visits for initiation and titration ACEI	1 GP visit 5 GP nurse visits	Expert opinion – see Table 15
Visits for initiation and titration ARB	1 GP visit 5 GP nurse visits	Expert opinion – see Table 15
Visits for initiation and titration MRA	1 GP visit 2 GP nurse visits	Expert opinion – see Table 15
Additional follow-up visits per year	zero	Expert opinion
Treatment escalation per year	zero	Assumed
Adverse events for BB, ACEI, ARB	Zero	Assumed zero due to lack of data

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; GP: General practitioner, MRA: Mineralocorticoid receptor antagonist;

Even assuming no gain in quality of life, the model suggests all treatments (beta-blockers, ACE inhibitors, ARBs and spironolactone) are likely to be highly cost-effective (see Table 11 and Table 12). It should be noted however that the ICERs associated with beta-blockers, ACE inhibitors and ARBs are an underestimate as they do not account for adverse events.

Table 11: Cost-effectiveness of beta-blockers, ACE inhibitors and ARB compared with no medicine for people with heart failure and mildly reduced ejection fraction

Strategy	Mean cost per person	Mean QALYs per person	Incremental cost vs No medicine	Incremental benefit vs No medicine	Incremental cost per QALY gained (i.e. ICER) vs No medicine	Net health benefit at £20,000/QALY
No medicine	£2,552	5.789	-	-	-	5.661
BB	£3,144	6.406	£592	0.616	£961	6.248
ACEI	£3,213	6.517	£661	0.728	£909	6.356
ARB	£2,784	6.409	£232	0.620	£375	6.269

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker ICER: Incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table 12: Cost-effectiveness of MRAs compared with no medicine for people with heart failure and mildly reduced ejection fraction

Strategy	Mean cost per person	Mean QALYs per person	Incremental cost	Incremental benefit	Incremental cost per QALY gained (i.e. ICER)	Net health benefit at £20,000/QALY
No medicine	£5,144	5.784	-	-	-	5.527
Spironalactone	£7,439	6.028	£2,295	0.244	£9,412	5.656

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

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 13: Unit cost of selected medicines – NHS drug tariff (28th March 2025)

Class	Drug	Tablets/pack	Price/ pack	Tablets per day	Cost per year at max dose	Dose	Indication	Proportion on each drug
ACEI	Enalapril maleate	28	£0.90	2	£23.48	Initially 2.5mg once daily, increased if tolerated to 10-20mg twice daily, dose to be increased gradually over 2-4 weeks	Heart failure	4.13%
ACEI	Ramipril	28	£0.79	2	£20.61	Initially 1.25mg once daily, increased if tolerated to 10mg daily in 1-2 divided doses, daily dose preferably taken in 2 divided doses, increase dose gradually at intervals of 1-2 weeks	Symptomatic heart failure (adjunct) (under close medical supervision)	63.91%
ACEI	Lisinopril	28	£2.16	1	£28.18	Initially 2.5mg once daily; increased in steps of up to 10mg at least every 2 weeks; maximum 35mg per day	Heart failure (adjunct) (under close medical supervision)	22.23%
ACEI	Perindopril-erbumine	30	£1.23	1	£14.98	Initially 2mg once daily for at least 2 weeks, dose to be taken in the morning, then increased if tolerated to 4mg once daily	Heart failure (adjunct) (under close medical supervision)	9.73%
ARB	Candesartan cilexetil	28	£1.24	1	£16.18	Initially 4mg once daily, increased to up to 32mg once daily, dose to be increased at intervals of at least 2 weeks to 'target' dose of 32mg once daily or to maximum tolerated dose	**[Off-label For HFmrEF.]** Heart failure with impaired left ventricular systolic function when ACE inhibitors are not tolerated Heart failure with impaired left ventricular systolic function in conjunction with	17.53%

Class	Drug	Tablets/pack	Price/ pack	Tablets per day	Cost per year at max dose	Dose	Indication	Proportion on each drug
							an ACE inhibitor (under expert supervision)	
ARB	Losartan	28	£1.66	1	£21.65	Initially 12.5mg once daily, increased if tolerated to up to 150mg once daily, doses to be increased at weekly intervals	Chronic heart failure when ACE inhibitors are unsuitable or contra-indicated	82.47%
BB	Bisoprolol fumarate	28	£0.68	1	£8.87	Initially 1.25mg once daily for 1 week, dose to be taken in the morning, then increased if tolerated to 2.5mg once daily for 1 week, then increased if tolerated to 3.75mg once daily for 1 week, then increased if tolerated to 5mg once daily for 4 weeks, then increased if tolerated to 7.5mg once daily for 4 weeks, then increased if tolerated to 10mg once daily	Adjunct in heart failure	91.26%
BB	Carvedilol	28	£1.16	2	£30.26	Initially 12.5mg twice daily for 2 days, then increased to 25mg twice daily	Adjunct to diuretics, digoxin, or ACE inhibitors in symptomatic chronic heart failure	8.21%
BB	Nebivolol	28	£27.75	1	£361.99	Initially 1.25 mg once daily for 1-2 weeks, then increased if tolerated to 2.5mg once daily for 1-2 weeks, then increased if tolerated to 5mg once daily for 1-2 weeks, then increased if tolerated to 10mg once daily	Adjunct in stable mild to moderate heart failure	0.53%
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 HFmrEF.]** 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	

Class	Drug	Tablets/pack	Price/ pack	Tablets per day	Cost per year at max dose	Dose	Indication	Proportion on each drug
							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 heart failure]** Chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes	
ARNI	Sacubitril with valsartan	56	£91.56	2	£1,194.37	Initially 24/26mg twice daily for 3-4 weeks, increased if tolerated to 49/51mg twice daily for 3-4 weeks, then increased if tolerated to 97/103mg twice daily	**[Off-label For HFmrEF.]** Symptomatic chronic heart failure with reduced ejection fraction (in patients not currently taking an ACE inhibitor or angiotensin II receptor antagonist, or stabilised on low doses of either of these agents)	
ARNI	Sacubitril with valsartan	56	£91.56	2	£1,194.37	Initially 49/51mg twice daily for 2-4 weeks, increased if tolerated to 97/103mg twice daily, consider a starting dose of 24/26mg if systolic blood pressure less than 110mmHg	**[Off-label For HFmrEF.]** Symptomatic chronic heart failure with reduced ejection fraction (in patients currently stabilised on an ACE inhibitor or angiotensin II receptor antagonist)	
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	

ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

In the absence of economic evidence and given the differences in resource use for titration between treatments, the resource use associated with titration and one year of treatment was estimated to inform 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 to support the estimation of annual treatment costs. Data on resource use during the titration phase were collected from three GPs and four nurses. The total annual costs of treatments based on the mode (most common response), minimum and maximum number of visits reported are presented in Table 14.

It was assumed that:

- SGLT2 inhibitors and ARNI are initiated at a cardiology outpatient appointment at a cost of £186 (NHS National cost collection 2023/24)
- Other medicines can be initiated by a GP (assuming a duration of 15 minutes) at a cost of £74.10 (PSSRU 2023)
- All other visits are by a Band 7 nurse assuming a cost of £37 based on a 30-minute visit (PSSRU 2023, Section 9.2)

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 14: Annual costs associated with treatment and titration

Drug class	Drug name	Cost per year at max dose	Total number of visits for initiation and titration Mode (minimum, maximum)	Total cost of visits Mode (minimum, maximum)	Total annual costs Mode (minimum, maximum)
ACEI	Enalapril maleate	£23.48	6 (3, 10)	£259 (£148, £407)	£282 (£171, £430)
ACEI	Ramipril	£20.61	6 (3, 10)	£259 (£148, £407)	£280 (£169, £428)
ACEI	Lisinopril	£28.18	6 (3, 10)	£259 (£148, £407)	£287 (£176, £435)
ACEI	Perindopril-erbumine	£14.98	6 (3, 10)	£259 (£148, £407)	£274 (£163, £422)
ARB	Candesartan cilexetil	£16.18	6 (4, 10)	£259 (£185, £407)	£275 (£201, £423)
ARB	Losartan	£21.65	6 (4, 10)	£259 (£185, £407)	£281 (£207, £429)
BB	Bisoprolol fumarate	£8.87	5 (4, 5)	£222 (£185, £222)	£231 (£194, £231)
BB	Carvedilol	£30.26	5 (4, 5)	£222 (£185, £222)	£252 (£215, £252)
BB	Nebivolol	£361.99	5 (4, 5)	£222 (£185, £222)	£584 (£547, £584)

Drug class	Drug name	Cost per year at max dose	Total number of visits for initiation and titration Mode (minimum, maximum)	Total cost of visits Mode (minimum, maximum)	Total annual costs Mode (minimum, maximum)
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)
ARNI	Sacubitril with valsartan	£1,194.37	3 (3, 4)	£260 (£260, £297)	£1454 (£1454, £1491)
SGLT2	Dapagliflozin	£477.30	2 (1, 2)	£223 (£186, £223)	£700 (£663, £700)
SGLT2	Empagliflozin	£477.30	2 (1, 2)	£223 (£186, £223)	£700 (£663, £700)

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

Table 15: Weighted average by treatment class

Drug class	Cost per year at max dose	Total number of visits for initiation and titration average (minimum, maximum)	Total cost of visit (minimum, maximum)	Total annual costs average (minimum, maximum)
ACEI	£21.86	6 (3, 10)	£259 (£148, £407)	£281 (£170, £429)
ARB	£20.69	6 (4, 10)	£259 (£185, £407)	£280 (£206, £428)
BB	£12.50	5 (4, 5)	£222 (£185, £222)	£235 (£198, £235)
ACE, BB and MRA (spironolactone)	£72.72	6 (3, 10)	£259 (£148, £407)	£332 (£221, £480)
ARB (losartan), BB and MRA (spironolactone)	£71.55	6 (4, 10)	£259 (£185, £407)	£331 (£257, £479)
ACEI and SGLT2i	£499.17	6 (3, 10)	£371 (£260, £519)	£870 (£759, £1018)

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1 The outcomes that matter most

The committee considered the outcomes of all-cause mortality, cardiovascular mortality, health-related quality of life, unplanned hospitalisations or visits (HF-related) and specific adverse events: withdrawal due to drug-related adverse events, acute kidney injury, hyponatraemia, hyperkalaemia and falls. For the purposes of decision making, all outcomes were rated as critical. For this review there was no outcome data for some of the specific adverse events of interest: acute kidney injury, hyponatraemia and falls.

All-cause mortality, cardiovascular mortality and unplanned hospitalisations or visits (HF-related) were each preferred as time-to-event outcomes. However, the dichotmous data for these were also included, but downgraded for indirectness.

In some cases, reporting of effect sizes in the papers did not allow the calculation of anticipated absolute effects, for example when overall event rates were reported for a total subgroup (not per treatment group) or event rates were presented per 100 person years. In such instances the committee used the relative effects (hazard ratios) to inform their decision-making.

1.1.11.2 The quality of the evidence

Five comparisons were presented in the evidence, with four medicine classes compared with a placebo comparator (beta-blocker, ACE inhibitor, ARB and MRA), and a single between-medicine class comparison between ARNI and ARB. One study contributed to the evidence for each of the following comparisons: beta-blockers versus placebo; ACEI versus placebo; ARB versus placebo; and ARNI versus ARB. This comprised a total of three RCTs and one IPD meta-analysis. For the comparison of MRAs versus placebo, evidence was available from two RCTs; this is the only comparison where pooling of the data was conducted.

The findings in this evidence review are based on prespecified or post hoc subgroups of larger trials (and an IPD) that investigated pharmacological treatment for patients with a wider range of LVEF. In each case, a population subgroup was identified that met the study protocol definition of heart failure with mildly reduced ejection fraction (HFmrEF). Accordingly, the sample size of studies contributing evidence was often considerably smaller than that from the main trials. The committee discussed the appropriateness of using data from older trials, as patient context or care could have changed over time, but overall considered any changes to be minimal and so agreed that it was still appropriate to use such evidence.

Using GRADE criteria, the certainty of the evidence for all outcomes ranged from very low to moderate. Overall, evidence was downgraded most often for imprecision, which is to be expected with single studies using data from a smaller population subgroup. In some instances, downgrading also took account of outcome, population and intervention indirectness, and some concerns about risk of bias.

Evidence for outcomes for the comparison of beta-blockers versus placebo ranged from very low to low certainty due to some concerns about risk of bias of the IPD meta-analysis and imprecision. Evidence for all outcomes for the comparison of ACE inhibitor versus placebo were assessed as very low certainty. This is because of downgrading for population, outcome and intervention indirectness and for imprecision. For the comparison of ARB versus placebo, the certainty of the evidence was low to moderate. Downgrading was done to account for issues with risk of bias and imprecision. For the comparison of MRA versus placebo, the certainty of evidence was very low to low; downgrading was done to account for issues with risk of bias, imprecision and indirectness. For the comparison of ARNI versus

ARB, certainty of evidence was low to moderate, with downgrading taking place due to imprecision only.

The committee commented on concerns about the quality of evidence from the TOPCAT trial as issues have been previously noted about substantial regional differences in patients recruited in the Russia/Georgia region, amongst whom there were very few patients admitted to hospital, raising concerns about whether they truly had heart failure. To address this, separate analyses using TOPCAT data from the Americas region only were also presented to the committee to inform their discussions. Pooled estimates based on TOPCAT Americas data (instead of all TOPCAT data for HFmrEF participants) together with FINEARTS-HF, did not substantially change the pooled estimate of effects on mortality and hospitalisation. However, the size of the subgroup of TOPCAT Americas data for HFmrEF participants was very small and therefore unreliable so has not been formally presented in the evidence review.

With an absence of current NICE recommendations on pharmacological treatment for patients with HFmrEF, the committee considered it important to make recommendations to address this gap. Although evidence from some of the trials had a small sample size and some uncertainty, the consistency in beneficial effects across outcomes supported decision making.

1.1.11.3 Benefits and harms

Beta-blocker vs placebo

Evidence for this comparison came from an IPD meta-analysis and did not enable absolute effects to be calculated. However, all HRs were <1 suggesting some benefit of beta-blockers on all-cause mortality (HR: 0.79, 95%CI 0.51 to 1.23), and cardiovascular mortality (HR: 0.60, 95%CI 0.35 to 1.04); however, the effect size for and unplanned hospitalisation (HF-related) was very small (HR: 0.98, 95%CI 0.73- 1.33). This pattern is consistent with the committee's observations in clinical practice, but the uncertainty in the estimates was noted.

The IPD meta-analysis reported results for participants with sinus rhythm and atrial fibrillation separately but these were pooled in our analyses as atrial fibrillation was not a pre-specified subgroup of interest in the protocol. However, the subgroups of participants with sinus rhythm and atrial fibrillation are visible in the forest plots because this data was extracted from the paper. The committee discussed the subgroups of participants with sinus rhythm and atrial fibrillation and concluded that the beneficial effect on mortality is more convincing in those with sinus rhythm, albeit that the atrial fibrillation group had a smaller sample size. The committee considered that the differential effects of beta-blockers in patients with HFrEF with/without atrial fibrillation is well known, and that clinicians will adapt their use of this class of medicine to patients with HFmrEF accordingly. It was noted that beta-blockers would usually be prescribed to patients with atrial fibrillation for other reasons, but they would not impact mortality rate.

It was also noted that most of the participants analysed had heart failure with an ischaemic aetiology, which is the dominant cause of heart failure seen in practice. However, the recommendation was not restricted to those with CHF and ischaemic heart disease because, beta-blockers also have other plausible benefits including rhythm stability.

ACE inhibitor vs placebo

The evidence on ACE inhibitors showed a clinically important benefit for all-cause mortality (25 fewer deaths per 1000 in ACE inhibitor group) and cardiovascular mortality (11 fewer deaths per 1000 in ACE inhibitor group) and a consistent benefit, albeit smaller, for hospitalisations for HF (3 fewer per 1000 in the ACE inhibitor group).

Indirectness was noted as this study included people with ischemic heart failure and mildly reduced ejection fraction without clear evidence of symptomatic heart failure. This evidence was included in the absence of any directly applicable trial data, but the committee acknowledged the limitations of this data as the benefits may be due to the effectiveness of ACE inhibitor in the treatment of ischaemic heart disease rather than symptomatic heart failure. Nevertheless, in the experience of the committee, it is biologically plausible that this benefit can be extrapolated to those with symptomatic heart failure with mildly reduced ejection fraction based on the known benefit for chronic heart failure with reduced ejection fraction and the generalisability of this to the mildly reduced ejection fraction cohort, with some attenuation of effect expected. This recommendation is also in line with clinical practice, as ACE inhibitors are commonly used for patients with heart failure and mildly reduced ejection fraction.

Furthermore, the ACE inhibitor used in the study was trandolapril, which is not licensed for CHF in the UK but is used in other countries. The committee expected the effectiveness of other ACE inhibitors to be equivalent and for there to be a medicine class effect.

ARB vs placebo

The evidence showed clinically important benefits for all-cause mortality (32 fewer per 1000 in the ARB group), cardiovascular mortality (22 fewer per 1000 in the ARB group) and HF hospitalisation (45 per 1000 fewer and 6.4 fewer per 100 person years in the ARB group). The committee noted that ARBs in the larger trial on participants with a wider range of LVEF (reduced and preserved ejection fraction) did not decrease mortality. Therefore, the benefit on mortality seen in small HFmrEF subgroup might not be correct. Nevertheless, the clinically important benefit for HF hospitalisation seen in HFmrEF was considered sufficient to support a recommendation.

MRA vs placebo

The evidence showed clinically important benefits for all-cause mortality (11 fewer per 1000 in the MRA group), cardiovascular mortality (17 fewer per 1000 in the MRA group) and first HF hospitalisation or visit (43 fewer per 1000), when expressed as dichotomous events. For total repeat unplanned hospitalisations or visits, there was also a suggested benefit, though this was difficult to quantify as an absolute effect because the effect size was expressed as a rate ratio (2.8 less per 100 person years in the MRA group). When expressed as time-to-event data, the mortality and hospitalisation outcomes also suggested some clinical benefit as HRs were <1 (0.91 for all-cause mortality, 0.81 for cardiovascular mortality and 0.77 for first unplanned hospitalisation or visit, HF-related). The evidence showed no clinically important difference for health-related quality of life and treatment discontinuation due to adverse events. However, evidence for the adverse event hyperkalaemia showed a clinically important harm, with 78 more events per 1000.

The committee discussed the risk of hyperkalaemia in patients taking MRAs, in terms of the need for regular monitoring. It was felt that an increase in potassium levels is expected when taking MRAs, but hyperkalaemia is a greater risk if a patient also has chronic kidney disease. It was further noted that hyperkalaemia is asymptomatic until it becomes life threatening, so it is an important parameter to monitor after introduction of MRAs. Such monitoring is best left to clinical judgement as individual clinical situations impact on the frequency of monitoring and extent of risk. Overall, the committee considered potassium levels to be important to monitor, but that hyperkalaemia is not a harm that outweighs the clinically important benefit of MRAs on mortality and hospitalisation for HF. The committee also wanted to avoid clinicians stopping provision of MRAs unnecessarily, due to rigid restrictions on monitoring of potassium levels. Guiding principles on monitoring are provided in recommendations 1.7.6 to 1.7.9.

The committee expected a medicine class effect, despite evidence on two different MRAs, and decided not to make recommendations based on specific medicines or doses.

ARNI vs ARB

Although anticipated absolute effects were not available for the outcomes under this comparison, the rate ratio for total HF hospitalisations was 0.73 (95%CI 0.50 to 1.07), suggesting some benefit of ARNI over ARB. However, the HR for CV mortality was 0.98, suggesting no clear clinically important difference. The background treatment of patients when adding ARNI is an important consideration that impacts on the potential clinical effectiveness. It was noted that without a placebo comparison it is difficult to assess the effect of ARNI against other trial data as other comparisons were against a placebo. The committee agreed that there was some uncertainty about the clinical effectiveness of ARNI and required further information on cost-effectiveness.

Summary

The committee agreed that there was evidence to suggest a benefit of ACE inhibitors, ARBs, beta-blockers and MRA each compared to placebo in people with heart failure and mildly reduced ejection fraction for reducing heart failure hospitalisation, which is an indication of clinical deterioration of CHF, and possibly mortality. There was uncertainty in these effects due to the evidence being derived from subgroups of larger trials and having limited power to show a clear benefit, as well as the ACE inhibitor data being in an indirect population. However, the committee noted that the findings were in line with what they see in practice and are biologically plausible. It was agreed that as the left ventricular ejection fraction increases, the benefit of these interventions will decrease. The committee agreed to make a consider recommendation for these 4 classes of medicines so that clinicians can incorporate their use for people with chronic heart failure and mildly reduced ejection fraction when appropriate based on individual circumstances and preferences.

The committee discussed that clinical judgement should be exercised when deciding which medicine to use first, for example an ACE inhibitor may be used first if the person has diabetes mellitus or fluid overload. An ARB should be used if an ACE inhibitor cannot be tolerated, usually due to a persistent cough. Although not considered as part of this evidence review, the SGLT2 inhibitors dapagliflozin and empagliflozin should be offered in accordance with the NICE technology appraisals (TA902 and TA929).

1.1.11.4 Cost effectiveness and resource use

No published economic evidence was available for the committee to review. The committee considered the costs of the treatments which are within the scope of the review question.

Given the low acquisition costs of ACE inhibitor, ARB, beta-blocker and some MRAs, economic modelling for these treatments was not prioritised. However, given the differences in the number of monitoring visits required during titration, the resource use associated with treatment monitoring during the period of titration and the first year of treatment was calculated. These treatments were not compared with SGLT2 inhibitors or with each other; however, the costs of SGLT2 inhibitors were used as a benchmark, as dapagliflozin and empagliflozin are the only treatment options recommended by NICE for this population (TA902 and TA929).

The cost of treatment was significantly lower with ACE inhibitor, ARB, beta-blockers and spironolactone than SGLT2 inhibitors. However, this lower cost does not apply to finerenone and sacubitril/valsartan.

An original economic analysis was conducted that showed, ACE inhibitor, ARB, beta-blocker and spironolactone were highly cost-effective compared with no medicine using the trial

evidence in people with mildly reduced ejection fraction in the economic model developed to evaluate medicines for people with reduced ejection fraction. This analysis was tentative, as some of the parameters came from a reduced ejection fraction population including demographics and longer-term outcomes. The ICERs for ACE inhibitor, ARB and beta-blocker were underestimated because these analyses did not capture adverse events. However, the committee concluded that they all of these medicines are likely to be cost-effective and so recommended them as options.

The committee considered that although beta-blockers, ACE inhibitor/ARB and MRA have not been previously recommended by NICE in this subpopulation, most people are prescribed a combination of these medicines if not contraindicated and depending on comorbidities. So, this is not expected to have a significant resource impact. Where there is an increase in prescribing there will be extra staff time involved for titration of treatments. However, there should also be a reduction in hospitalisation for heart failure.

MRAs

Some of the clinical evidence for MRAs was based on studies of finerenone. The committee discussed that the evidence supported a class effect; however, finerenone is associated with a high cost.

Finerenone is expected to have a more favourable side effect profile than spironolactone. However, given its significantly higher acquisition cost and the lack of evidence for greater clinical effectiveness, the cost effectiveness of finerenone remains uncertain.

ARNI

The committee wanted to consider cost effectiveness modelling of ARNI for the treatment of people with HFmrEF. Although the drug has a high acquisition costs, potential cost savings from reductions in the numbers of hospitalisations were also taken into account. The committee reviewed the results of the economic model comparing ARNI with ARB alongside the clinical evidence for this population. The model showed that ARNI had an ICER over £100,000, which is substantially higher than NICE's £20,000 threshold.

The committee noted that, although the model assumed no difference in mortality between treatments, applying the modest trend observed in the trial (HR = 0.98) would still not result in an ICER below the £20,000 per QALY gained threshold. Given the high cost per QALY observed in the deterministic base-case analysis, additional scenario analyses were not conducted, as ARNI was unlikely to be cost effective in this population. Consequently, the committee decided not to recommend ARNI for people with HFmrEF.

1.1.11.5 Other factors the committee took into account

The committee emphasised the importance of not treating people based on LVEF alone. This is applicable to all types of heart failure affecting the left ventricle. It is essential that the complete phenotype of heart failure is determined and that the aetiology has been investigated. This requires excluding alternative or associated 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.

In weighing up the evidence on ACE inhibitor or ARB versus placebo, the committee felt that clinical judgement would be important. Although the evidence reviewed suggests a greater benefit from ARB compared to placebo, than for ACE inhibitor compared to placebo, both show beneficial effects on outcomes. Therefore, a clinician can use their specialist knowledge and judgement to decide the sequence of introduction of agents to the patient, and which agent should be chosen.

When deliberating the benefits and harms of MRAs, the committee discussed the requirements for monitoring of patients following the introduction of a new class of medicine. It was agreed that a 'one size fits all' recommendation for monitoring was not appropriate, because requirements vary according to the clinical situation. For example, patients with CKD may be more likely to experience an increase in serum potassium after starting MRAs, and so require more frequent monitoring; older patients with frailty may experience barriers to attending clinics for regular blood tests. Although the committee appreciated the value of clinical judgement to inform monitoring requirements, the committee agreed it is important to develop guiding principles to inform judgements on monitoring. Therefore, as part of this guideline update, the committee developed broad guidance on monitoring, that clinicians can be signposted to (see recommendations 1.7.6 to 1.7.9).

The committee noted a need to be pragmatic in making recommendations because the medicine classes under consideration are always prescribed in combination. With the evidence available it is not possible to tease out minor differences between medicine classes.

Despite the lack of direct evidene for ACE inhibitors, the committee noted that the ESC guidelines recommend this medicine class in those with heart failure and mildy reduced ejection fraction. This is based on the consideration that many will also have coronary artery disease, hypertension, or post-myocardial infarction left ventricular systolic dysfunction and so already be treated with an ACE inhibitor.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendation 1.5.1 and 1.5.2.

1.1.13 References

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Appendices

Appendix A Review protocols

A.1 Review protocol for pharmacological treatment of chronic heart failure with mildly reduced left ventricular ejection fraction

Field	Content
Review title	Pharmacological treatment of chronic heart failure with mildly reduced ejection fraction (HFmrEF).
Review question	Is it clinically- and cost-effective to use any of the following first-line pharmacological interventions, alone or in combination, in adults with chronic heart failure with mildly reduced left ventricular ejection fraction: • ACE inhibitor • angiotensin-receptor blocker • angiotensin receptor neprilysin inhibitor • beta blocker • mineralocorticoid receptor antagonist
Objective	The current recommendations in NG106 do not cover people with mildly reduced ejection fraction, but new evidence is emerging that the use of the 'four pillars' may be appropriate in this group of patients who have traditionally been treated as HFpEF (i.e., co-morbidities and diuretics only). Therefore, the aim of this review is to update the recommendations on pharmacological management for people with chronic heart failure and mildly reduced ejection fraction.
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:

Field	Content
	• Date limitations – from date of searches in CG5, 2003 • English language studies • Human studies Other searches: Inclusion lists of relevant systematic reviews Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details). The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.
Condition or domain being studied	Chronic heart failure with mildly reduced ejection fraction
Population	**Inclusion**: Adults diagnosed with heart failure due to left ventricular dysfunction with mildly reduced ejection fraction. 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. Ongoing treatment after discharge for an acute episode of heart failure will be included. **Exclusion**: • Children • Acute heart failure in hospital • Heart failure with preserved EF (normal EF, diastolic dysfunction) • 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 MI (within 3 months of the event)

Field	Content
	• Treatment with chemotherapy
Intervention	**Inclusion** Pharmacological agents alone or in combination: • Angiotensin converting enzyme (ACE) inhibitor • Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan) • Angiotensin receptor antagonist / blocker (ARB) • Beta-adrenergic antagonist/blocker (BB) • Mineralocorticoid receptor antagonist (MRA) • Combinations of the above (e.g. ACE-I/ARB/ARNI + BB + MRA) **Mode of delivery:** oral. **Analysis groupings:** a class effect will be assumed. **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-arrhythmics. Studies will be included, but downgraded for indirectness if >20% of participants are also receiving therapies initiated by a specialist as part of their 'standard care' (e.g., ivabradine, hydralazine-nitrate, vericiguat) **Exclusion** • SGLT2 inhibitors are excluded because there are relevant technology appraisals in this population that will be incorporated in the guideline. • Calcium channel blockers are excluded because they are not used in current practice. • Medicines to manage oedema (except as background treatment), for example: o loop diuretics o thiazide diuretics • The following therapies (except as background treatment): o Digoxin

Field	Content
	○ Ivabradine ○ Hydralazine-Nitrate ○ Omecamtiv mecarbil ○ Vericiguat • Medicines to manage comorbidities (except as part of background treatment): ○ Anticoagulants ○ Anti-arrhythmics
Comparator	Other active treatment alone or in combination Placebo + usual CHF care or usual CHF care alone
Types of study to be included	**Inclusion:** • 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 **Note**: Post hoc subgroup analyses from RCTs may have to be considered for inclusion if there is insufficient evidence from prespecified analyses.
Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	This review will partially update NICE guideline NG106.
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause mortality (time-to-event) • CV 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)

Field	Content
	○ 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) **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** • 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 research fellow. This includes checking:

Field	Content
	• 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 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. • WinBUGS will be used for network meta-analysis, if possible given the data identified.

Field	Content		
Analysis of sub-groups	**Subgroups that will be investigated if heterogeneity is present**: • Renal function (Abnormal (EGFR < 30mL/min); Normal (EGFR 30-60mL/min; >60mL/min)) • Age (18-75 years; Over 75 years) • Ethnicity (Afro-Caribbean; south Asian; Caucasian; other)		
Type and method of review	☑	Intervention	
	☐	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	February 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	☑	☑

Field	Content		
	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 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.		

Field	Content	
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: https://www.nice.org.uk/guidance/indevelopment/gid-ng10405	
Other registration details	NA	
Reference/URL for published protocol	https://www.nice.org.uk/guidance/indevelopment/gid-ng10405/documents	
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.	
Keywords	Heart failure; pharmacological; four pillars; ACE inhibitors; sacubitril valsartan; beta-blockers; mineralocorticoid receptor antagonists; SGLT2 inhibitors.	
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	NA	
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; HFpEF: Heart failure with a preserved 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.2 Health economic review protocol

Table 1616: 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.
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.

	All questions – health economic evidence
	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: 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.

	All questions – health economic evidence
	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.

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Appendix B Literature search strategies

Chronic heart failure with mildly reduced left ventricular 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 (including NG106 and CG5). 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.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of 1st October 2002 to current was applied, as stated in the review protocol from when searches were conducted for CG5.

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 search covers two review protocols.

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)	11th February 2024	Wiley	Issue 2 of 12, February 2024	22
Cochrane Central Register of Controlled Trials (CENTRAL)	11th February 2024	Wiley	Issue 2 of 12, February 2024	4480
Embase	11th February 2024	Ovid	Embase <1974 to 2024 February 09>	12044
MEDLINE	11th February 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to February 06, 2024	5182
Epistemonikos	11th February 2024	Epistemonikos	11/02/2024	299

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	335
Embase	9th January 2025	Ovid	Embase <1974 to 2025 January 07>	1290
MEDLINE	9th January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 06, 2025>	510

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Epistemonikos	9th January 2025	Epistemonikos	9/01/2025	3

Search strategy history

Database name: Cochrane Database of Systematic Reviews (CDSR)

Searches		
ID	Search	Hits
#1	MeSH descriptor: [Heart Failure] explode all trees	14344
#2	MeSH descriptor: [Cardiomyopathy, Dilated] this term only	669
#3	MeSH descriptor: [Shock, Cardiogenic] this term only	477
#4	MeSH descriptor: [Ventricular Dysfunction] explode all trees	2900
#5	MeSH descriptor: [Cardiac Output, Low] this term only	456
#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	19141
#7	(((congestive or acute or decompensat* or chronic or left) NEAR/2 "heart failure")):ti,ab,kw	15552
#8	(((cardia* or cardio*) NEAR/2 (renal or reno) NEAR/2 syndrome*)):ti,ab,kw	93
#9	((cardiorenal NEAR/2 syndrome*)):ti,ab,kw	169
#10	(((cardiac or heart) NEAR/2 (edema* or oedema*))):ti,ab,kw	245
#11	(((dilated or congestive or idiopathic) NEAR/2 cardiomyopath*)):ti,ab,kw	1409
#12	(((cardiogenic or cardiocirculatory) NEAR/2 (shock or collapse))):ti,ab,kw	1630
#13	((("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) NEAR/2 (failure* or insufficien* or dysfunction*))):ti,ab,kw	6989
#14	(((mid range or mild* or minimal* or normal or preserved or reduced) NEAR/3 (ejection fraction or EF or LVEF))):ti,ab,kw	5262
#15	((HFnEF or HFmrEF or HFpEF or HFrEF or lvsd)):ti,ab,kw	2404
#16	(((low or subnormal or depressed) NEAR/2 (cardiac NEAR/2 output))):ti,ab,kw	797
#17	((forward NEAR/2 failure*)):ti,ab,kw	193
#18	{or #1-#17}	34821
#19	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees	5804
#20	MeSH descriptor: [Receptors, Adrenergic, beta] explode all trees	636
#21	((beta* NEAR/2 (adrenergic* or adrenoceptor* or adrenolytic* or antiadrenergic* or antagonist* or block* or receptor* or sympathicolytic* or sympatholytic*))):ti,ab,kw	18820
#22	MeSH descriptor: [Bisoprolol] this term only	484
#23	MeSH descriptor: [Metoprolol] this term only	1941
#24	MeSH descriptor: [Nebivolol] this term only	288
#25	((bisoprolol* or cardicor* or carvedilol* or metoprolol* or nebilet* or nebivolol*)):ti,ab,kw	5706
#26	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees	5299
#27	(((angiotensin* or dipeptidyl* or "kininase ii") NEAR/3 (antagonist* or convert* or enzyme* or inhibit* or recept* or block*))):ti,ab,kw	15664
#28	((ace NEAR inhibit*)):ti,ab,kw	4779

Searches
#29 (acei):ti,ab,kw 1944
#30 ((accupro* or captopril* or coversyl* or enalapril* or fosinopril* or imidapril* or lisinopril* or perindopril* or innovace* or quinapril* or ramipril* or tanatril* or trandolapril* or tritace* or zestril*)):ti,ab,kw 10092
#31 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees 3023
#32 ((angiotensin* NEAR/3 receptor* NEAR/3 (antagonist* or block*))):ti,ab,kw 5582
#33 ((arb or arbs)):ti,ab,kw 2934
#34 ((amias* or candesartan* or cozaar* or diovan* or losartan* or valsartan*)):ti,ab,kw 6503
#35 MeSH descriptor: [Neprilysin] this term only and with qualifier(s): [antagonists & inhibitors - AI] 167
#36 (((endopeptidase* or enkephalinase* or neprilysin*) NEAR/2 (inhibit* or antagonist*))):ti,ab,kw 549
#37 (arni):ti,ab,kw 296
#38 ((sacubitril* or entresto*)):ti,ab,kw 707
#39 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees 922
#40 (((mineralocorticoid* or aldosterone*) NEAR/2 (antagonist* or block* or inhibit*))):ti,ab,kw 2251
#41 ((aldactone* or spironolactone* or eplerenone* or inspra*)):ti,ab,kw 2665
#42 ((finerenone* or kerendia*)):ti,ab,kw 168
#43 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] this term only 971
#44 (("sglt 2" NEAR/2 inhibitor*)):ti,ab,kw 381
#45 (SGLT2):ti,ab,kw 1735
#46 ((sodium NEAR/2 glucose NEAR/2 (inhibitor* or transporter* or cotransporter* or co-transporter*))):ti,ab,kw 2517
#47 ((dapagliflozin* or empagliflozin* or forxiga* or jardiance*)):ti,ab,kw 3760
#48 {or #19-#47} 50298
#49 #18 AND #48 8374
#50 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 494409
#51 #49 NOT #50 7194
#52 conference:pt 236547
#53 #51 NOT #52 with Cochrane Library publication date Between Oct 2002 and Feb 2024, in Cochrane Reviews 22
#54 #51 NOT #52 5987

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

Searches	
ID	Search Hits
#1	MeSH descriptor: [Heart Failure] explode all trees 14344

Searches	
#2	MeSH descriptor: [Cardiomyopathy, Dilated] this term only 669
#3	MeSH descriptor: [Shock, Cardiogenic] this term only 477
#4	MeSH descriptor: [Ventricular Dysfunction] explode all trees 2900
#5	MeSH descriptor: [Cardiac Output, Low] this term only 456
#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 19141
#7	(((congestive or acute or decompensat* or chronic or left) NEAR/2 "heart failure")):ti,ab,kw 15552
#8	(((cardia* or cardio*) NEAR/2 (renal or reno) NEAR/2 syndrome*)):ti,ab,kw 93
#9	((cardiorenal NEAR/2 syndrome*)):ti,ab,kw 169
#10	(((cardiac or heart) NEAR/2 (edema* or oedema*))):ti,ab,kw 245
#11	(((dilated or congestive or idiopathic) NEAR/2 cardiomyopath*)):ti,ab,kw 1409
#12	(((cardiogenic or cardiocirculatory) NEAR/2 (shock or collapse))):ti,ab,kw 1630
#13	((("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) NEAR/2 (failure* or insufficien* or dysfunction*))):ti,ab,kw 6989
#14	(((mid range or mild* or minimal* or normal or preserved or reduced) NEAR/3 (ejection fraction or EF or LVEF))):ti,ab,kw 5262
#15	((HFnEF or HFmrEF or HFpEF or HFrEF or lvsd)):ti,ab,kw 2404
#16	(((low or subnormal or depressed) NEAR/2 (cardiac NEAR/2 output))):ti,ab,kw 797
#17	((forward NEAR/2 failure*)):ti,ab,kw 193
#18	{or #1-#17} 34821
#19	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees 5804
#20	MeSH descriptor: [Receptors, Adrenergic, beta] explode all trees 636
#21	((beta* NEAR/2 (adrenergic* or adrenoceptor* or adrenolytic* or antiadrenergic* or antagonist* or block* or receptor* or sympathicolytic* or sympatholytic*))):ti,ab,kw 18820
#22	MeSH descriptor: [Bisoprolol] this term only 484
#23	MeSH descriptor: [Metoprolol] this term only 1941
#24	MeSH descriptor: [Nebivolol] this term only 288
#25	((bisoprolol* or cardicor* or carvedilol* or metoprolol* or nebilet* or nebivolol*)):ti,ab,kw 5706
#26	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees 5299
#27	(((angiotensin* or dipeptidyl* or "kininase ii") NEAR/3 (antagonist* or convert* or enzyme* or inhibit* or recept* or block*))):ti,ab,kw 15664
#28	((ace NEAR inhibit*)):ti,ab,kw 4779
#29	(acei):ti,ab,kw 1944
#30	((accupro* or captopril* or coversyl* or enalapril* or fosinopril* or imidapril* or lisinopril* or perindopril* or innovace* or quinapril* or ramipril* or tanatril* or trandolapril* or tritace* or zestril*)):ti,ab,kw 10092
#31	MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees 3023
#32	((angiotensin* NEAR/3 receptor* NEAR/3 (antagonist* or block*))):ti,ab,kw 5582
#33	((arb or arbs)):ti,ab,kw 2934
#34	((amias* or candesartan* or cozaar* or diovan* or losartan* or valsartan*)):ti,ab,kw 6503

Searches
#35 MeSH descriptor: [Neprilysin] this term only and with qualifier(s): [antagonists & inhibitors - AI] 167
#36 (((endopeptidase* or enkephalinase* or neprilysin*) NEAR/2 (inhibit* or antagonist*))):ti,ab,kw 549
#37 (arni):ti,ab,kw 296
#38 ((sacubitril* or entresto*)):ti,ab,kw 707
#39 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees 922
#40 (((mineralocorticoid* or aldosterone*) NEAR/2 (antagonist* or block* or inhibit*))):ti,ab,kw 2251
#41 ((aldactone* or spironolactone* or eplerenone* or inspra*)):ti,ab,kw 2665
#42 ((finerenone* or kerendia*)):ti,ab,kw 168
#43 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] this term only 971
#44 (("sglt 2" NEAR/2 inhibitor*)):ti,ab,kw 381
#45 (SGLT2):ti,ab,kw 1735
#46 ((sodium NEAR/2 glucose NEAR/2 (inhibitor* or transporter* or cotransporter* or co-transporter*))):ti,ab,kw 2517
#47 ((dapagliflozin* or empagliflozin* or forxiga* or jardiance*)):ti,ab,kw 3760
#48 {or #19-#47} 50298
#49 #18 AND #48 8374
#50 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 494409
#51 #49 NOT #50 7194
#52 conference:pt 236547
#53 #51 NOT #52 with Cochrane Library publication date Between Oct 2002 and Feb 2024, in Cochrane Reviews 22
#54 #51 NOT #52 5987

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/ 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

Searches
9 ((cardiac or heart) adj2 (edema* or oedema*)).tw. 1605
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 exp beta adrenergic receptor blocking agent/ 344256
19 exp beta adrenergic receptor/ 42444
20 (beta* adj2 (adrenergic* or adrenoceptor* or adrenolytic* or antiadrenergic* or antagonist* or block* or receptor* or sympathicolytic* or sympatholytic*)).tw. 171528
21 (bisoprolol* or cardicor* or carvedilol* or metoprolol* or nebilet* or nebivolol*).tw. 21969
22 dipeptidyl carboxypeptidase inhibitor/ 139333
23 ((angiotensin* or dipeptidyl* or kininase ii) adj3 (antagonist* or convert* or enzyme* or inhibit* or recept* or block*)).tw. 106665
24 (ace adj inhibit*).tw. 31996
25 acei.tw. 10734
26 (accupro* or captopril* or coversyl* or enalapril* or fosinopril* or imidapril* or lisinopril* or perindopril* or innovace* or quinapril* or ramipril* or tanatril* or trandolapril* or tritace* or zestril*).tw. 39003
27 exp angiotensin receptor antagonist/ 124501
28 (angiotensin* adj3 receptor* adj3 (antagonist* or block*)).tw. 27013
29 (arb or arbs).tw. 18682
30 (amias* or candesartan* or cozaar* or diovan* or losartan* or valsartan*).tw. 26534
31 enkephalinase inhibitor/ 3275
32 ((endopeptidase* or enkephalinase* or neprilysin*) adj2 (antagonist* or inhibit*)).tw. 3966
33 arni.tw. 1572
34 (sacubitril* or entresto*).tw. 3572
35 exp mineralocorticoid antagonist/ 108815
36 ((mineralocorticoid* or aldosterone*) adj2 (antagonist* or block* or inhibit*)).tw. 11965
37 (aldactone* or spironolactone* or eplerenone* or inspra*).tw. 14081
38 (finerenone* or kerendia*).tw. 576
39 sodium glucose cotransporter 2 inhibitor/ or dapagliflozin/ or empagliflozin/ 24929
40 (sglt 2 adj2 inhibitor*).tw. 2469
41 SGLT2.tw. 9834
42 (sodium adj2 glucose adj2 (inhibitor* or transporter* or cotransporter* or co-transporter*)).tw. 13674

Searches		
43	(dapagliflozin* or empagliflozin* or forxiga* or jardiance*).tw.	9147
44	or/18-43	709929
45	17 and 44	109258
46	random*.ti,ab.	2031514
47	factorial*.ti,ab.	48684
48	(crossover* or cross over*).ti,ab.	128676
49	((doubl* or singl*) adj blind*).ti,ab.	279700
50	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1295040
51	crossover procedure/	76894
52	single blind procedure/	53564
53	randomized controlled trial/	806896
54	double blind procedure/	215796
55	or/46-54	2995094
56	Systematic review/	452268
57	Meta-Analysis/	306026
58	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	376888
59	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	475612
60	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	69522
61	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	105900
62	(search* adj4 literature).ab.	131331
63	(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.	476063
64	cochrane.jw.	24975
65	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	7406
66	or/56-65	982079
67	55 or 66	3684772
68	45 and 67	20840
69	limit 68 to english language	19726
70	Nonhuman/ not human/	5382202
71	69 not 70	18995
72	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5832293
73	71 not 72	14846
74	(letter or editorial).pt.	2103817
75	73 not 74	14494
76	limit 75 to dc=20021001-20240229	12044

Database name: MEDLINE

Searches		
1	exp Heart Failure/	151655
2	Cardiomyopathy, Dilated/	17386
3	Shock, Cardiogenic/	11068
4	exp Ventricular Dysfunction/	43989

Searches
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
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 exp Adrenergic beta-Antagonists/ 87534
20 exp Receptors, Adrenergic, beta/ 22701
21 (beta* adj2 (adrenergic* or adrenoceptor* or adrenolytic* or antiadrenergic* or antagonist* or block* or receptor* or sympathicolytic* or sympatholytic*)).tw. 131548
22 Bisoprolol/ or Metoprolol/ or Nebivolol/ 7587
23 (bisoprolol* or cardicor* or carvedilol* or metoprolol* or nebilet* or nebivolol*).tw. 12905
24 exp Angiotensin-Converting Enzyme Inhibitors/ 47870
25 ((angiotensin* or dipeptidyl* or kininase ii) adj3 (antagonist* or convert* or enzyme* or inhibit* or recept* or block*)).tw. 80328
26 (ace adj inhibit*).tw. 20304
27 acei.tw. 4999
28 (accupro* or captopril* or coversyl* or enalapril* or fosinopril* or imidapril* or lisinopril* or perindopril* or innovace* or quinapril* or ramipril* or tanatril* or trandolapril* or tritace* or zestril*).tw. 26732
29 exp Angiotensin Receptor Antagonists/ 28387
30 (angiotensin* adj3 receptor* adj3 (antagonist* or block*)).tw. 17935
31 (arb or arbs).tw. 9296
32 (amias* or candesartan* or cozaar* or diovan* or losartan* or valsartan*).tw. 16601
33 Neprilysin/ai [Antagonists & Inhibitors] 1435
34 ((endopeptidase* or enkephalinase* or neprilysin*) adj2 (antagonist* or inhibit*)).tw. 2851
35 arni.tw. 671
36 (sacubitril* or entresto*).tw. 1788
37 exp Mineralocorticoid Receptor Antagonists/ 10719
38 ((mineralocorticoid* or aldosterone*) adj2 (antagonist* or block* or inhibit*)).tw. 7825

Searches		
39	(aldactone* or spironolactone* or eplerenone* or inspra*).tw.	7822
40	(finerenone* or kerendia*).tw.	374
41	Sodium-Glucose Transporter 2 Inhibitors/	6245
42	(sglt 2 adj2 inhibitor*).tw.	1331
43	SGLT2.tw.	5537
44	(sodium adj2 glucose adj2 (inhibitor* or transporter* or cotransporter* or co-transporter*)).tw.	9620
45	(dapagliflozin* or empagliflozin* or forxiga* or jardiance*).tw.	4749
46	or/19-45	314979
47	18 and 46	31996
48	Randomized Controlled Trial/	608500
49	controlled clinical trial.pt.	95551
50	randomi#ed.ti,ab.	821015
51	placebo.ab.	245631
52	randomly.ti,ab.	427811
53	Clinical Trials as topic.sh.	201753
54	trial.ti.	302656
55	or/48-54	1638292
56	Meta-Analysis/	194877
57	exp Meta-Analysis as Topic/	29139
58	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	296958
59	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	396261
60	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	56616
61	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	88515
62	(search* adj4 literature).ab.	104793
63	(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.	391489
64	cochrane.jw.	16695
65	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	3992
66	or/56-65	740585
67	55 or 66	2205675
68	47 and 67	8778
69	limit 68 to english language	8011
70	animals/ not humans/	5160739
71	69 not 70	7554
72	limit 71 to (letter or historical article or comment or editorial or news or case reports)	336
73	71 not 72	7218
74	limit 73 to ed=20021001-20240229	4743
75	limit 73 to dt=20021001-20240229	5133
76	74 or 75	5182

Database name: Epistemonikos

Searches
Search 1 title:("heart failure") AND title:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*) 38 abstract:("heart failure") AND abstract:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*) 117
Search 2
title:(HFnEF OR HFmrEF OR HFpEF OR HFrEF OR lvsd) AND title:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*) 5 results 0 abstract:(HFnEF OR HFmrEF OR HFpEF OR HFrEF OR lvsd) AND abstract:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*) 10
Search 3
title:("left ventricular" OR "left ventricle" OR lv OR systolic* OR diastolic*) AND title:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR

Searches	
valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*)	7
abstract:("left ventricular" OR "left ventricle" OR lv OR systolic* OR diastolic*) AND abstract:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*)	123
Search 4	
title:("cardiorenal syndrome" OR "heart edema" OR "heart oedema") AND title:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*)	0
abstract:("cardiorenal syndrome" OR "heart edema" OR "heart oedema") AND abstract:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*)	0
Search 5	
title:(cardiomyopath*) AND title:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii" OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*)	0
abstract:(cardiomyopath*) AND abstract:(beta* OR bisoprolol* OR cardicor* OR carvedilol* OR metoprolol* OR nebilet* OR nebivolol* OR angiotensin* OR dipeptidyl* OR "kininase ii"	

Searches
OR ace OR acei OR accupro* OR captopril* OR coversyl* OR enalapril* OR fosinopril* OR imidapril* OR lisinopril* OR perindopril* OR innovace* OR quinapril* OR ramipril* OR tanatril* OR trandolapril* OR tritace* OR zestril* OR arb OR arbs OR amias* OR candesartan* OR cozaar* OR diovan* OR losartan* OR valsartan* OR endopeptidase* OR enkephalinase* OR neprilysin* OR arni OR sacubitril* OR entresto* OR mineralocorticoid* OR aldosterone* OR aldactone* OR spironolactone* OR eplerenone* OR inspra* OR finerenone* OR kerendia* OR "sglt 2" OR SGLT2 OR "sodium glucose" OR dapagliflozin* OR empagliflozin* OR forxiga* OR jardiance*) 4 Limited from 2002-current; publication type: systematic review; Cochrane review: no; Systematic Review Question: interventions

Additional search methods

Studies identified in the original version 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) ALL 1946 to July 24, 2024	2546

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

Searches	
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
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

Searches
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
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

Searches		
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
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

Searches
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
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

Searches	
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
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

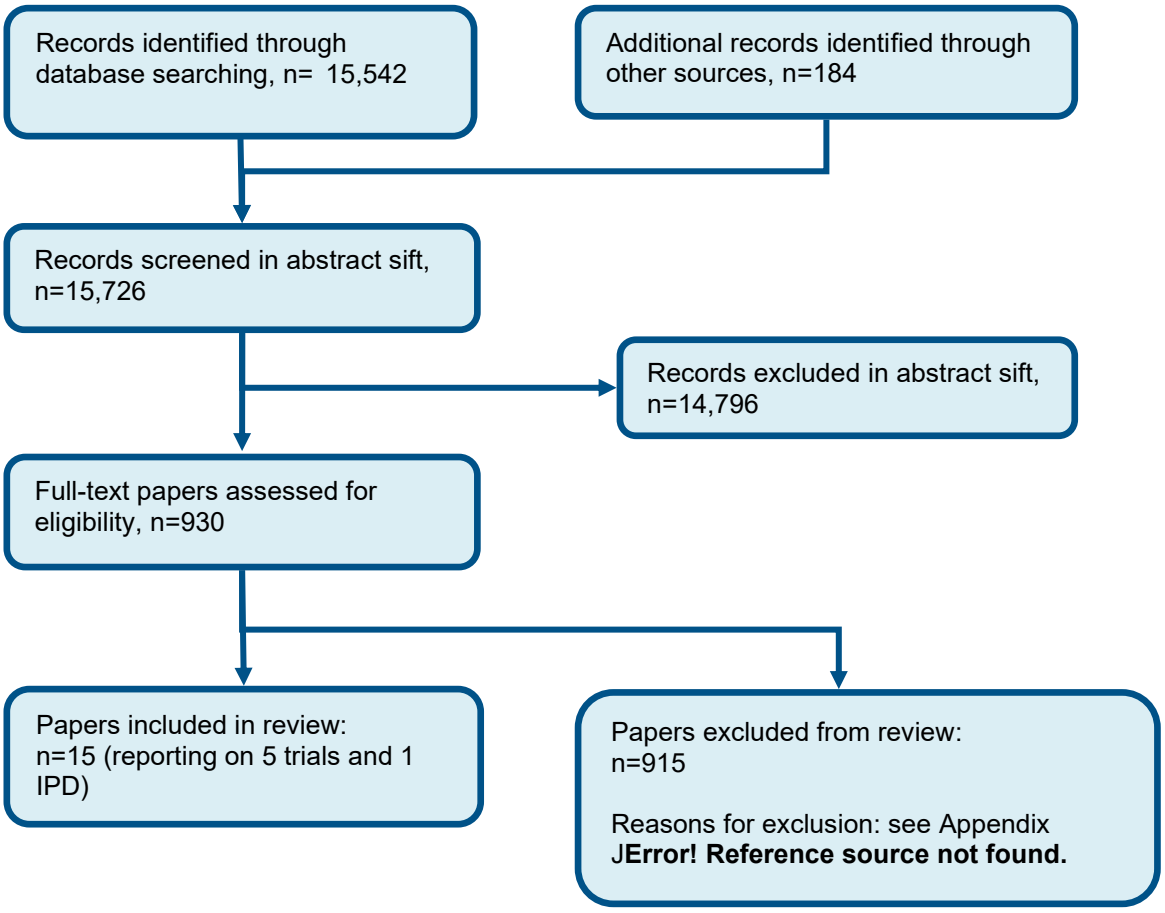
Database name: Medline Quality of Life

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

Searches		
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
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 pharmacological management of HFmrEF



Appendix D Effectiveness evidence

Alzahrani, 2018

Bibliographic Reference	Alzahrani, Talal; Tiu, John; Panjrath, Gurusher; Solomon, Allen; The effect of angiotensin-converting enzyme inhibitors on clinical outcomes in patients with ischemic cardiomyopathy and midrange ejection fraction: a post hoc subgroup analysis from the PEACE trial.; Therapeutic advances in cardiovascular disease; 2018; vol. 12 (no. 12); 351-359

Study details

Secondary publication of another included study- see primary study for details	None
Other publications associated with this study included in review	Braunwald 2004, Pfeffer 1998
Trial name / registration number	PEACE trial
Study location	Not specified
Study setting	Multicentre setting
Study dates	Not specified

Sources of funding	No specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Inclusion criteria	Patients with a left ventricular EF between 40-50% Inclusion criteria from Braunwald, 2004: Age 50 years or older Coronary artery disease documented by at least one of the following: Myocardial infarction at least 3 months before enrolment Coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty at least 3 months before enrolment Obstruction of ≥50% of the luminal diameter of at least one native vessel on coronary angiography Left ventricular ejection fraction > 40% on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of left ventricular wall-motion abnormalities on echocardiography Toleration of the medication and successful completion of the run-in phase, with ≥80% compliance with the medication
Exclusion criteria	Exclusion criteria from Braunwald, 2004: Current use or a current condition requiring use of an ACE inhibitor or a contraindication to ACE inhibitors Current use of an angiotensin II-receptor antagonist Hospitalization for unstable angina within the preceding 2 months Valvular heart disease deemed to require surgical intervention Coronary-artery bypass grafting or percutaneous transluminal angioplasty within the preceding 3 months

	Planned elective coronary revascularization Serum creatinine >2.0 mg/dl (177 µmol/litre) Serum potassium >5.5 mmol/litre Limited change of 5 year survival Psychosocial condition precluding long-term adherence Unable or unwilling to give consent Female sex and of childbearing potential and not using contraception Current use in a research trial of medication not approved by the U.S. Food and Drug Administration or the Health Protection Branch of the Canadian Department of National Health and Welfare
Recruitment / selection of participants	Potentially eligible subjects participated in a two-week run-in phase during which they were requested to take trandolapril at a dose of 2mg per day. Consenting patients who successfully completed the run-in phase were randomly assigned to receive either trandolapril or a matching placebo. (Recruitment information from Braunwald, 2004)
Intervention(s)	Patients were initially started on 2mg/day of trandolapril, which was then increased to 4mg/day for those who tolerated the 2mg after 6 months. Background treatment: Beta-blockers 59%
Comparator	Placebo Background treatment: Beta-blockers 60%
Population subgroups	The patients with a left ventricular EF between 40-50% were the pre-specified subgroup from the primary study in the PEACE trial (Braunwald, 2004)

Number of participants	2512 participants
Duration of follow-up	Total of 7 years of follow-up (mean 4.7 years)
Indirectness	Yes- intervention indirectness due to indication for patients with ischemic cardiomyopathy. Trandolapril is indicated for hypertension. Events data -outcome indirectness as not TTE
Method of analysis	Intention-to-treat analysis was used.
Additional comments	Related studies: *Braunwald 2004 (primary paper; 15357561)* *Pfeffer 1998 (study design paper; 15357561)* Canadian Cardiovascular Society functional classification (% of patients): Class I: Trandolapril= 72.13% Placebo= 74.62% Class II: Trandolapril = 17.83% Placebo= 16.13% Class III: Trandolapril = 8.76% Placebo= 8.06% Class IV: Trandolapril= 1.29% Placebo= 1.19%

Study arms

ACE-inhibitor (trandolapril) (N = 1247)

Patients were initially started on 2mg/day of trandolapril and were then increased to 4mg/day for those who tolerated 2 mg dose after 6 months.
Background treatment: Beta-blockers 59%

Placebo (N = 1265)

Background treatment: Beta-blockers 60%

Characteristics

Arm-level characteristics

Characteristic	ACE-inhibitor (trandolapril) (N = 1247)	Placebo (N = 1265)
% Female Sample size	n = NR ; % = 15.4	n = NR ; % = 14.23
Age Mean (SD)	65 (8)	64 (8)
LVEF Mean (SD)	47 (3)	47 (3)

Characteristic	ACE-inhibitor (trandolapril) (N = 1247)	Placebo (N = 1265)
Type 2 diabetes with hypertension or diastolic blood pressure greater than or equal to 90 or systolic blood pressure greater than or equal to 140mmHg Sample size	n = NR ; % = 12.67	n = NR ; % = 11.38
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	77 (18)	78 (20)
Background (non-randomised) heart failure medications Sample size	n = NR ; % = NR	n = NR ; % = NR
Calcium channel blocker Sample size	n = NR ; % = 32.77	n = NR ; % = 31.43
Beta-blocker Sample size	n = NR ; % = 58.63	n = NR ; % = 59.7
Aspirin or antiplatelet medication Sample size	n = NR ; % = 89.09	n = NR ; % = 90.74
Lipid-lowering drug	n = NR ; % = 65.43	n = NR ; % = 68.59

Characteristic	ACE-inhibitor (trandolapril) (N = 1247)	Placebo (N = 1265)
Sample size		
Diuretic agent Sample size	n = NR ; % = 10.36	n = NR ; % = 10.92
Potassium-sparing diuretic Sample size	n = NR ; % = 3.13	n = NR ; % = 2.69
Digitalis Sample size	n = NR ; % = 4.82	n = NR ; % = 4.43
Antiarrhythmic agent Sample size	n = NR ; % = 2.33	n = NR ; % = 2.53
Anticoagulant Sample size	n = NR ; % = 6.43	n = NR ; % = 5.85
Insulin Sample size	n = NR ; % = 3.61	n = NR ; % = 3.87
Hormone replacement therapy	n = NR ; % = 3.85	n = NR ; % = 3.72

Characteristic	ACE-inhibitor (trandolapril) (N = 1247)	Placebo (N = 1265)
Sample size		

Outcomes

Study timepoints

4.7 year

Dichotomous outcomes

Outcome	ACE-inhibitor (trandolapril), 4.7 year, N = 1247	Placebo, 4.7 year, N = 1265
All-cause mortality (number of patients) No of events	n = 101 ; % = 8.1	n = 134 ; % = 10.6
Cardiovascular mortality (number of patients) No of events	n = 53 ; % = 4.3	n = 67 ; % = 5.3
Hospitalisation for nonfatal congestive heart failure (number of patients) No of events	n = 47 ; % = 3.8	n = 51 ; % = 4

All-cause mortality - Polarity - Lower values are better

Cardiovascular mortality - Polarity - Lower values are better

Hospitalisation for nonfatal congestive heart failure - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT 2 HFmrEF

All-cause mortality- dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirectly applicable due to trandolapril not being typically used for heart failure (intervention indirectness), population not symptomatic heart failure (population indirectness), and because outcome not TTE (outcome indirectness))*

Cardiovascular mortality- dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Low risk of bias)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirectly applicable due to trandolapril not being typically used for heart failure (intervention indirectness),*

Section	Question	Answer
		population not symptomatic heart failure (population indirectness), and because outcome not TTE (outcome indirectness))

Hospitalisation for nonfatal congestive heart failure- dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Low risk of bias)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirectly applicable due to trandolapril not being typically used for heart failure (intervention indirectness), population not symptomatic heart failure (population indirectness), and because outcome not TTE (outcome indirectness))*

Braunwald, 2004

Bibliographic Reference	Braunwald, Eugene; Domanski, Michael J; Fowler, Sarah E; Geller, Nancy L; Gersh, Bernard J; Hsia, Judith; Pfeffer, Marc A; Rice, Madeline M; Rosenberg, Yves D; Rouleau, Jean L; Angiotensin-converting-enzyme inhibition in stable coronary artery disease.; The New England journal of medicine; 2004; vol. 351 (no. 20); 2058-68

Study details

Secondary publication of another included study- see primary study for details	Alzahrani, 2018
Other publications associated with this study included in review	Provides background information for Alzahrani, 2018 (PEACE)
Trial name / registration number	PEACE

Cleland, 2018

Bibliographic Reference	Cleland, John G F; Bunting, Karina V; Flather, Marcus D; Altman, Douglas G; Holmes, Jane; Coats, Andrew J S; Manzano, Luis; McMurray, John J V; Ruschitzka, Frank; van Veldhuisen, Dirk J; von Lueder, Thomas G; Bohm, Michael; Andersson, Bert; Kjekshus, John; Packer, Milton; Rigby, Alan S; Rosano, Giuseppe; Wedel, Hans; Hjalmarson, Ake; Wikstrand, John; Kotecha, Dipak; Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials.; European heart journal; 2018; vol. 39 (no. 1); 26-35

Study Characteristics

Study design	Systematic review with IPD meta-analysis
Search details: dates and databases searched	Data request to trialists December 2010. Studies identified by the BB-HF group: The BB-HF group is a collaborative, multinational effort to combine individual data from the major randomized controlled trials (RCTs) investigating the use of betablockers in chronic HF. The group consists of the leading investigators of these trials and international experts, with the support of the four pharmaceutical companies that have marketed beta-blockers in HF (AstraZeneca, GlaxoSmithKline, Merck Serono and Menarini). A standardized data request form was generated to obtain IPD from each eligible trial . At the time of this publication, individual data on 15,922 participants (representing 10 of the 11 trials) have been received by the coordinating center, the Clinical Trials and Evaluation Unit, Royal Brompton & Harefield NHS Trust/Imperial College London. To ensure a complete assessment of the evidence, published or unpublished RCTs were identified through computer aided searches (for example, Medline and Current Contents), scrutiny of reference lists of trials, trials registries, meeting abstracts, review articles and discussion with members of the collaborative group and with the pharmaceutical manufacturers.
Sources of funding	Menarini Farmaceutica Internazionale provided an unrestricted research grant for administrative costs; GlaxoSmithKline provided data extraction support; and IRCCS San Raffaele a collaborative research grant.
Study and participant inclusion criteria	Only unconfounded (in which one treatment group differed from another only by the beta-blocker therapy of interest) placebo-controlled trials were eligible that recruited >300 patients, with a planned follow-up of >6 months and explicit reporting of mortality. All trials had appropriate ethical approval. Trials must include patients with documented symptomatic HF. Study included all patients with baseline LVEF and an electrocardiogram (ECG) that showed either sinus rhythm or AF/atrial flutter (for the purposes of this report, reference to AF therefore includes atrial flutter). Due to demonstration of an interaction of treatment effect with heart rhythm,7 patients with sinus rhythm and AF were analysed separately.

Study and participant exclusion criteria	See above
Intervention(s)	Beta-blockers (no further details supplied)
Comparator(s)	Placebo
Number of studies included in the systematic review	11 studies
Studies from the systematic review that are relevant for use in the current review	In this analysis, the baseline value of LVEF recorded in individual patient case report forms or core laboratory assessment was used, which in some patients was above the entry criterion according to that particular study. LVEF was analysed as a continuous variable to model interactions with outcomes, and classified as <20%, 20–25%, 26– 34%, 35–39%, 40–49%, and>_50%, as well as <40%, 40–49%, >_50% to align with guideline phenotypes.
Studies from the systematic review that are not relevant for use in the current review	None
Analysis methods	All analyses followed the principle of intention-to-treat. Patients were classified by heart rhythm and LVEF. Outcomes were analysed using a Cox proportional hazards regression model, stratified by study. This is a one-stage fixed effects approach and assumes that all trials are estimating a common treatment effect with baseline hazards that vary across studies.

Study arms

Beta-blockers (N = 716)

716 = total n for subgroup LVEF 40-49%. NR per arm

Placebo (N = 716)

716 = total n for subgroup LVEF 40-49%. NR per arm

Outcomes

Study timepoints

1.3 year (Median FUP)

Contrast outcomes

Outcome	Beta-blockers vs Placebo, 1.3 year, N2 = NR, N1 = NR
All cause mortality (n=716)	
Sinus rhythm n=570 Hazard ratio/95% CI	0.59 (0.34 to 1.03)

Outcome	Beta-blockers vs Placebo, 1.3 year, N2 = NR, N1 = NR
Atrial fibrillation n=146 Hazard ratio/95% CI	1.3 (0.63 to 2.67)
CV mortality (cardiovascular death)	
Sinus rhythm n=570 Hazard ratio/95% CI	0.48 (0.24 to 0.97)
Atrial fibrillation n=146 Hazard ratio/95% CI	0.86 (0.36 to 2.03)
Unplanned hospitalisation HF-related (cardiovascular hospitalisation)	
Sinus rhythm n=566 Hazard ratio/95% CI	0.95 (0.68 to 1.32)
Atrial fibrillation n=143 Hazard ratio/95% CI	1.15 (0.57 to 2.32)

All-cause mortality - Polarity - Lower values are better

CV mortality (cardiovascular death) - Polarity - Lower values are better

Unplanned hospitalisation HF-related (cardiovascular hospitalisation) - Polarity - Lower values are better

Results for subgroup 40-49% LVEF

Critical appraisal - RoB Assessment of Individual Participant Data Meta-analysis studies 2 HFmrEF

Section	Question	Answer
Use of a systematic review	Is the IPD meta-analysis part of a systematic review?	Yes, and a pre-specified protocol is available *(More details in Kotecha et al (2013))*
Identification of eligible studies	Were All Eligible Trials Identified?	Unclear *(Brief description of search of electronic databases but no flowchart showing assessment of papers identified and considered for inclusion. No detailed search strategy available.)*
Ability to obtain IPD data	Were IPD Obtained from Most Trials?	Probably yes *(No issues reported on gaining access to IPD data)*
IPD data integrity	Was the Integrity of the IPD Checked?	Yes *(All data were cross-checked across different trial databases and compared with published reports. Discrepancies, inconsistencies, and incomplete data were checked against original case report forms and trial documentation to ensure IPD integrity. All 11 trial databases were then harmonized according to the standardized data request form to match patient characteristics and outcomes across all trials.)*

Section	Question	Answer
Planned analyses	Were the Analyses Prespecified in Detail?	Yes *(See Kotecha 2013 (design and rationale paper))*
Assessment of risk of bias of the included studies	Was the risk of bias of included trials assessed?	Yes *(Using Cochrane RoB tool)*
Methods of analysis	Were the methods of analysis appropriate overall?	Probably yes *(One-stage model and regression model considering participant characteristics)*
Reporting standards	Does any report of the results adhere to the Preferred Reporting Items for a Systematic review and Meta-analysis of IPD (The PRISMA-IPD Statement)?	Yes *(Paper states reports according to PRISMA-IPD statement)*
Overall judgement of study quality	What is the overall judgement of study quality?	Moderate *(Most aspects of IPD conduct high quality but some concerns about identification of all relevant trials (no clear search strategy reported or available, and no flowchart to show assessment of papers against inclusion criteria).)*
Overall judgement of study quality	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; vol. 0 (no. 0)

Study details

Other publications associated with this study included in review	Solomon 2024 (EPPI ID: 15978369): FINEARTS-HF primary results paper Solomon 2024a (EPPI ID: 15978368): FINEARTS-HF baseline characteristics paper Vaduganathan 2024 (EPPI ID: 15978367): FINEARTS-HF design and rationale paper
Trial name / registration number	FINEARTS-HF: NCT04435626.
Study type	Randomised controlled trial (RCT) RCT: pre-specified subgroup
Study location	654 sites across 37 countries in North America, South America, Europe, Asia and Australasia
Study setting	Hospitalised, recently hospitalised or ambulatory
Study dates	September 2020 to June 2024
Sources of funding	Industry: Bayer
Inclusion criteria	Key inclusion criteria were: • age >40 years, • symptomatic heart failure in New York Heart Association (NYHA) functional class II-IV, • treatment with a diuretic for >30 days before randomization,

	• a left ventricular ejection fraction (LVEF) >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: 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). Other details • Both ambulatory and hospitalized patients were eligible. • Patients with prior LVEF <40% with subsequent improvement to ≥40% were also eligible for enrolment provided that ongoing heart failure symptoms were present and all other inclusion criteria were satisfied.
Exclusion criteria	Key exclusion criteria were: • eGFR <25 ml/min/1.73 m2 , • serum/plasma potassium >5.0 mmol/L at screening or randomisation, • symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or randomisation • MRA use 30 days prior to randomisation • cardiogenic shock
Recruitment / selection of participants	Patients could be enrolled irrespective of clinical care setting (whether hospitalized, recently hospitalized, or ambulatory). The proportion of patients without a recent worsening HF event within 3 months of randomisation was capped globally at approximately 50% of the original planned sample size.
Intervention(s)	Finerenone 10, 20 or 40 mg based on eGFR. Starting dose was selected based on baseline eGFR. Participants with an eGFR ≤60 ml/min/1.73 m2 started 10 mg once daily with a maximum maintenance dose of 20 mg once daily, whereas participants with an eGFR >60 ml/min/1.73 m2 started 20 mg once daily with a maximum maintenance dose of 40 mg once daily. Up-titration to the maximum tolerated dose if potassium <5.0 mmol/L and eGFR decrease <30%

Comparator	Matching placebo
Population subgroups	Prespecified analyses according to LVEF categories (<50%, ≥50 to <60%, and ≥60%) with LVEF available in >99% of participants
Number of participants	Subgroup <50% = 2172 (36% of total participants)
Duration of follow-up	The median duration of follow-up was 32 months in the overall population
Indirectness	Intervention not licensed for CHF
Method of analysis	ITT

Study arms

MRA (finerenone) (N = 1093)

Subgroup with LVEF <50% Maximum dose of 20 mg or 40 mg once daily

Placebo (N = 1079)

Subgroup with LVEF <50%

Characteristics

Study-level characteristics

Characteristic	Study (N = 2172)
% Female Sample size	n = 679 ; % = 31.3
Age Mean (SD)	69.6 (10.1)
Ethnicity - Asian Sample size	n = 432 ; % = 19.9
Ethnicity - Black Sample size	n = 23 ; % = 1.1
Ethnicity - white Sample size	n = 1659 ; % = 76.4
Ethnicity - Other Sample size	n = 58 ; % = 2.7
NYHA class - II Sample size	n = 1499 ; % = 69
NYHA class - III/IV Sample size	n = 673 ; % = 31

Characteristic	Study (N = 2172)
LVEF (%) Mean (SD)	44.4 (2.8)
Type 2 diabetes Sample size	n = 866 ; % = 39.9
Atrial fibrillation on baseline ECG Sample size	n = 771 ; % = 35.5
Previous heart failure hospitalisation Sample size	n = 1450 ; % = 66.8
Renal function (eGFR; mL/min/1.73m2) - Mean eGFR Mean (SD)	64.8 (20.1)
Renal function (eGFR; mL/min/1.73m2) - eGFR <60 Sample size	n = 929 ; % = 42.8
Background (non-randomised) heart failure medications - b-blocker Sample size	n = 1919 ; % = 88.4
Background (non-randomised) heart failure medications - ACEI Sample size	n = 870 ; % = 40.1

Characteristic	Study (N = 2172)
Background (non-randomised) heart failure medications - ARB Sample size	n = 616 ; % = 28.4
Background (non-randomised) heart failure medications - ARNI Sample size	n = 341 ; % = 15.7
Background (non-randomised) heart failure medications - SGLT2i Sample size	n = 336 ; % = 15.5
Background (non-randomised) heart failure medications - CCB Sample size	n = 515 ; % = 23.7
KCCQ - Total Symptom Score Mean (SD)	69.3 (23.9)

Outcomes

Study timepoints

- Baseline
- 12 month
- 32 month (median follow up)

Dichotomous and rate outcomes

Outcome	MRA (finerenone), 32 month, N = 1093	Placebo, 32 month, N = 1079
All-cause mortality No of events	n = 192 ; % = 17.6	n = 201 ; % = 18.6
Cardiovascular mortality No of events	n = 103 ; % = 9.4	n = 119 ; % = 11
First worsening heart failure event No of events	n = 175 ; % = 16	n = 219 ; % = 20.3
Total number of worsening heart failure events rate data Nominal	311	377

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better
First worsening heart failure event - Polarity - Lower values are better
Total number of worsening heart failure events - Polarity - Lower values are better

Hazard ratios, rate ratios and mean difference (adjusted)

Outcome	MRA (finerenone) vs Placebo, 12 month, N2 = 1093, N1 = 1079	MRA (finerenone) vs Placebo, 32 month, N2 = 1093, N1 = 1079
All-cause mortality adjusted for the following baseline variables: randomized treatment (finerenone or	NR	0.96 (0.78 to 1.17)

Outcome	MRA (finerenone) vs Placebo, 12 month, N2 = 1093, N1 = 1079	MRA (finerenone) vs Placebo, 32 month, N2 = 1093, N1 = 1079
placebo), age, sex, eGFR, NYHA functional class, heart rate, systolic blood pressure, BMI, (log)NT-proBNP, and a history of type 2 diabetes, prior heart failure hospitalization, atrial fibrillation, and myocardial infarction. All models were stratified by geographic region Hazard ratio/95% CI		
Cardiovascular mortality adjusted for the following baseline variables: randomized treatment (finerenone or placebo), age, sex, eGFR, NYHA functional class, heart rate, systolic blood pressure, BMI, (log)NT-proBNP, and a history of type 2 diabetes, prior heart failure hospitalization, atrial fibrillation, and myocardial infarction. All models were stratified by geographic region Hazard ratio/95% CI	NR	0.85 (0.65 to 1.11)
First worsening heart failure event (defined as either an unplanned hospitalisation for heart failure or an urgent heart failure visit) adjusted for the following baseline variables: randomized treatment (finerenone or placebo), age, sex, eGFR, NYHA functional class, heart rate, systolic blood pressure, BMI, (log)NT-proBNP, and a history of type 2 diabetes, prior heart failure hospitalization, atrial fibrillation, and myocardial infarction. All models were stratified by geographic region Hazard ratio/95% CI	NR	0.77 (0.63 to 0.95)
Total number of worsening heart failure events (defined as either an unplanned hospitalisation for heart failure or an urgent heart failure visit) (Rate ratio (95% CI))	NR	0.83 (0.65, 1.05)

Outcome	MRA (finerenone) vs Placebo, 12 month, N2 = 1093, N1 = 1079	MRA (finerenone) vs Placebo, 32 month, N2 = 1093, N1 = 1079
adjusted for the following baseline variables: randomized treatment (finerenone or placebo), age, sex, eGFR, NYHA functional class, heart rate, systolic blood pressure, BMI, (log)NT-proBNP, and a history of type 2 diabetes, prior heart failure hospitalization, atrial fibrillation, and myocardial infarction. All models were stratified by geographic region Custom value		
Change in KCCQ-TSS from baseline to month 12 (mean difference) using a linear regression model, adjusted for baseline value and geographic region. Mean (SD)	NR	NR
Change in KCCQ-TSS from baseline to month 12 (mean difference) using a linear regression model, adjusted for baseline value and geographic region. Mean (95% CI)	1.39 (-0.19 to 2.97)	NR

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better
First worsening heart failure event (defined as either an unplanned hospitalisation for heart failure or an urgent heart failure visit) - Polarity - Lower values are better
Total number of worsening heart failure events (defined as either an unplanned hospitalisation for heart failure or an urgent heart failure visit) - Polarity - Lower values are better
Change in KCCQ-TSS from baseline to month 12 - Polarity - Higher values are better

Continuous outcomes

Outcome	MRA (finerenone), 12 month, N = 1093	Placebo, 12 month, N = 1079
Change in KCCQ-TSS from baseline to month 12 (least square mean) Mean (95% CI)	8.17 (6.98 to 9.35)	6.78 (5.61 to 7.94)

Change in KCCQ-TSS from baseline to month 12 - Polarity - Higher values are better

Adverse events

Outcome	MRA (finerenone), 32 month, N = 1092	Placebo, 32 month, N = 1078
Treatment discontinuation due to adverse event No of events	n = 31 ; % = 2.8	n = 30 ; % = 2.8

Treatment discontinuation due to adverse event - Polarity - Lower values are better

Hyperkalaemia

Outcome	MRA (finerenone), 32 month, N = 1060	Placebo, 32 month, N = 1038
Hyperkalaemia Potassium >5.5 mmol/L No of events	n = 161 ; % = 15.2	n = 77 ; % = 7.4

Hyperkalaemia - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT 2 HFmrEF

All-cause mortality (dichotomous)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Intervention indirectness: Finerenone not licensed for CHF; Outcome indirectness: dichotomous, not time-to-event)*

Cardiovascular mortality (dichotomous)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Intervention indirectness: Finerenone not licensed for CHF; Outcome indirectness: dichotomous, not time-to-event)*

First worsening heart failure event (dichotomous)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Intervention indirectness: Finerenone not licensed for CHF; Outcome indirectness: dichotomous, not time-to-event)*

All-cause mortality (HR)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Cardiovascular mortality (HR)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

First worsening heart failure event (HR)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Total number of worsening heart failure events (rate ratio)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Change in KCCQ-TSS (12 months)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Treatment discontinuation due to adverse event

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Hyperkalaemia

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Protocol deviations in subgroup definitions of LVEF categories)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention indirectness: Finerenone not licensed for CHF)*

Kotecha, 2013

Bibliographic Reference	Kotecha, Dipak; Manzano, Luis; Altman, Douglas G; Krum, Henry; Erdem, Guliz; Williams, Nicola; Flather, Marcus D; Individual patient data meta-analysis of beta-blockers in heart failure: rationale and design.; Systematic reviews; 2013; vol. 2; 7

Study Characteristics

Search details: dates and	Provides background information for Cleland (2018)

databases searched	

Lund, 2018

Bibliographic Reference	Lund, Lars H; Claggett, Brian; Liu, Jiankang; Lam, Carolyn S; Jhund, Pardeep S; Rosano, Giuseppe M; Swedberg, Karl; Yusuf, Salim; Granger, Christopher B; Pfeffer, Marc A; McMurray, John J V; Solomon, Scott D; Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum.; European journal of heart failure; 2018; vol. 20 (no. 8); 1230-1239

Study details

Secondary publication of another included study- see primary study for details	None
Other publications associated with this study included in review	Swedberg, 1999
Trial name / registration number	CHARM Alternative: NCT00634400 CHARM Added: NCT00634309

	CHARM Preserved: NCT00634712
Study location	Not specified. (Participants were from 26 countries- Swedburg, 1999)
Study setting	Not specified
Study dates	Not specified
Sources of funding	The CHARM Programme was funded and sponsored by AstraZeneca. L.H.L. was supported by grants for a broad HFpEF research program from the Swedish Research Council (grant 2013-23897-104604-23), the Swedish Heart Lung Foundation (grant 20150063) and the Stockholm County Council (grants 20090556 and 20110120).
Inclusion criteria	(Identified from Swedburg, 1999) Men or women aged 18 years or older with symptomatic chronic heart failure according to NYHA class II-IV for ≥4 weeks before randomisation. Documentation of LVEF has to be performed by either contrast ventriculography, radionuclide ventriculography, or quantitative echocardiography within the previous 6 months. The most recent measure was used. In patients with LVEF >40% and not treated with an ACE-inhibitor: patients should have a history of hospitalisation for a cardiac reason and no current treatment, or continued need for treatment with an ACE inhibitor.
Exclusion criteria	(Identified from Swedburg, 1999) • Current serum-creatinine ≥265mmol/L (≥3 mg/dL) • Current serum-potassium ≥5.5 mmol/L (≥5.5 mEq/L) • Or history of marked ACE inhibitor-induced hyperkalaemia resulting in either a serum-potassium greater than or equal to 6.0 mmol/L (≥6.0) or a life-threatening adverse event • Known bilateral renal artery stenosis • current symptomatic hypotension • Persistent systolic or diastolic hypertension • Stroke • Acute myocardial infarction

	• Open heart surgery within the last 4 weeks • Previous heart transplant or heart transplant expected to be performed within the next 6 months • Presence of any noncardiac disease (e.g. cancer) that is likely to significantly shorten life expectancy to less than 2 years
Recruitment / selection of participants	(Identified from Swedburg, 1999) Participants are a part of the Candesartan in Heart Failure- Assessment of Reduction in Mortality and Morbidity (CHARM) programme. All symptomatic CHF patients will be eligible regardless of LV function and tolerability of ACE inhibitors.
Intervention(s)	Candesartan, titrated from 4 to 8 mg/day up to the target dose of 32 mg Background treatment: ACEI 27%, beta-blocker 58% and MRA 11%
Comparator	Placebo Background treatment: ACEI 27%, beta-blocker 58% and MRA 11%
Population subgroups	Not specified
Number of participants	1322 participants with ejection fraction between 40-49%

Duration of follow-up	Mean follow-up= 2.9 years
Indirectness	None
Method of analysis	Not specified

Study arms

ARB (Candesartan) (N = 667)
HFmrEF patients with an ejection fraction range between 40-49%. Candesartan, titrated from 4 to 8 mg/day up to the target dose of 32 mg Background treatment: ACEI 27%, beta-blocker 58% and MRA 11%

Placebo (N = 665)
Background treatment: ACEI 27%, beta-blocker 58% and MRA 11%

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1322)**
% Female Sample size	n = 395 ; % = 29.9
Age Mean (SD)	65 (11)

Characteristic	Study (N = 1322)
European Sample size	n = 1237 ; % = 93.6
Black Sample size	n = 43 ; % = 3.3
Other Sample size	n = 42 ; % = 3.2
NYHA Class II Sample size	n = 763 ; % = 57.7
NYHA Class III Sample size	n = 550 ; % = 41.6
NYHA class IV Sample size	n = 9 ; % = 0.7
Ischaemic Sample size	n = 885 ; % = 66.9
Idiopathic Sample size	n = 173 ; % = 13.1

Characteristic	Study (N = 1322)
Hypertensive Sample size	n = 168 ; % = 12.7
LVEF Mean (SD)	44 (NR)
Type 2 diabetes Sample size	n = 378 ; % = 28.6
Atrial fibrillation Sample size	n = 339 ; % = 25.6
ACE-inhibitor Sample size	n = 359 ; % = 27.2
Beta-blocker Sample size	n = 763 ; % = 57.7
Spironolactone Sample size	n = 151 ; % = 11.4
Pacemaker Sample size	n = 100 ; % = 7.6

Characteristic	Study (N = 1322)
Implantable cardioverter-defibrillator Sample size	n = 21 ; % = 1.6

Outcomes

Study timepoints

- 2.9 year

Contrast outcomes

Outcome	ARB (Candesartan) vs Placebo, 2.9 year, N2 = 1322, N1 = NR
All-cause mortality Unadjusted Hazard ratio/95% CI	0.79 (0.6 to 1.04)
Cardiovascular mortality Unadjusted Hazard ratio/95% CI	0.81 (0.6 to 1.11)
Unplanned hospitalisations or visits, HF-related (HF hospitalisation) Unadjusted	0.72 (0.55 to 0.95)

Outcome	ARB (Candesartan) vs Placebo, 2.9 year, N2 = 1322, N1 = NR
Hazard ratio/95% CI	
Unplanned hospitalisations or visits, HF-related (repeat) (recurrent HF hospitalisation) Unadjusted Custom value	IRR: 0.48 (0.33-0.70)

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better
Unplanned hospitalisations or visits, HF-related (HF hospitalisation) - Polarity - Lower values are better
Unplanned hospitalisations or visits, HF-related (repeat) (recurrent HF hospitalisation) - Polarity - Lower values are better
Only total n for mrEF subgroup reported, not by arm.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT 2 HFmrEF

All-cause mortality-Hazard Ratio FUP 2.9y

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and not able to assess baseline characteristics.)*
Overall bias and Directness	Overall Directness	Directly applicable

Cardiovascular mortality-Hazard Ratio FUP 2.9y

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and not able to assess baseline characteristics.)*
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisations or visits, HF-related (HF hospitalisation)-Hazard Ratio FUP 2.9y

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and not able to assess baseline characteristics.)*
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisations or visits, HF-related (repeat) (recurrent HF hospitalisation)-IRR (95%CI) FUP 2.9 y

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and not able to assess baseline characteristics.)*
Overall bias and Directness	Overall Directness	Directly applicable

Pfeffer, 1998

Bibliographic Reference	Pfeffer, MA; Domanski, M; Rosenberg, Y; Verter, J; Geller, N; Albert, P; Hsia, J; Braunwald, E; Prevention of events with angiotensin-converting enzyme inhibition (the PEACE study design). Prevention of Events with Angiotensin-Converting Enzyme Inhibition; American journal of cardiology; 1998; vol. 82 (no. 3a); 25H-30H

Study details

Other publications associated with this study included in review	Provides background information for Alzahrani 2018 (PEACE)

Pitt, 2014

Bibliographic Reference	Pitt B; Pfeffer MA; Assmann SF; Boineau R; Anand IS; Claggett B; Clausell N; Desai AS; Diaz R; Fleg JL; Gordeev I; Harty B; Heitner JF; Kenwood CT; Lewis EF; O'Meara E; Probstfield JL; Shaburishvili T; Shah SJ; Solomon SD; Sweitzer NK; Yang S; McKinlay SM; ; Spironolactone for heart failure with preserved ejection fraction.; The New England journal of medicine; 2014; vol. 370 (no. 15)

Study details

Other publications associated with this study included in review	Provides background information for Solomon 2016 (TOPCAT)

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	None
Other publications associated with this study included in review	Pitt 2014
Trial name / registration number	TOPCAT/NCT00094302

Study type	Randomised controlled trial (RCT)
Study location	Americas, Republic of Georgia and Russia 'Americas' defined as the United States, Canada, Argentina, and Brazil.
Study setting	Study centres
Study dates	Not specified
Sources of funding	This work was funded by the National Heart, Lung, and Blood Institute and National Institute of Health (contract HHSN268200425207C).
Inclusion criteria	Aged 50 years or older With at least one sign and one symptom of heart failure Controlled blood pressure Serum potassium level of <5.0 mmol/L
Exclusion criteria	(Exclusion criteria information from Desai, 2011) Severe systemic illness with life expectancy < 3 years from randomisation. Severe chronic obstructive pulmonary disease (e.g. requiring home oxygen or chronic oral steroid therapy) Known restrictive/ infiltrative cardiomyopathy, hypertrophic cardiomyopathy, or constrictive pericarditis

	Hemodynamically significant valvular heart disease (e.g. 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 Myocardial infarction, 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	Participants (LVEF ≥45%) who had either had a hospitalisation within the past year for which heart failure was a major component or had an elevated natriuretic peptide level (BNP >150 or NT-proBNP >360).
Intervention(s)	Spironolactone (titrated to 45 mg/day if tolerated)
Comparator	Placebo
Population subgroups	Study population is divided by ejection fraction: EF <50% (N= 520), EF 50-54.99% (N=712), EF 55-59.99% (N=879), EF≥60% (N=1333)
Number of participants	520
Duration of follow-up	3.4 years (median)

Method of analysis	Intention to treat (from Desai, 2011)
Additional comments	The primary endpoint was a composite of cardiovascular death, aborted cardiac arrest, or hospitalisation for heart failure

Study arms

MRA (spironolactone) (N = 520)

Ejection fraction <50% N=520 for total subgroup (not available per arm)

Placebo (N = 520)

Total N for both arms= 520

Characteristics

Study-level characteristics

Characteristic	Study (N = 520)
% Female Sample size	n = 190 ; % = 36.5
Age Mean (SD)	66 (9)

Characteristic	Study (N = 520)
Ethnicity Sample size	n = NR ; % = NR
Black race Sample size	n = 38 ; % = 7.3
NYHA class Sample size	n = NR ; % = NR
Class 1 Sample size	n = 18 ; % = 3.5
Class 2 Sample size	n = 318 ; % = 61.2
Class 3 Sample size	n = 181 ; % = 34.8
Class 4 Sample size	n = 3 ; % = 0.6
Previous heart failure hospitalisation	n = 374 ; % = 71.9

Characteristic	Study (N = 520)
Sample size	
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	69.6 (19.9)
Background (non-randomised) heart failure medications Sample size	n = NR ; % = NR
ACE/ARB Sample size	n = 458 ; % = 88.1
Beta-blockers Sample size	n = 407 ; % = 78.3
Diuretics Sample size	n = 396 ; % = 76.2

Outcomes

Study timepoints

3.4 year

Hazard ratios

Outcome	MRA (spironolactone) vs Placebo, 3.4 year, N2 = NR, N1 = NR
Death Treatment effect (HR) Hazard ratio/95% CI	0.73 (0.49 to 1.09)
CV death Treatment effect (HR) Hazard ratio/95% CI	0.69 (0.43 to 1.11)
HFHospitalisation Treatment effect (HR) Hazard ratio/95% CI	0.76 (0.46 to 1.26)

Death - Polarity - Lower values are better

Cardiovascular death - Polarity - Lower values are better

Heart failure hospitalisation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT 2 HFmrEF

Death-Treatment effect(HR)-3.4 y

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

Cardiovascular death-Treatment effect (HR)-3.4 y

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

Heart failure hospitalisation-Treatment effect (HR)-3.4 y

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

Solomon, 2019

Bibliographic Reference	Solomon, Scott D; McMurray, John J V; Anand, Inder S; Ge, Junbo; Lam, Carolyn S P; Maggioni, Aldo P; Martinez, Felipe; Packer, Milton; Pfeffer, Marc A; Pieske, Burkert; Redfield, Margaret M; Rouleau, Jean L; van Veldhuisen, Dirk J; Zannad, Faiez; Zile, Michael R; Desai, Akshay S; Claggett, Brian; Jhund, Pardeep S; Boytsov, Sergey A; Comin-Colet, Josep; Cleland, John; Dungen, Hans-Dirk; Goncalvesova, Eva; Katova, Tzvetana; Kerr Saraiva, Jose F; Lelonek, Malgorzata; Merkely, Bela; Senni, Michele; Shah, Sanjiv J; Zhou, Jingmin; Rizkala, Adel R; Gong, Jianjian; Shi, Victor C; Lefkowitz, Martin P; Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction.; The New England journal of medicine; 2019; vol. 381 (no. 17); 1609-1620

Study details

Secondary publication of another included study- see primary study for details	Parent study (used as background for Solomon 2020)
Other publications associated with this study included in review	Solomon 2020
Trial name / registration number	PARAGON-HF; NCT01920711
Study location	848 centres in 43 countries
Study setting	NR

Study dates	From July 18, 2014, through December 16, 2016, we screened 10,359 patients were screened.
Sources of funding	Novartis
Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed 2. ≥50 years of age, male or female 3. LVEF ≥45% by echocardiography during the screening epoch, or within 6 months prior to screening visit (any local LVEF measurement made using echocardiography only) 4. Symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening visit 5. Current symptom(s) of HF (NYHA functional class II to IV) at screening visit 6. Structural heart disease evidenced by at least 1 of the following echocardiography findings (any local measurement made during the screening epoch or within the 6 months prior to screening visit): a) LA enlargement defined by at least 1 of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm2 or LA volume ≥55 ml or LA volume index ≥29 ml/m2 b) LVH defined by septal thickness or posterior wall thickness ≥1.1 cm 7. Patients with at least 1 of the following: a) HF hospitalization (defined as HF listed as the major reason for hospitalization) within 9 months prior to screening visit and NT-proBNP >200 pg/ml for patients not in AF or >600 pg/ml for patients in AF on screening ECG, or b) NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on the screening visit ECG
Exclusion criteria	1. Any prior echocardiographic measurement of LVEF <40% 2. Acute coronary syndrome (including MI), cardiac surgery, other major cardiovascular surgery, or urgent PCI within the 3 months prior to visit 1 or an elective PCI within 30 days prior to visit 1 3. Any clinical event within the 6 months prior to visit 1 that could have reduced the LVEF (e.g., MI, CABG), unless an echocardiographic measurement was performed after the event confirming the LVEF to be ≥45% 4. Current acute decompensated HF requiring augmented therapy with diuretic agents, vasodilator agents, and/or inotropic drugs 5. Patients who require treatment with 2 or more of the following: an ACEI, an ARB, or a renin inhibitor 6. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes 7. Patients with a known history of angioedema 8. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue), such as significant pulmonary disease (including primary pulmonary hypertension), anaemia, or obesity. Specifically, patients with the following are excluded: a) Severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy, or chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months) or b) Haemoglobin <10 g/dl, or c) Body mass index >40 kg/m2 9. Patients with any of the following: a) SBP ≥180 mm Hg at visit 1, or b) SBP >150 mm Hg and <180 mm Hg at visit 1 unless the patient is receiving 3 or more antihypertensive drugs. Antihypertensive drugs include but are not limited to a thiazide or other diuretic, MRA, ACEI, ARB,

	beta blocker, and calcium channel blocker, or c) SBP <110 mm Hg at visit 1, or d) SBP <100 mm Hg or symptomatic hypotension as determined by the investigator at visit 103 or visit 199/201 10. Use of other investigational drugs at the time of enrolment, or within 30 days or 5 half-lives of enrolment, whichever is longer 11. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy-induced cardiomyopathy, or viral myocarditis 12. Evidence of right-sided HF in the absence of left-sided structural heart disease 13. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy 14. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF 15. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator 16. Stroke, transient ischemic attack, carotid surgery, or carotid angioplasty within the 3 months prior to visit 1 17. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial 18. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and AF or atrial flutter with a resting ventricular rate >110 beats per minute 19. Patients with a cardiac resynchronization therapy device 20. Patients with prior major organ transplant or intent to transplant (i.e., on transplant list) 21. Any surgical or medical condition that in the opinion of the investigator may place the patient at higher risk from his/her participation in the study or is likely to prevent the patient from complying with the requirements of the study or completing the study 22. Any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following: any history of pancreatic injury, pancreatitis, or evidence of impaired pancreatic function/injury within the past 5 years 23. Evidence of hepatic disease as determined by any 1 of the following: SGOT (AST) or SGPT (ALT) values exceeding 3 the upper limit of normal, bilirubin >1.5 mg/dl at visit 1 24. Patients with 1 of the following: a) eGFR <30 ml/min/1.73 m2 as calculated by the Modification in Diet in Renal Disease formula at visit 1, or b) eGFR <25 ml/min/1.73 m2 at visit 103 or visit 199/201, or c) eGFR reduction >35% (compared with visit 1) at visit 103 or visit 199/201 25. Presence of known functionally significant bilateral renal artery stenosis 26. Patients with either of the following: a) Serum potassium >5.2 mmol/l (mq/l) at visit 1 b) Serum potassium >5.4 mmol/l (mq/l) at visit 103 or visit 199/201 27. History or presence of any other disease with a life expectancy of <3 years 28. History of noncompliance to medical regimens and patients who are considered potentially unreliable 29. History or evidence of drug or alcohol abuse within the past 12 months 30. Persons directly involved in the execution of this protocol 31. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases 32. 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 gonadotropin laboratory test 33. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days off study drug

Recruitment / selection of participants	Eligible patients entered the initial single-blind run-in phase and received valsartan 40 mg or 80 mg twice daily for one to two weeks. If started on 40 mg twice daily, the dose was increased to 80 mg twice daily after one week. If patients tolerated valsartan according to prespecified criteria, they were switched to sacubitril/valsartan 49/51mg twice daily for 2 to 4 weeks. Those who tolerated sacubitril/valsartan at this dose were eligible for randomization.
Intervention(s)	ARNI - sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily)
Comparator	ARB - valsartan (target dose, 160 mg twice daily)
Population subgroups	Not relevant (study info used as background for Solomon 2020)
Number of participants	4822 randomised
Duration of follow-up	Median duration of follow-up was 35 months (interquartile range, 30 to 41) in each group.
Indirectness	
Method of analysis	ITT The primary efficacy outcome was evaluated with the use of the semiparametric proportional rates method of Lin et al. and a joint gamma frailty model stratified according to geographic region. Ghosh–Lin and Kaplan–Meier curves were used to show the cumulative recurrent and first events, respectively.
Additional comments	

Study arms

ARNI (sacubitril/valsartan) (N = 2419)

Target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily. Background treatment: ACEI or ARB 86.2%; MRA 24.6%; beta-blocker 79.9%. n=12 removed from study due to issues at one site with GCP, leaving n=2407

ARB (valsartan) (N = 2403)

Valsartan target dose, 160 mg twice daily Background treatment: ACEI or ARB 86.4%; MRA 27.1%; beta-blocker 79.5%. n=14 removed from study due to issues at one site with GCP, leaving n=2389

Solomon, 2020

Bibliographic Reference	Solomon, Scott D; Vaduganathan, Muthiah; L Claggett, Brian; Packer, Milton; Zile, Michael; Swedberg, Karl; Rouleau, Jean; A Pfeffer, Marc; Desai, Akshay; Lund, Lars H; Kober, Lars; Anand, Inder; Sweitzer, Nancy; Linssen, Gerard; Merkely, Bela; Luis Arango, Juan; Vinereanu, Dragos; Chen, Chen-Huan; Senni, Michele; Sibulo, Antonio; Boytsov, Sergey; Shi, Victor; Rizkala, Adel; Lefkowitz, Martin; McMurray, John J V; Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure.; Circulation; 2020; vol. 141 (no. 5); 352-361

Study details

Secondary publication of another included study- see primary study for details	This paper combined data from PARADIGM -HF and PARAGON-HF PARADIGM-HF:

	McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077 PARAGON-HF: Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381:1609–1620. doi: 10.1056/NEJMoa1908655
Other publications associated with this study included in review	
Trial name / registration number	NCT01920711 (PARAGON-HF), NCT01035255 (PARADIGM-HF).
Study location	Multi-centre studies
Study setting	
Study dates	PARAGON-HF: From July 18, 2014, through December 16, 2016, we screened 10,359 patients were screened. PARADGM-HF: From December 8, 2009, through November 23, 2012, a total of 10,521 patients at 1043 centres in 47 countries entered the run-in period.
Sources of funding	Novartis funded both PARAGON-HF and PARADIGM-HF
Inclusion criteria	Entry criteria in both trials were largely similar except for age (≥18 years for PARADIGM-HF and ≥50 years for PARAGON-HF), and LVEF, which was required to be ≤40% in PARADIGM-HF and ≥45% in PARAGON-HF. Both trials required patients to have signs or symptoms of HF (New York Heart Association II to IV functional class), to have been on diuretic therapy in the month before enrolment, and to have elevation in natriuretic peptides. In PARADIGM-HF, B-type natriuretic

	peptide (BNP) were required to be ≥150pg/ mL or N-terminal proBNP (NT-proBNP) ≥600pg/mL (≥100pg/ mL or ≥400pg/mL, respectively, if hospitalized in the previous year). In PARAGON-HF, NT-proBNP>300pg/mL (>900pg/ mL if in atrial fibrillation on screening electrocardiogram) was required. If patients were hospitalized for HF within 9 months, NT-proBNP>200pg/mL (or >600pg/mL for atrial fibrillation) was required. In PARAGON-HF, patients were further required to have evidence of structural heart disease, evidenced by left atrial enlargement or left ventricular hypertrophy
Exclusion criteria	See Solomon 2019 for exclusion criteria of PARAGON-HF
Recruitment / selection of participants	NR
Intervention(s)	ARNI Sacubitril/valsartan 97/103mg twice daily
Comparator	ARB Valsartan 160mg twice daily
Number of participants	730 for subgroup of interest
Duration of follow-up	The median follow-up in PARAGON-HF was 35 months
Indirectness	Results reported here for subgroup with >40% to 50% LVEF (n=730)

Method of analysis	Data were collected in both trials to allow for assessment of both time to first event and recurrent event end points. Treatment effects comparing sacubitril/valsartan to the active RAS comparator (enalapril or valsartan) were assessed within each category for the primary outcome and its components using Cox proportional hazards models and expressed as hazard ratios (HR).

NOTE: Data from PARAGON-HF and PARADIGM-HF combined in this analysis. However, note that the eligibility criteria for PARADIGM-HF mean that relevant subgroup data must come from PARAGON-HF so ARNI V ARB, FUP 35 months.

Study arms

ARNI (N = 1427)

Sacubitril/valsartan 97/103mg twice daily N for relevant subgroup not reported per arm, n=730 total for subgroup

ARB (N = 1427)

Valsartan 160mg twice daily N for relevant subgroup not reported per arm, n=730 total for subgroup

Characteristics

Study-level characteristics

Characteristic	Study (N = 1427)
% Female Sample size	n = 564 ; % = 40
Age Mean (SD)	71 (9)
White Sample size	n = 1177 ; % = 82
Black Sample size	n = 24 ; % = 2
Asian Sample size	n = 167 ; % = 12
Other Sample size	n = 59 ; % = 4
NYHA class one Sample size	n = 36 ; % = 3
NYHA class two	n = 1082 ; % = 76

Characteristic	Study (N = 1427)
Sample size	
NYHA class three Sample size	n = 300 ; % = 21
NYHA class Four Sample size	n = 9 ; % = 1
LVEF Mean (SD)	48.6 (2.2)
Type 2 diabetes Sample size	n = 627 ; % = 44
Atrial fibrillation Sample size	n = 480 ; % = 34
Previous heart failure hospitalisation Sample size	n = 733 ; % = 51
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	65 (20)

Characteristic	Study (N = 1427)
ACE-inhibitor Sample size	n = 673 ; % = 47
ARBs Sample size	n = 590 ; % = 41
ACEI or ARB Sample size	n = 1257 ; % = 88
Beta-blockers Sample size	n = 1175 ; % = 82
MRAs Sample size	n = 430 ; % = 30

Baseline characteristics only available by categories of LVEF. Baseline characteristics for subgroup LVEF 42.5-52.5% (n=1427) as closest to the population of interest.

Outcomes (Data from PARAGON-HF and PARADIGM-HF combined in this analysis. However, note that the eligibility criteria for PARADIGM-HF mean that this subgroup data must come from PARAGON-HF so ARNI V ARB, FUP 35 months)

Study timepoints

31 month (27 median and 35 median months FUP for the two studies)

Contrast outcomes

Outcome	ARNI vs ARB, 35 month, N2 = NR, N1 = NR
CV mortality (CV death) Treatment effect for EF category >40% to 50%. Total n for subgroup is 730 Hazard ratio/95% CI	0.98 (0.66 to 1.46)
Unplanned hospitalisations or visits HF related (total HF hospitalisation) Hazard ratio/95% CI	0.73 (0.5 to 1.07)

CV mortality (CV death) - Polarity - Lower values are better

Unplanned hospitalisations or visits HF related (total HF hospitalisation) - Polarity - Lower values are better

Treatment effect for EF category >40% to 50%. Total n for subgroup is 730

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT 2 HFmrEF

CV mortality (CV death)-Hazard Ratio- FUP 35 mo

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

Unplanned hospitalisations or visits HF related (total HF hospitalisation)-Hazard Ratio-FUP 35 mo

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, SD; McMurray, JJV; Vaduganathan, M; Claggett, B; Jhund, PS; Desai, AS; Henderson, AD; Lam, CSP; Pitt, B; Senni, M; Shah, SJ; Voors, AA; Zannad, F; Abidin, IZ; Alcocer-Gamba, MA; Atherton, JJ; Bauersachs, J; Chang-Sheng, M; Chiang, CE; Chioncel, O; Chopra, V; Comin-Colet, J; Filippatos, G; Fonseca, C; Gajos, G; Goland, S; Goncalvesova, E; Kang, S; Katova, T; Kosiborod, MN; Latkovskis, G; Lee, AP; Linssen, GCM; Llamas-Esper?n, G; Mareev, V; Martinez, FA; Melenovsk?, V; Merkely, B; Nodari, S; Petrie, MC; Saldarriaga, CI; Saraiva, JFK; Sato, N; Schou, M; Sharma, K; Troughton, R; Udell, JA; Ukkonen, H; Vardeny, O; Verma, S; von Lewinski, D; Voronkov, L; Yilmaz, MB; Zieroth, S; Lay-Flurrie, J; van Gameren, I; Amarante, F; Kolkhof, P; Viswanathan, P; Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction.; The New England journal of medicine; 2024

Study details

Other publications associated with this study included in review	Docherty 2024 (EPPI ID) 16110103: FINEARTS-HF secondary paper with outcomes for LVEF subgroups Solomon 2024a (EPPI ID: 15978368): FINEARTS-HF baseline characteristics paper Vaduganathan 2024 (EPPI ID: 15978367): FINEARTS-HF design and rationale paper (This is the primary study for FINEARTS-HF. Population does not match this review protocol.)

Solomon, 2024a

Bibliographic Reference	Solomon, SD; Ostrominski, JW; Vaduganathan, M; Claggett, B; Jhund, PS; Desai, AS; Lam, CSP; Pitt, B; Senni, M; Shah, SJ; Voors, AA; Zannad, F; Abidin, IZ; Alcocer-Gamba, MA; Atherton, JJ; Bauersachs, J; Ma, CS; Chiang, CE; Chioncel, O; Chopra, V; Comin-Colet, J; Filippatos, G; Fonseca, C; Gajos, G; Goland, S; Goncalvesov?, E; Kang, SM; Katova, T; Kosiborod, MN; Latkovskis, G; Lee, AP; Linssen, GCM; Llamas-Esper?n, G; Mareev, V; Martinez, FA; Melenovsk?, V; Merkely, B; Nodari, S; Petrie, MC; Saldarriaga, CI; Saraiva, JFK; Sato, N; Schou, M; Sharma, K; Troughton, R; Udell, JA; Ukkonen, H; Vardeny, O; Verma, S; von Lewinski, D; Voronkov, LG; Yilmaz, MB; Zieroth, S; Lay-Flurrie, J; van Gameren, I; Amarante, F; Viswanathan, P; McMurray, JJV; Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: The FINEARTS-HF trial.; European journal of heart failure; 2024; vol. 26 (no. 6); 1334-1346

Study details

Other publications associated with this study included in review	Docherty 2024 (EPPI ID) 16110103: FINEARTS-HF secondary paper with outcomes for LVEF subgroups Solomon 2024 (EPPI ID: 15978369): FINEARTS-HF primary results paper Vaduganathan 2024 (EPPI ID: 15978367): FINEARTS-HF design and rationale paper

Swedberg, 1999

Bibliographic Reference	Swedberg, K; Pfeffer, M; Granger, C; Held, P; McMurray, J; Ohlin, G; Olofsson, B; Ostergren, J; Yusuf, S; Candesartan in heart failure--assessment of reduction in mortality and morbidity (CHARM): rationale and design. Charm-Programme Investigators.; Journal of cardiac failure; 1999; vol. 5 (no. 3); 276-82

Study details

Other publications associated with this study included in review	Provides background information for Lund 2018 (CHARM)
Trial name / registration number	CHARM

Vaduganathan, 2024

Bibliographic Reference	Vaduganathan, M; Claggett, BL; Lam, CSP; Pitt, B; Senni, M; Shah, SJ; Voors, AA; Zannad, F; Desai, AS; Jhund, PS; Viswanathan, P; Bomfim Wirtz, A; Schloemer, P; Lay-Flurrie, J; McMurray, JJV; Solomon, SD; 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; 2024; vol. 26 (no. 6); 1324-1333

Study details

Other publications associated with	Docherty 2024 (EPPI ID) 16110103: FINEARTS-HF secondary paper with outcomes for LVEF subgroups

this study included in review	Solomon 2024 (EPPI ID: 15978369): FINEARTS-HF primary results paper Solomon 2024a (EPPI ID: 15978368): FINEARTS-HF baseline characteristics paper

Appendix E Forest plots

E.1 Beta-blocker versus placebo

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

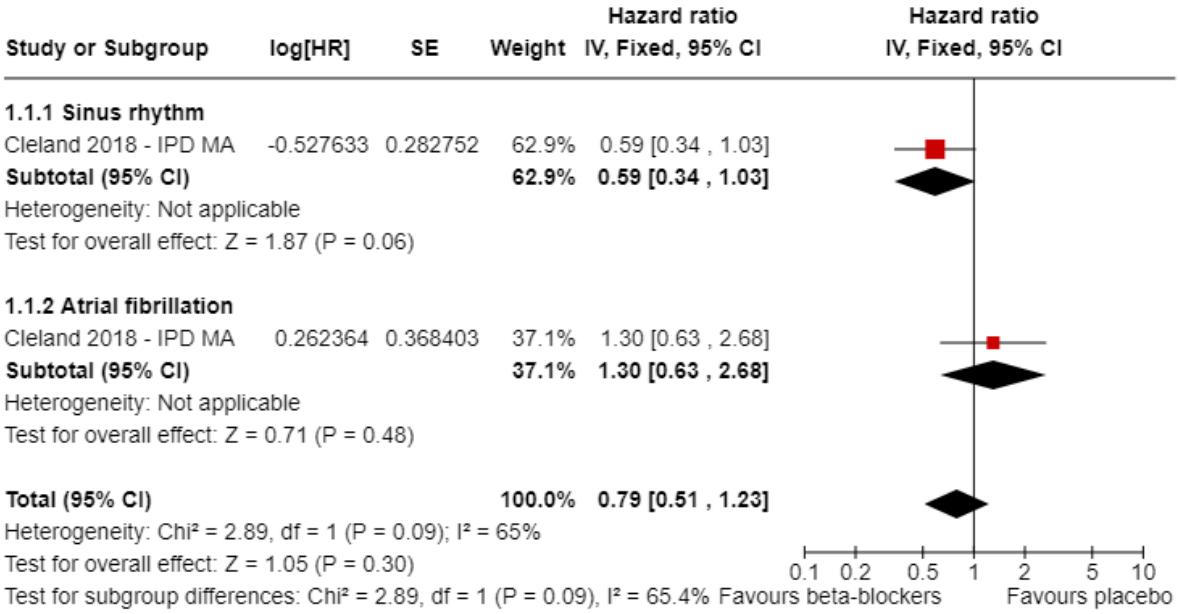


Figure 3: Cardiovascular mortality (time-to-event)

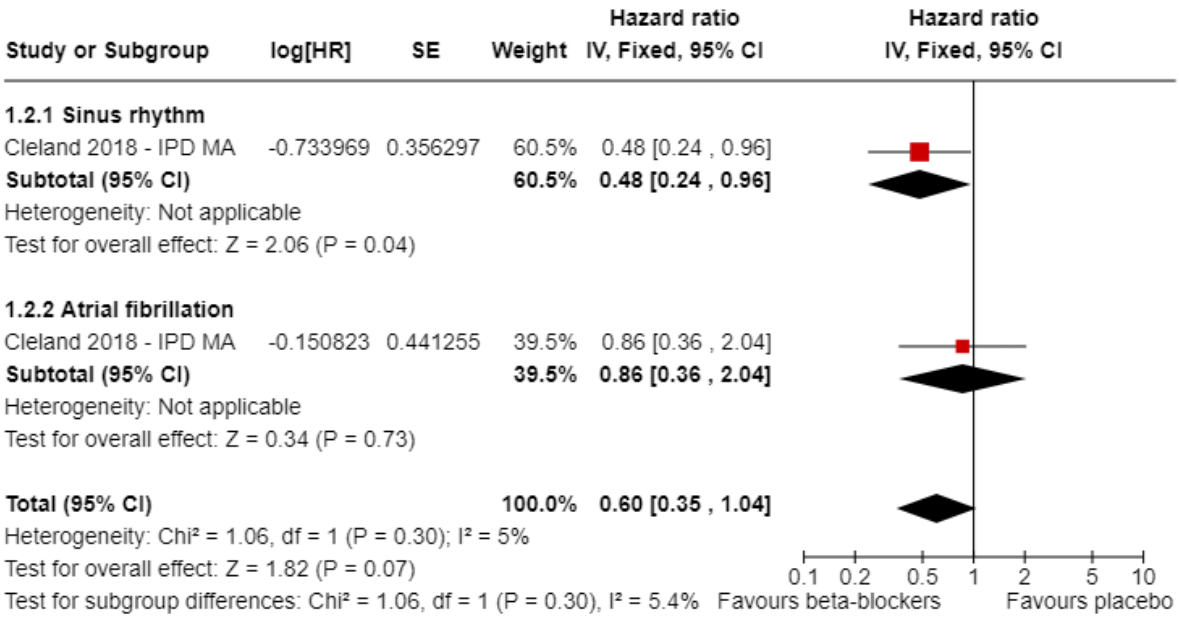
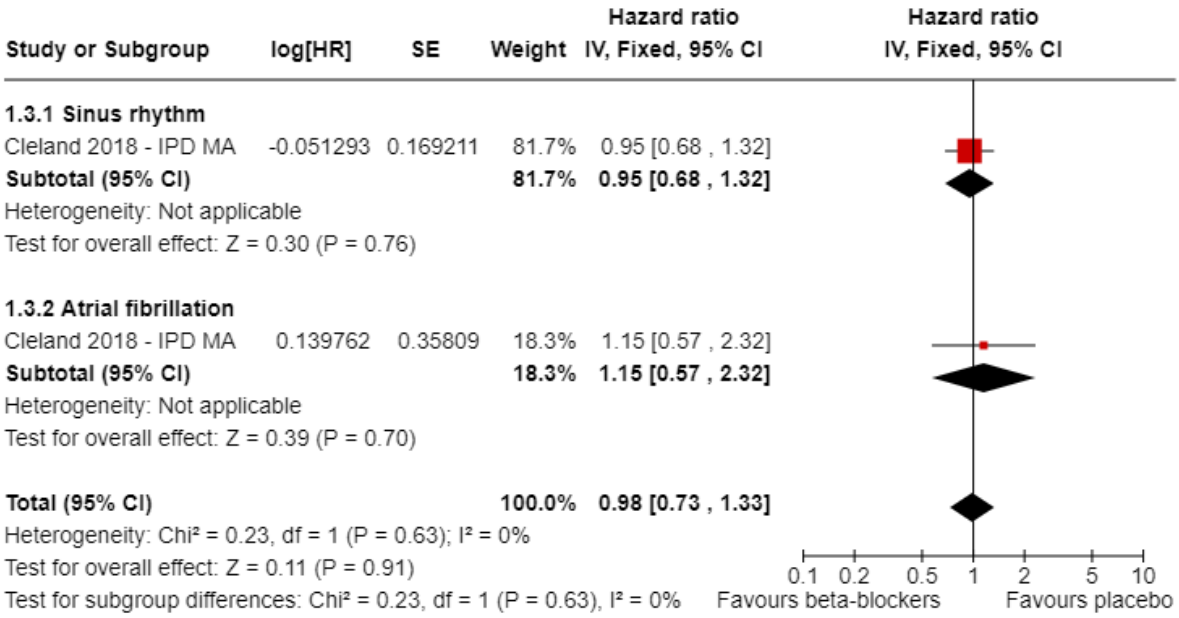


Figure 4: Unplanned hospitalisation, HF-related (cardiovascular hospitalisation; time-to-event)



E.2 ACE inhibitor versus placebo

Figure 5: All-cause mortality (dichotomous)

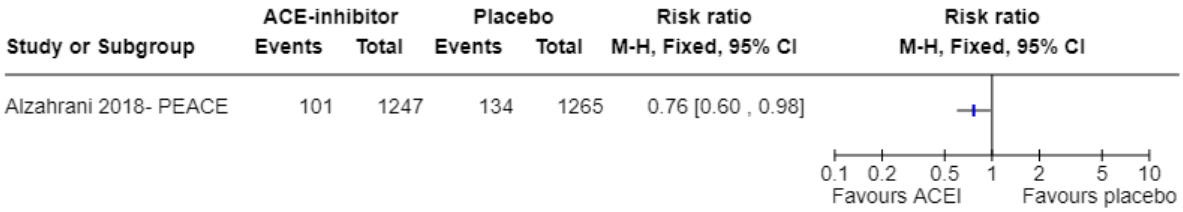


Figure 6: Cardiovascular mortality (dichotomous)

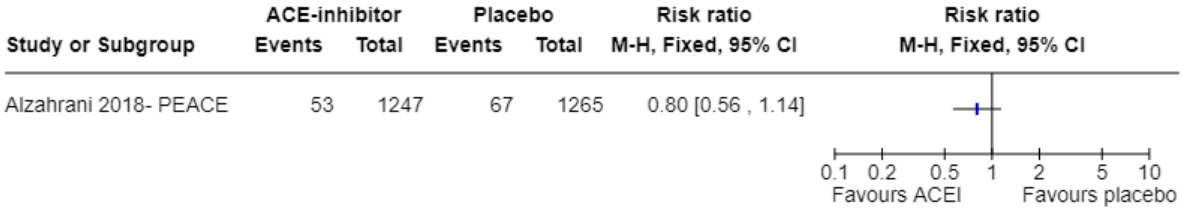
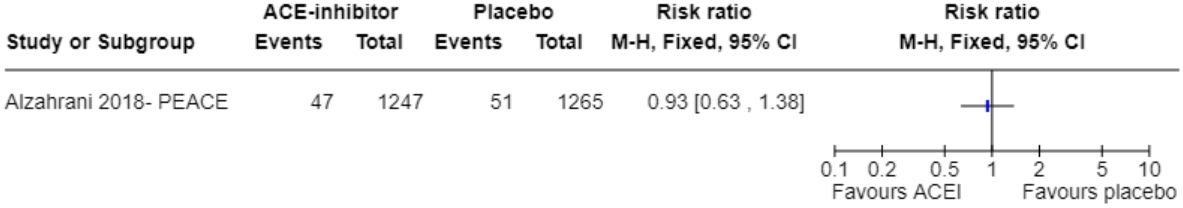


Figure 7: Unplanned hospitalisation, HF-related (hospitalisation for non-fatal congestive HF; dichotomous)



E.3 ARB versus placebo

Figure 8: All-cause mortality (time-to-event)

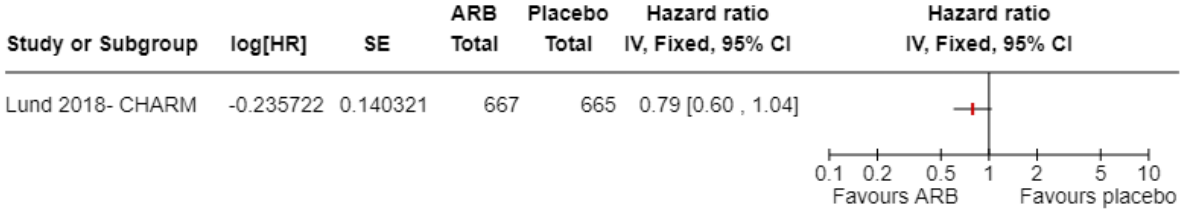


Figure 9: Cardiovascular mortality (time-to-event)

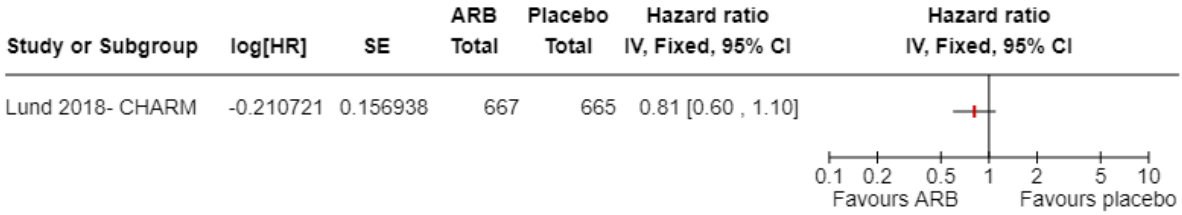


Figure 10: Unplanned hospitalisation, HF-related (time-to-event)

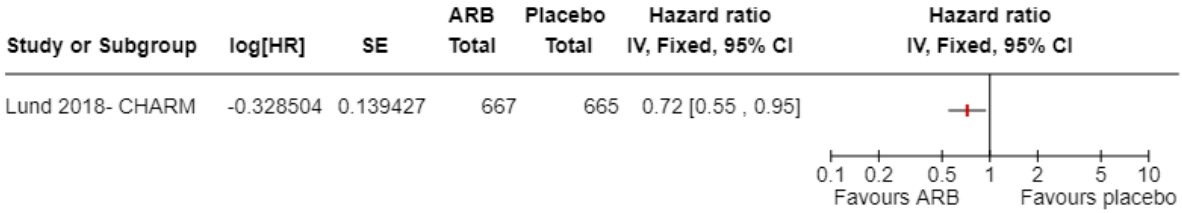
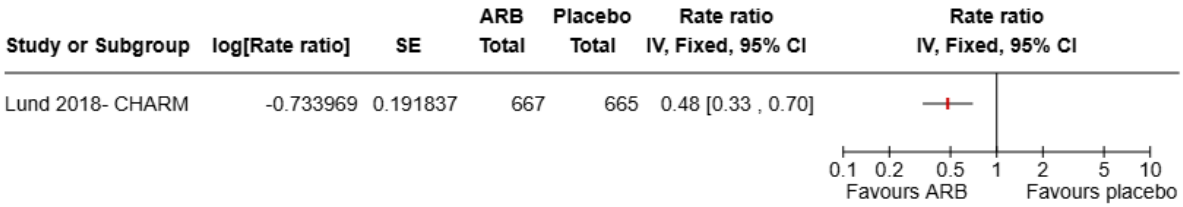


Figure 11: Recurrent unplanned hospitalisation, HF-related (incidence rate)



E.4 MRA versus placebo

Figure 12: All-cause mortality (events)

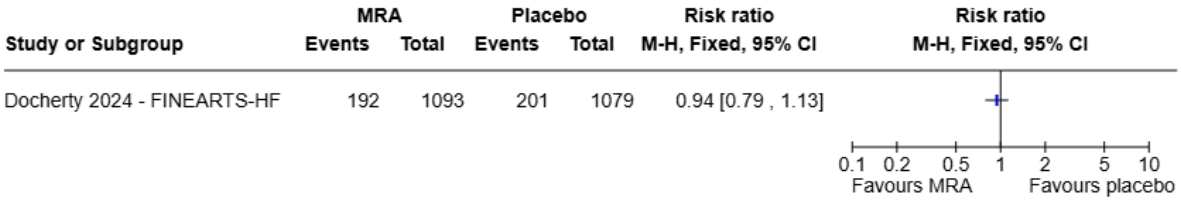


Figure 13: All-cause mortality (time-to-event)

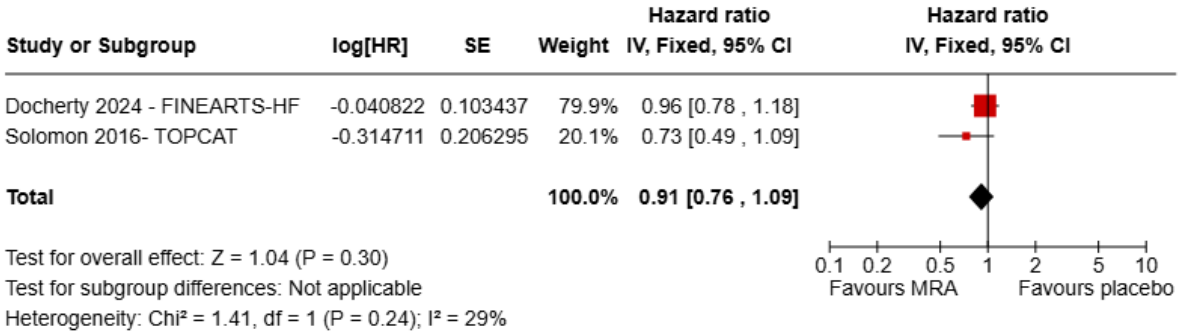


Figure 14: Cardiovascular mortality (events)

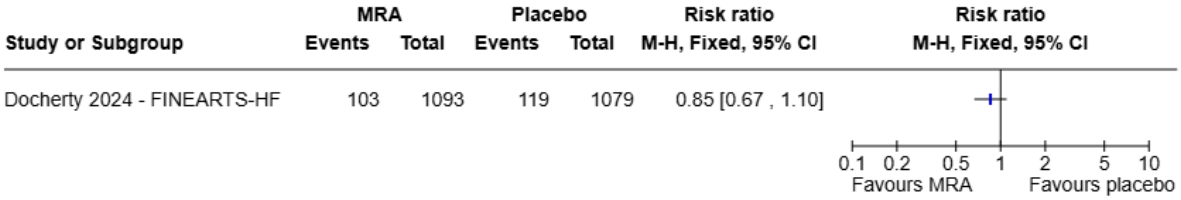


Figure 15: Cardiovascular mortality (time-to-event)

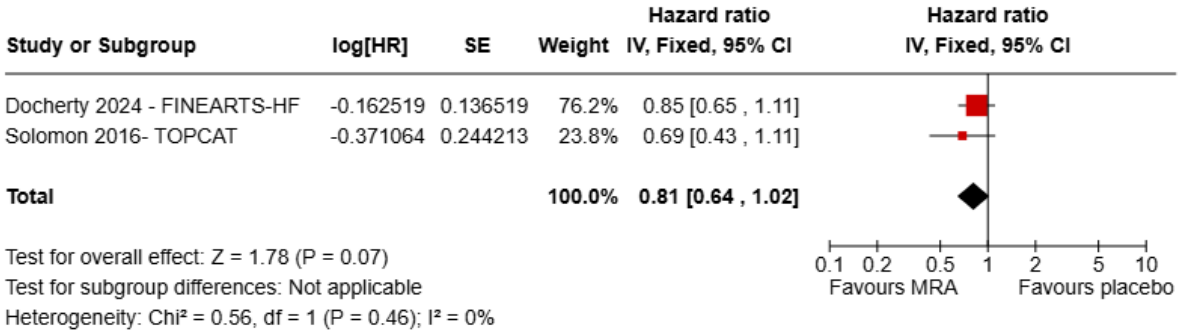


Figure 16: Health-related quality of life (KCCQ- total symptom score, higher values are better, range 0-100,change score, adjusted)

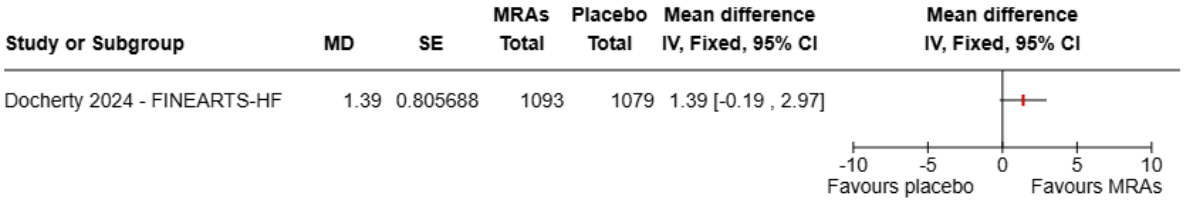


Figure 17: First unplanned hospitalisation or visit, HF-related (worsening HF events) (events)

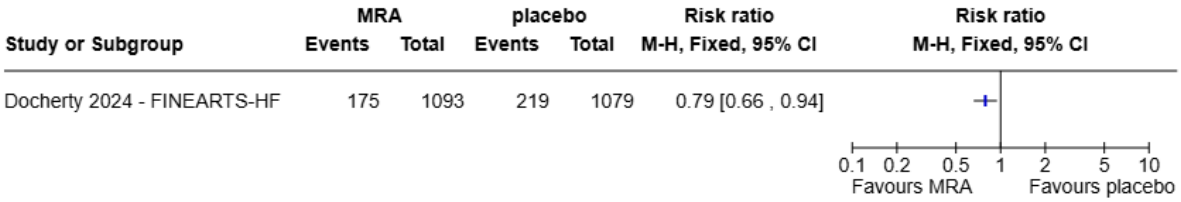


Figure 18: First unplanned hospitalisation or visit, HF-related (worsening HF events) (time-to-event)

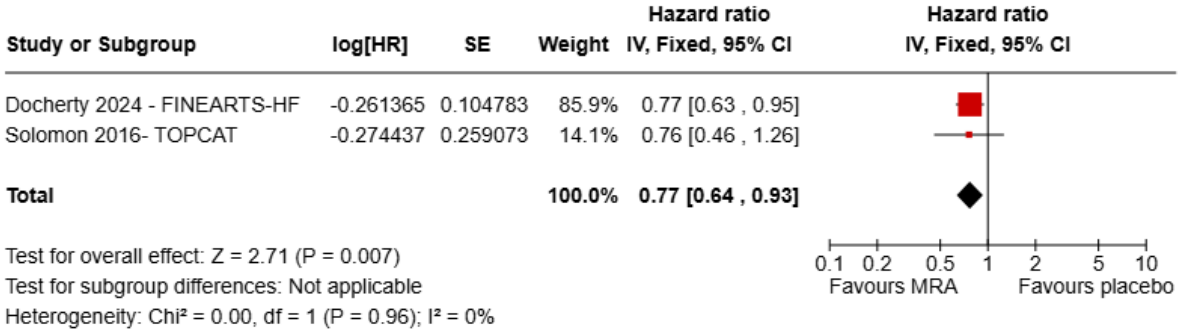


Figure 19: Repeat unplanned hospitalisations or visits, HF-related (worsening HF events) (rate ratios)

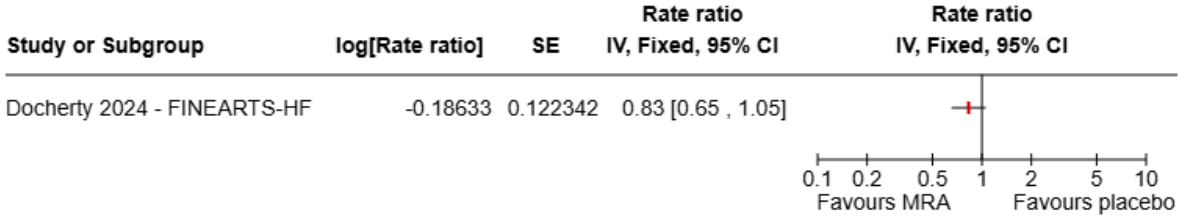


Figure 20: Withdrawal due to drug-related adverse events (treatment discontinuation due to adverse event) (events)

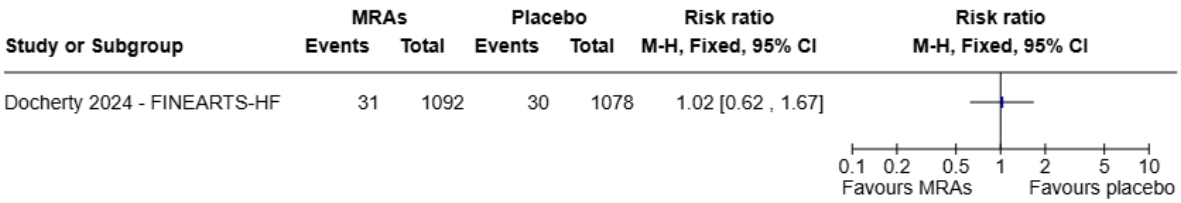
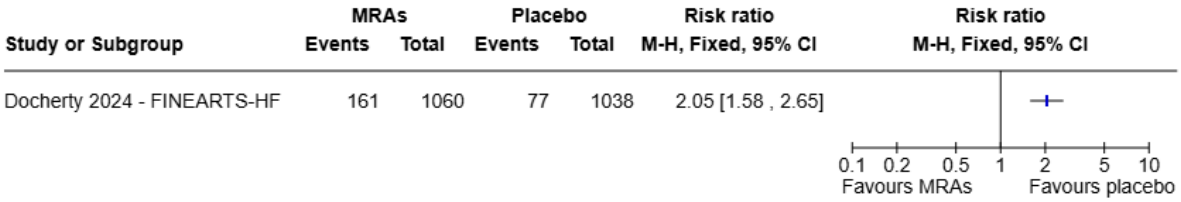


Figure 21: Hyperkalaemia (events)



E.5 ARNI versus ARB

Figure 22: Cardiovascular mortality (time-to-event)

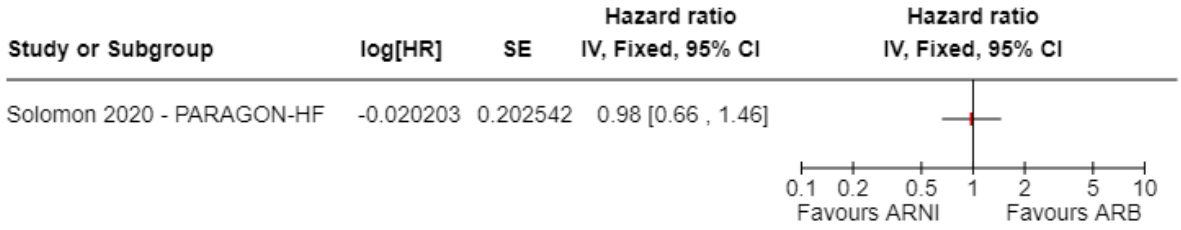
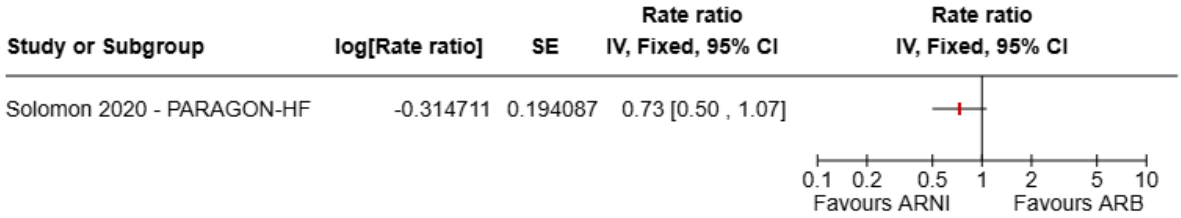


Figure 23: Unplanned hospitalisation, HF-related (total HF hospitalisations; rate ratio)



Appendix F GRADE tables

Table 17: Clinical evidence profile: Beta-blockers versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta blockers	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 1.3 years)												
11	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	716		HR 0.79 (0.51 to 1.23)	**Not estimable**	⨁⨁◯◯ Low	CRITICAL
Cardiovascualr mortality (follow-up: 1.3 years)												
11	randomised trials	serious[a]	not serious	not serious	serious[b]	none	716		HR 0.60 (0.35 to 1.04)	**Not estimable**	⨁⨁◯◯ Low	CRITICAL
Unplanned hospitalisation, HF-related (cardiovascular hospitalisation) - total (follow-up: 1.3 years)												
11	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	709		HR 0.98 (0.73 to 1.33)	**Not estimable**	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; HF: Heart failure; IPD: Individual participant data; HR: Hazard ratio
a. Downgraded by 1 increment for risk of bias because of some concerns about identification of all relevant trials (no clear search strategy reported or available, and no flowchart to show assessment of papers against inclusion criteria).
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).

Table 18: Clinical evidence profile: ACEI versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACEI	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: mean 4.7 years)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	101/1247 (8.1%)	134/1265 (10.6%)	RR 0.76 (0.60 to 0.98)	**25 fewer per 1,000** (from 42 fewer to 2 fewer)	⨁◯◯◯ Very low	CRITICAL
Cardiovascular mortality (follow-up: mean 4.7 years)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	53/1247 (4.3%)	67/1265 (5.3%)	RR 0.80 (0.56 to 1.14)	**11 fewer per 1,000** (from 23 fewer to 7 more)	⨁◯◯◯ Very low	CRITICAL
Unplanned hospitalisation or visits, HF-related (hospitalisation for nonfatal congestive heart failure) (follow-up: mean 4.7 years)												
1	randomised trials	not serious	not serious	very serious[a]	very serious[b]	none	47/1247 (3.8%)	51/1265 (4.0%)	RR 0.93 (0.63 to 1.38)	**3 fewer per 1,000** (from 15 fewer to 15 more)	⨁◯◯◯ Very low	CRITICAL

ACEI; Angiotensin converting enzyme inhibitor; CI: confidence interval; HF: Heart failure; RR: Relative risk
a. Downgraded by 2 increments for indirectness: intervention indirectness due to the intervention indication for hypertension; outcome indirectness due to the outcome not being TTE as specified in the protocol; population indirectness because the population included people with ischemic cardiomyopathy and mildly reduced ejection fraction without clear evidence of symptomatic heart failure.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).

Table 19: Clinical evidence profile: ARB versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: mean 2.9 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	667 participants	665 participants	**HR 0.79** (0.60 to 1.04)	1.2 fewer per 100 person years[c]	⨁⨁◯◯ Low	CRITICAL
Cardiovascular mortality (follow-up: mean 2.9 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	667 participants	665 participants	**HR 0.81** (0.60 to 1.11)	0.9 fewer per 100 person years[c]	⨁⨁◯◯ Low	CRITICAL
Unplanned hospitalisation or visits, HF-related (heart failure hospitalisation) (follow-up: mean 2.9 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	667 participants	665 participants	**HR 0.72** (0.55 to 0.95)	2.0 fewer per 100 person years[c]	⨁⨁◯◯ Low	CRITICAL
Repeat unplanned hospitalisation or visits, HF-related (recurrent heart failure hospitalisation) (follow-up: mean 2.9 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	667 participants	665 participants	**Rate** ratio **0.48** (0.33 to 0.70)	6.4 fewer per 100 person years[c]	⨁⨁⨁◯ Moderate	CRITICAL

ARB: Angiotensin receptor antagonist / blocker; CI: confidence interval; HF: Heart failure; HR: Hazard ratio
a. Downgraded by 1 increment for risk of bias because of some concerns about reporting of randomisation method and not able to assess baseline characteristics.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).
c. Absolute effect calculated from rate per 100 person years reported in the paper (not possible to estimate the variance).

Table 20: Clinical evidence profile: MRA versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) (follow-up: range 2.6 years to 3.4 years)												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	2692		**HR 0.91** (0.76 to 1.09)	**Not estimable**	⨁◯◯◯ Very low[a,b,c]	CRITICAL
All-cause mortality (dichotomous) (follow-up: median 32 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	very serious[d]	serious[c]	none	192/1093 (17.6%)	201/1079 (18.6%)	**RR 0.94** (0.79 to 1.13)	**11 fewer per 1,000** (from 39 fewer to 24 more)	⨁◯◯◯ Very low[a,c,d]	CRITICAL
Cardiovascular mortality (HR) (follow-up: range 2.6 years to 3.4 years)												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	2692		**HR 0.81** (0.64 to 1.02)	**Not estimable**	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Cardiovascular mortality (dichotomous) (follow-up: median 32 months)												
1	randomised trials	serious[a]	not serious	very serious[d]	serious[c]	none	103/1093 (9.4%)	119/1079 (11.0%)	**RR 0.85** (0.67 to 1.10)	**17 fewer per 1,000** (from 36 fewer to 11 more)	⨁◯◯◯ Very low[a,c,d]	CRITICAL
Health-related quality of life (KCCQ-TSS change score; adjusted) (follow-up: mean 12 months)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	1093	1079	-	MD **1.39 higher** (0.19 lower to 2.97 higher)	⨁⨁◯◯ Low[a,b]	CRITICAL
First unplanned hospitalisation or visits, HF related (HR) (follow-up: range 2.6 years to 3.4 years)												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	2692		**HR 0.77** (0.64 to 0.93)	**Not estimable**	⨁◯◯◯ Very low[a,b,c]	CRITICAL
First unplanned hospitalisation or visit - HF related (dichotomous) (follow-up: median 32 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	very serious[d]	serious[c]	none	175/1093 (16.0%)	219/1079 (20.3%)	**RR 0.79** (0.66 to 0.94)	**43 fewer per 1,000** (from 69 fewer to 12 fewer)	⨁◯◯◯ Very low[a,c,d]	CRITICAL
Total number of worsening heart failure events (rate ratio) (follow-up: median 32 months)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	311/1093	377/1079	**Rate ratio 0.83** (0.65 to 1.05)	**28 fewer per 1000 patient(s) per years[e]**	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Treatment discontinuation due to adverse event (dichotomous) (follow-up: median 32 months)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	31/1092 (2.8%)	30/1078 (2.8%)	**RR 1.02** (0.62 to 1.67)	**1 more per 1,000** (from 11 fewer to 19 more)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Hyperkalaemia (dichotomous) (follow-up: median 32 months)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	161/1060 (15.2%)	77/1038 (7.4%)	**RR 2.05** (1.58 to 2.65)	**78 more per 1,000** (from 43 more to 122 more)	⨁⨁◯◯ Low[a,b]	CRITICAL

CI: confidence interval; HF: Heart failure; HR: Hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire total symptom score*; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk*

a. Downgraded by 1 increment because of some concerns about risk of bias (protocol deviations in subgroup definitions of LVEF categories)

b. Downgraded by 1 increment for intervention indirectness (finerenone not licensed for CHF).

c. Downgraded by 1 increment for imprecision if the confidence interval crossed one MID and by 2 increments if the 95% confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous and time-to-event outcomes; KCCQ TSS MID is 5)

d. Downgraded by 2 increments for indirectness of intervention (finerenone not licensed for CHF) and outcome (dichotomous, not time-to-event).

e. Absolute effect calculated from rate per 100 person years reported in the paper (not possible to estimate the variance).

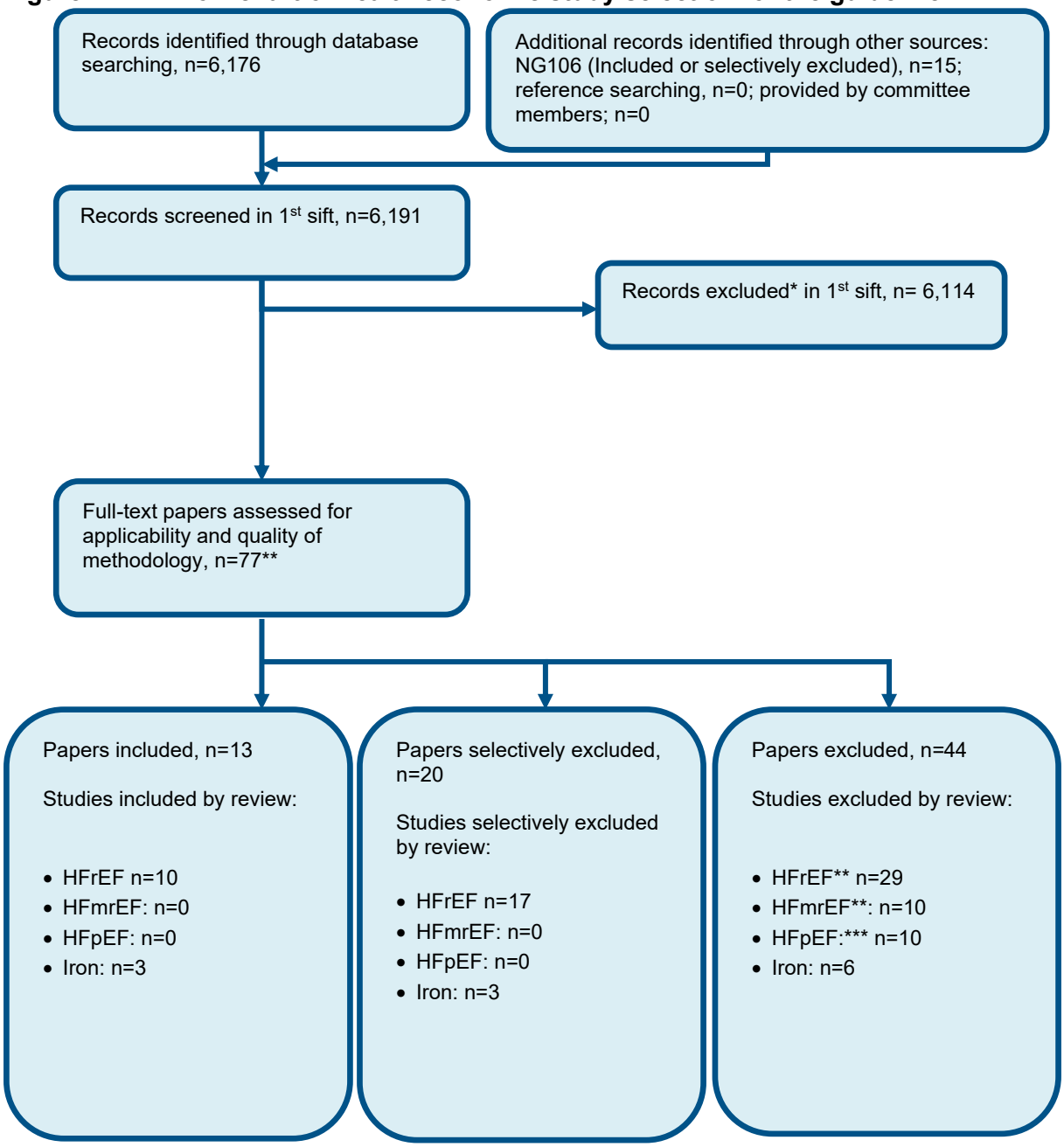
Table 21: Clinical evidence profile: ARNI versus ARB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI	ARB	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular mortality (follow-up: median 35 months)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	730		**HR 0.98** (0.66 to 1.46)	**Not estimable**	⨁⨁◯◯ Low	CRITICAL
Unplanned hospitalisation or visits, Hf-related (total HF hospitalisations) (follow-up: median 35 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	730		**R**ate ratio **0.73** (0.50 to 1.07)	**Not estimable**	⨁⨁⨁◯ Moderate	CRITICAL

ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; CI: confidence interval; HF: Heart failure; HR: Hazard ratio
a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs=0.8 and 1.25 for dichotomous and time-to-event outcomes).

Appendix G Economic evidence study selection

Figure 24: Flow chart of health economic study selection for the guideline



* 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 health economic modelling is reported in the main text – see 1.1.9 Economic model.

Appendix J Excluded studies

J.1 Clinical evidence studies

Table 22: Studies excluded from the clinical review

Study	Exclusion reason
(1993) Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet (London, England) 342(8875): 821-828	- Population not relevant to this review protocol *Acute MI*
(1994) A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation 90(4): 1765-1773	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
(1995) Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. Circulation 92(2): 212-218	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
(1996) Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). The American journal of cardiology 78(8): 902-907	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
(1996) New beta blocker reduces heart failure mortality by two-thirds. Geriatrics 51(1): 16-19	- Publication type not relevant to review protocol *Commentary article*
(1997) Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. Lancet (London, England) 349(9049): 375-380	- Population not relevant to this review protocol *HFrEF: not combination treatment*
(1997) The effect of digoxin on mortality and morbidity in patients with heart failure. The New England journal of medicine 336(8): 525-533	- Study does not contain an intervention relevant to this review protocol *HFrEF: digoxin*
(1999) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet (London, England) 353(9169): 2001-2007	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
(1999) The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet (London, England) 353(9146): 9-13	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*

Study	Exclusion reason
(2000) Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy : the randomized evaluation of strategies for left ventricular dysfunction pilot study. Circulation 101(4): 378-384	- Comparator in study does not match that specified in this review protocol *Results include events in 2 randomisation periods with different interventions that cannot be analysed separately*
(2024) The efficacy of dapagliflozin in a hierarchical kidney outcome in heart failure. Nature Medicine 30(5): 1253	- Not a peer-reviewed publication
, Eichhorn EJ, Domanski MJ et al. (2001) A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. The New England journal of medicine 344(22): 1659-1667	- Study does not contain an intervention relevant to this review protocol *Bucindolol*
, Yusuf S, Pitt B et al. (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The New England journal of medicine 325(5): 293-302	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Abdin, Amr, Kondo, Toru, Bohm, Michael et al. (2024) Effects of dapagliflozin according to QRS duration across the spectrum of left ventricular ejection fraction: An analysis of DAPA-HF and DELIVER. European journal of heart failure 26(9): 1952-1963	- Population not relevant to this review protocol *Combination of 2 trials with preserved and reduced EF* - Study does not contain any outcome data relevant to this review protocol *Does not contain extra outcomes to those in main DAPA-HF trial and excludes patients with a paced rhythm and cardiac resynchronization therapy*
Abdulla, Jawdat, Burchardt, Hans, Z Abildstrom, Steen et al. (2003) The angiotensin converting enzyme inhibitor trandolapril has neutral effect on exercise tolerance or functional class in patients with myocardial infarction and reduced left ventricular systolic function. European heart journal 24(23): 2116-22	- Population not relevant to this review protocol *Acute MI*
Abedi, Farshad, Mohammadpour, Amir Hooshang, Ghavami, Vahid et al. (2024) The effects of empagliflozin on ventricular arrhythmias in heart failure patients with an implantable cardioverter-defibrillator: a double-blind randomized controlled trial. Naunyn-Schmiedeberg's archives of pharmacology 397(12): 10191-10201	- Study does not contain any outcome data relevant to this review protocol
Abraham, William T, Lindenfeld, JoAnn, Ponikowski, Piotr et al. (2021) Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without	- Population not relevant to this review protocol *Reduced LVEF*

Study	Exclusion reason
type 2 diabetes. European heart journal 42(6): 700-710	
Abuelazm, Mohamed, Badr, Amr, Turkmani, Mustafa et al. (2024) The efficacy and safety of new potassium binders on renin-angiotensin-aldosterone system inhibitor optimization in heart failure patients: a systematic review and meta-analysis. ESC heart failure 11(1): 28-43	- Systematic review does not contain a protocol intervention *Mixed LVEF: MRA combined with new potassium binders*
Adamo, M., Pagnesi, M., Mebazaa, A. et al. (2023) NT-proBNP and high intensity care for acute heart failure: the STRONG-HF trial. European Heart Journal 44(31): 2947-2962	- Secondary publication of an included study that does not provide any additional relevant information *HFrEF: STRONG-HF Sub-study exploring NT-proBNP at baseline*
Adamopoulos C, Ahmed A, Fay R et al. (2009) Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: insights from the EPHESUS trial. European journal of heart failure 11(11): 1099-1105	- Study design not relevant to this review protocol *Post hoc analysis based on median time-to-randomisation after AMI* - Population not relevant to this review protocol *Acute MI*
Adamou, Anastasia, Chlorogiannis, David Dimitris, Kyriakoulis, Ioannis G et al. (2024) Sodium-glucose cotransporter-2 inhibitors in heart failure patients across the range of body mass index: a systematic review and meta-analysis of randomized controlled trials. Internal and emergency medicine 19(2): 565-573	- Systematic review indirectly matches the review protocol: used as source of primary studies *2 of 3 included RCTS are reduced LVEF. Both already included in analyses (DAPA-HF and Emperor-reduced)*
Adamson, Carly, Docherty, Kieran F, Heerspink, Hiddo J L et al. (2022) Initial Decline (Dip) in Estimated Glomerular Filtration Rate After Initiation of Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction: Insights From DAPA-HF. Circulation 146(6): 438-449	- Study design not relevant to this review protocol *Post hoc analysis*
Adamson, Carly, Jhund, Pardeep S, Docherty, Kieran F et al. (2021) Efficacy of dapagliflozin in heart failure with reduced ejection fraction according to body mass index. European journal of heart failure 23(10): 1662-1672	- Secondary publication of an included study that does not provide any additional relevant information *Paper has been cross-referenced with parent paper. Secondary analysis of DAPA-HF. No additional outcomes reported.*
Addo, Basilio, Agyeman, Walter, Ibrahim, Sammudeen et al. (2024) Dapagliflozin in Heart Failure: A Comprehensive Meta-analysis on Functional Capacity, Symptoms, and Safety Outcomes. American journal of cardiovascular drugs : drugs, devices, and other interventions 24(6): 753-773	- Systematic review indirectly matches the review protocol: used as source of primary studies *No additional studies identified. Amiguet, 2023 not listed in the references (LVEF fits definition for HFrEF); post hoc subanalysis of included study. Ibrahim, 2020 not picked up in the search*

Study	Exclusion reason
	(LVEF fits definition for HFrEF; but acute HF in hospital).
Adji, A.S., Billah, A., Baraja, A. et al. (2022) A Systematic Review and Meta-analysis of Randomized Placebo-controlled Trials 1 Year after Starting Sodium-glucose Transporter-2 Inhibitors in Heart Failure Patients with Reduced Ventricular Ejection Fraction. Open Access Macedonian Journal of Medical Sciences 10: 1-6	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Insufficient information regarding risk of bias assessment.*
Adji, Arga Setyo; Widjaja, Jordan Steven; de Liyis, Bryan Gervais (2024) Effectiveness and safety of mineralocorticoid receptor antagonists in heart failure patients with and without diabetes: a systematic review and meta-analysis. The Egyptian heart journal : (EHJ) : official bulletin of the Egyptian Society of Cardiology 76(1): 150	- Systematic review indirectly matches the review protocol: used as source of primary studies *Systematic Review checked for references but no extra studies identified.*
Afshani, Mohammad Reza, Torfi, Ekhlas, Akiash, Nehzat et al. (2024) Effect of empagliflozin on left ventricular volumes in type 2 diabetes or prediabetes heart failure patients with reduced ejection fraction. Acta cardiologica 79(4): 419-425	- Comparator in study does not match that specified in this review protocol *Background treatment (to specify the comparator of interest) is not reported adequately in the paper*
Agostoni P, Magini A, Andreini D et al. (2005) Spironolactone improves lung diffusion in chronic heart failure. European heart journal 26(2): 159-164	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions*
Agusti, Antonia, Bonet, Sara, Arnau, Josep Maria et al. (2003) Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction : meta-analysis of randomised clinical trials. Drug safety 26(12): 895-908	- Systematic review indirectly matches the review protocol: used as source of primary studies *Population does not meet protocol definition of HF, no information on LVEF status or background treatment of studies.*
Ahmed, Aymen, Ahmed, Warda, Arshad, Muhammad Sameer et al. (2023) Meta-Analysis Evaluating Risk of Hyperkalemia Stratified by Baseline MRA Usage in Patients with Heart Failure Receiving SGLT2 Inhibitors. Cardiovascular drugs and therapy	- Systematic review indirectly matches the review protocol: used as source of primary studies *3 included trials are a mix of HFrEF and HFpEF populations.*
Akbulut, Mehmet, Ozbay, Yilmaz, Ilkay, Erdogan et al. (2003) Effects of spironolactone and metoprolol on QT dispersion in heart failure. Japanese heart journal 44(5): 681-92	- Study does not contain any outcome data relevant to this review protocol
Albalushi, S., Zarif, A., Karaduman, S. et al. (2023) Effectiveness of SGLT2 inhibitor therapy in treatment of Heart failure: A Meta-Analysis. medRxiv	- Not a peer-reviewed publication *Article specified as 'not peer reviewed.'*
Aleksova, Aneta, Masson, Serge, Maggioni, Aldo P et al. (2012) Effects of Candesartan on Left Ventricular Function, Aldosterone and BNP	- Population not relevant to this review protocol

Study	Exclusion reason
in Chronic Heart Failure. Cardiovascular drugs and therapy 26(6): 131-143	*Mixed EF not matching either reduced or mildly reduced ejection fraction definitions. Results are not separated.*
Al-Gobari, M, El Khatib, C, Pillon, F et al. (2013) β-Blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. BMC cardiovascular disorders 13: 52	- Duplicate reference *Duplicate of an excluded study*
Al-Gobari, Muaamar, El Khatib, Chadia, Pillon, Francois et al. (2013) beta-Blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. BMC cardiovascular disorders 13: 52	- Systematic review indirectly matches the review protocol: used as source of primary studies *Population was comprised of participants with EF ranging 16-62%.*
Al-Hesayen, Abdul, Azevedo, Eduardo R, Floras, John S et al. (2005) Selective versus nonselective beta-adrenergic receptor blockade in chronic heart failure: differential effects on myocardial energy substrate utilization. European journal of heart failure 7(4): 618-23	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Ali, S.M. (2024) Safety of Dapagliflozinin Reducing Cardiac Events and Deaths among NYHA Class II and III Cardiac Failure Patients. Pakistan Journal of Medical and Health Sciences 18(1): 35	- Duration of follow up <3 months
Almansouri, Naiela E, Bakkannavar, Saloni, Faheem, Youmna et al. (2024) Efficacy of Angiotensin Receptor-Neprilysin Inhibitor and Its Renal Outcome in Heart Failure Patients: A Systematic Review of Randomized Clinical Trials. Cureus 16(2): e54501	- Systematic review indirectly matches the review protocol: used as source of primary studies *Systematic Review checked - no additional studies identified*
Al-Raheem, H.S.L., Al-Atrakji, M.Q.Y.M.-A., Hussein, M.F. et al. (2022) LISINOPRIL VERSUS LOSARTAN IN PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION: A COMPARATIVE STUDY. Biochemical and Cellular Archives 22(1): 623-630	- Population not relevant to this review protocol *Mixed EF not matching either reduced or mildly reduced ejection fraction definitions* - Study does not contain any outcome data relevant to this review protocol
Al-Temani, A.H., Abutalebqisi, E.M., Ahmed, I.E. et al. (2020) Dapagliflozin effects on hospitalization for heart failure reduction, and major adverse cardiovascular events. Australasian Medical Journal 13(1): 16-25	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies
Alyassi, A., Lokeskumar, Mohamed, A. et al. (2024) THE FUTURE OF HEART FAILURE MANAGEMENT: EMERGING THERAPIES AND TECHNOLOGIES. Journal of Population Therapeutics and Clinical Pharmacology 31(11): 254	- Population not relevant to this review protocol *Population comprised of different types of heart failure, congestive heart failure, and other populations not relevant to this review protocol.*

Study	Exclusion reason
Alyassi, A., Panneerselvam, A., Arshad, A. et al. (2024) HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF): TREATMENT OPTIONS AND PATIENT OUTCOMES. Journal of Population Therapeutics and Clinical Pharmacology 31(11): 1346	- Population not relevant to this review protocol *Population comprised of HFpEF participants*
Amano, Masashi, Izumi, Chisato, Watanabe, Hiroki et al. (2023) Effects of Long-Term Carvedilol Therapy in Patients With ST-Segment Elevation Myocardial Infarction and Mildly Reduced Left Ventricular Ejection Fraction. The American journal of cardiology 199: 50-58	- Population not relevant to this review protocol *Mildly reduced EF but all post MI and no CHF diagnosis*
Amat-Santos, Ignacio J, Lopez-Otero, Diego, Nombela-Franco, Luis et al. (2024) Ramipril After Transcatheter Aortic Valve Implantation in Patients Without Reduced Ejection Fraction: The RASTAVI Randomized Clinical Trial. Journal of the American Heart Association 13(19): e035460	- Population not relevant to this review protocol *Population comprised of preserved ejection fraction*
Ambrosio, Giuseppe, Flather, Marcus D, Bohm, Michael et al. (2011) beta-blockade with nebivolol for prevention of acute ischaemic events in elderly patients with heart failure. Heart (British Cardiac Society) 97(3): 209-14	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Ambrosy, A.P., Chang, A.J., Davison, B. et al. (2024) Titration of Medications After Acute Heart Failure Is Safe, Tolerated, and Effective Regardless of Risk. JACC: Heart Failure 12(9): 1566	- Secondary publication of an included study that does not provide any additional relevant information *STRONG HF: stratified by MAGGIC risk score and not by LVEF*
Ambrosy, Andrew P, Braunwald, Eugene, Morrow, David A et al. (2020) Angiotensin Receptor-Neprilysin Inhibition Based on History of Heart Failure and Use of Renin-Angiotensin System Antagonists. Journal of the American College of Cardiology 76(9): 1034-1048	- Duration of follow up <3 months *Duration 8 weeks*
Ambrosy, Andrew P, Sauer, Andrew J, Patel, Shachi et al. (2024) Baseline kidney function and the effects of dapagliflozin on health status in heart failure in DEFINE-HF and PRESERVED-HF. ESC heart failure	- Population not relevant to this review protocol *IPD of DEFINE-HF (reduced) and PRESERVE-HF (preserved), no results split by LVEF*
Ameri, Pietro, De Marzo, Vincenzo, Zoccai, Giuseppe Biondi et al. (2022) Efficacy of new medical therapies in patients with heart failure, reduced ejection fraction, and chronic kidney disease already receiving neurohormonal inhibitors: a network meta-analysis. European heart journal. Cardiovascular pharmacotherapy 8(8): 768-776	- Systematic review does not contain a protocol intervention *NMA does not include all interventions specified in the protocol*
Anand IS, Bishu K, Rector TS et al. (2009) Proteinuria, chronic kidney disease, and the	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. Circulation 120(16): 1577-1584	*HFrEF: not combination treatment in control group*
Anand, Inder S, Latini, Roberto, Florea, Viorel G et al. (2005) C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation 112(10): 1428-34	- Study design not relevant to this review protocol *Prognostic study - predictive value of C-reactive protein for long-term outcomes*
Andersen, Camilla Fuchs, Larsen, Julie Hempel, Jensen, Jesper et al. (2024) Empagliflozin to elderly and obese patients with increased risk of developing heart failure: Study protocol for the Empire Prevent trial program. American heart journal 271: 84-96	- Protocol for an excluded study *Protocol for study focussed on prevention*
Anderson, JL, Lutz, JR, Gilbert, EM et al. (1985) A randomized trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. The American journal of cardiology 55(4): 471-475	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Angelico-Goncalves, A., Leite, A.R., Neves, J.S. et al. (2023) Changes in health-related quality of life and treatment effects in chronic heart failure: a meta-analysis. International Journal of Cardiology 386: 65-73	- Systematic review indirectly matches the review protocol: used as source of primary studies *Does not report comparisons relevant to the protocol.*
Anker, Stefan D, Butler, Javed, Filippatos, Gerasimos et al. (2021) Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. Circulation 143(4): 337-349	- Population not relevant to this review protocol *Reduced LVEF*
Anker, Stefan D, Khan, Muhammad Shahzeb, Butler, Javed et al. (2023) Weight change and clinical outcomes in heart failure with reduced ejection fraction: insights from EMPEROR-Reduced. European journal of heart failure 25(1): 117-127	- Study does not contain any outcome data relevant to this review protocol
Anonymous (2000) Correction: Effects of An Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. The New England journal of medicine 342(10): 748	- Publication type not relevant to review protocol *Article correction only*
Anonymous (2004) Trial finds candesartan reduces cardiovascular deaths and hospital admissions in people with heart failure, but may not affect all cause mortality. Evidence-based cardiovascular medicine 8(1): 94-100	- Publication type not relevant to review protocol *Commentary only*
Anonymous (2024) The Role of SGLT2 Inhibitors on Heart Failure Outcomes in Nondiabetic Patients: A Systematic Review and	- Publication type not relevant to review protocol *Erratum*

Study	Exclusion reason
Meta-Analysis of Randomized Controlled Trials Erratum. Journal of cardiovascular pharmacology 83(4): 359	
Anonymous. (2004) Individualising heart failure patients to beta-blocker therapy. Cardiovascular journal of South Africa : official journal for Southern Africa Cardiac Society [and] South African Society of Cardiac Practitioners 15(2): 88-91	- Conference abstract
Ansara, A J; Kolanczyk, D M; Koehler, J M (2016) Neprilysin inhibition with sacubitril/valsartan in the treatment of heart failure: mortality bang for your buck. Journal of clinical pharmacy and therapeutics 41(2): 119-27	- Review article but not a systematic review *Narrative review*
Arnold, J Malcolm O, Yusuf, Salim, Young, James et al. (2003) Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (HOPE) Study. Circulation 107(9): 1284-90	- Population not relevant to this review protocol *The included patients were those who were at risk of cardiovascular events. Heart failure was listed as an excluded event.*
Aronow, WS; Ahn, C; Kronzon, I (1997) Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. The American journal of cardiology 80(2): 207-209	- Population not relevant to this review protocol *Preserved ejection fraction*
Arrigo, M., Biegus, J., Asakage, A. et al. (2023) Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure in elderly patients: A sub-analysis of the STRONG-HF randomized clinical trial. European Journal of Heart Failure 25(7): 1145-1155	- Secondary publication of an included study that does not provide any additional relevant information *HFrEF: STRONG-HF sub-study based on age*
Arrigo, Mattia, Davison, Beth, Edwards, Christopher et al. (2024) Characteristics, treatment, and outcomes of early vs. late enrollees of the STRONG-HF trial. American heart journal 274: 119-129	- Population not relevant to this review protocol *Acute HF*
Arshad, Muhammad Sameer, Ahmed, Aymen, Ejaz, Arooba et al. (2022) Effect of mineralocorticoid receptor antagonist at baseline on the efficacy of sodium-glucose cotransporter-2 inhibitors in patients with heart failure: a meta-analysis of randomized controlled trials. European journal of preventive cardiology 29(14): e334-e337	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included post hoc studies and all interventions focused on SGLT2i.*
Arvunescu, A.M., Dumitrescu, S.I., Zaharia, O. et al. (2024) DO ARNI AND SGLT2 INHIBITORS HAVE AN IMPACT ON	- Study design not relevant to this review protocol

Study	Exclusion reason
INFLAMMATION IN CHRONIC HEART FAILURE?. Archives of the Balkan Medical Union 59(3): 259	*Retrospective cohort*
Asakura, Masanori, Ito, Shin, Yamada, Takahisa et al. (2022) Efficacy and Safety of Early Initiation of Eplerenone Treatment in Patients with Acute Heart Failure (EARLIER trial): a multicentre, randomized, double-blind, placebo-controlled trial. European heart journal. Cardiovascular pharmacotherapy 8(2): 108-117	- Population not relevant to this review protocol *Reduced LVEF*
Asakura, Masanori, Yamamoto, Haruko, Asai, Kuniya et al. (2015) Rationale and Design of the Double-Blind, Randomized, Placebo-Controlled Multicenter Trial on Efficacy of Early Initiation of Eplerenone Treatment in Patients with Acute Heart Failure (EARLIER). Cardiovascular drugs and therapy 29(2): 179-85	- Population not relevant to this review protocol *Reduced LVEF*
Balmforth, Craig, Simpson, Joanne, Shen, Li et al. (2019) Outcomes and Effect of Treatment According to Etiology in HFrEF: An Analysis of PARADIGM-HF. JACC. Heart failure 7(6): 457-465	- Secondary publication of an included study that does not provide any additional relevant information *PARADIGM-HF*
Banerjee, Mainak, Maisnam, Indira, Pal, Rimesh et al. (2023) Mineralocorticoid receptor antagonists with sodium-glucose co-transporter-2 inhibitors in heart failure: a meta-analysis. European heart journal 44(37): 3686-3696	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Search strategy not provided*
Bangalore, Sripal; Kumar, Sunil; Messerli, Franz H (2013) When conventional heart failure therapy is not enough: angiotensin receptor blocker, direct renin inhibitor, or aldosterone antagonist?. Congestive heart failure (Greenwich, Conn.) 19(3): 107-15	- Systematic review in area where more recent reviews are available *Search conducted in 2011*
Bano, Shehar, Bai, Pooja, Kumar, Sameet et al. (2021) Comparison of Sacubitril/Valsartan Versus Enalapril in the Management of Heart Failure. Cureus 13(7): e16332	- Population not relevant to this review protocol *HFrEF: Patients were treatment naïve and were given one class of drugs.*
Baral, Nischit, Gautam, Swotantra, Yadav, Saroj A et al. (2021) Pharmacotherapies in Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Cureus 13(2): e13604	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included HFmrEF and HFpEF studies and non-protocol interventions.*
Barnes, Brian J and Howard, Patricia A (2005) Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure. The Annals of pharmacotherapy 39(1): 68-76	- Publication type not relevant to review protocol *Letter*
Barr CS, Lang CC, Hanson J et al. (1995) Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to	- Duration of follow up <3 months

Study	Exclusion reason
coronary artery disease. The American journal of cardiology 76(17): 1259-1265	
Bart, BA, Ertl, G, Held, P et al. (1999) Contemporary management of patients with left ventricular systolic dysfunction. Results from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Registry. European heart journal 20(16): 1182-1190	- Study design not relevant to this review protocol *Registry*
Baruch, Lawrence, Glazer, Robert D, Aknay, Nora et al. (2004) Morbidity, mortality, physiologic and functional parameters in elderly and non-elderly patients in the Valsartan Heart Failure Trial (Val-HeFT). American heart journal 148(6): 951-7	- Population not relevant to this review protocol *Elderly subgroup not in line with protocol (based on ages 65 years or older)*
Basile, Christian, Paolillo, Stefania, Gargiulo, Paola et al. (2023) Sacubitril/valsartan reduces cardiac decompensation in heart failure with preserved ejection fraction: a meta-analysis. Journal of cardiovascular medicine (Hagerstown, Md.) 24(1): 44-51	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included studies with HFmrEF and HFpEF populations*
Bazoukis, George, Papadatos, Stamatis S, Thomopoulos, Costas et al. (2021) Impact of SGLT2 inhibitors on major clinical events and safety outcomes in heart failure patients: a meta-analysis of randomized clinical trials. Journal of geriatric cardiology : JGC 18(10): 783-795	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *The review included studies with HFmrEF and HFrEF populations. However, the EF definition used was not in line with the protocol.*
Beldhuis, Iris E, Streng, Koen W, Ter Maaten, Jozine M et al. (2017) Renin-Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction: A Meta-Analysis of Published Study Data. Circulation. Heart failure 10(2)	- Systematic review indirectly matches the review protocol: used as source of primary studies *The pooled results are from different classes of drugs*
Belenkov, IuN, Skvortsov, AA, Mareev, VIu et al. (2003) Clinical, hemodynamic and neurohumoral effects of long-term therapy of patients with severe chronic heart failure with beta-adrenoblocker bisoprolol. Kardiologiia 43(10): 10-21	- Study not reported in English *Non-English language study*
Beller B, Bulle T, Bourge RC et al. (1995) Lisinopril versus placebo in the treatment of heart failure: the Lisinopril Heart Failure Study Group. Journal of clinical pharmacology 35(7): 673-680	- Population not relevant to this review protocol *Mixed LVEF; mean not stated* - Study does not contain an intervention relevant to this review protocol *For HFrEF review: no combination treatment*
Berardi, Cecilia, Braunwald, Eugene, Morrow, David A et al. (2020) Angiotensin-Neprilysin	- Duration of follow up <3 months *Follow-up period was 8 weeks*

Study	Exclusion reason
Inhibition in Black Americans: Data From the PIONEER-HF Trial. JACC. Heart failure 8(10): 859-866	
Berbenetz, Nicolas M and Mrkobrada, Marko (2016) Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC cardiovascular disorders 16(1): 246	- Systematic review indirectly matches the review protocol: used as source of primary studies *The review included studies with HFmrEF and HFrEF populations with various study definitions and did not meet the protocol.*
Berezin, AE (2001) Losartan in the therapy of heart failure patients. Asian cardiovascular & thoracic annals 9(4): 302-307	- Study does not contain any outcome data relevant to this review protocol
Berezin, AE (2002) Angiotensin-II receptor antagonist losartan dose-dependently improves the left ventricular remodelling in patients with congestive heart failure. Journal of clinical and basic cardiology 5(1): 83-86	- Study does not contain any outcome data relevant to this review protocol
Berg, David D, Jhund, Pardeep S, Docherty, Kieran F et al. (2021) Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients With Heart Failure With Reduced Ejection Fraction. JAMA cardiology 6(5): 499-507	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis for cardiovascular death and worsening HF*
Berry, Colin, Murphy, Niamh F, De Vito, Giuseppe et al. (2007) Effects of aldosterone receptor blockade in patients with mild-moderate heart failure taking a beta-blocker. European journal of heart failure 9(4): 429-34	- Population not relevant to this review protocol *Reduced LVEF*
Bhatt, Ankeet S, Kosiborod, Mikhail N, Vaduganathan, Muthiah et al. (2023) Effect of dapagliflozin on health status and quality of life across the spectrum of ejection fraction: Participant-level pooled analysis from the DAPA-HF and DELIVER trials. European journal of heart failure 25(7): 981-988	- Population not relevant to this review protocol *Pooled analysis of HFrEF and HFmrEF studies for SGLT2i (SGLT2i not included in HFmrEF protocol)*
Bhatt, Ankeet S, Vaduganathan, Muthiah, Claggett, Brian L et al. (2021) Effect of sacubitril/valsartan vs. enalapril on changes in heart failure therapies over time: the PARADIGM-HF trial. European journal of heart failure 23(9): 1518-1524	- Study does not contain any outcome data relevant to this review protocol
Bhattacharjee, Priyadarshini and Khan, Zahid (2023) Sacubitril/Valsartan in the Treatment of Heart Failure With Reduced Ejection Fraction Focusing on the Impact on the Quality of Life: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Cureus 15(11): e48674	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies
Bian, X, Ma, J, Su, Q et al. (2024) The efficacy of sacubitril/valsartan in patients receiving	- Population not relevant to this review protocol

Study	Exclusion reason
peritoneal dialysis with diabetes and heart failure with preserved ejection fraction. Clinical nephrology 102(5): 295-305	*preserved EF*
Biegus, J., Mebazaa, A., Davison, B. et al. (2024) Effects of Rapid Uptitration of Neurohormonal Blockade on Effective, Sustainable Decongestion and Outcomes in STRONG-HF. Journal of the American College of Cardiology 84(4): 323	- Study does not contain any outcome data relevant to this review protocol *No protocol outcomes; no additional info to main STRONG-HF paper*
Biegus, Jan, Voors, Adriaan A, Collins, Sean P et al. (2023) Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. European heart journal 44(1): 41-50	- Population not relevant to this review protocol *Patients admitted to hospital with the primary diagnosis of acute heart failure*
Biering-Sorensen, Tor, Lassen, Mats C Hojbjerg, Shah, Amil et al. (2023) The Effect of Sacubitril/Valsartan on Left Ventricular Myocardial Deformation in Heart Failure with Preserved Ejection Fraction (PARAMOUNT trial). Journal of cardiac failure 29(6): 968-973	- Study does not contain any outcome data relevant to this review protocol *HFmrEF*
Blanchet, Martine, Sheppard, Richard, Racine, Normand et al. (2005) Effects of angiotensin-converting enzyme inhibitor plus irbesartan on maximal and submaximal exercise capacity and neurohumoral activation in patients with congestive heart failure. American heart journal 149(5): 938e1-7	- Study does not contain any outcome data relevant to this review protocol
Boeuf-Gibot, Sylvaine, Pereira, Bruno, Imbert, Jeremy et al. (2021) Benefits and adverse effects of ACE inhibitors in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis. European journal of clinical pharmacology 77(3): 321-329	- Systematic review indirectly matches the review protocol: used as source of primary studies
Böhm M, Pogue J, Kindermann I et al. (2014) Effect of comorbidities on outcomes and angiotensin converting enzyme inhibitor effects in patients with predominantly left ventricular dysfunction and heart failure. European journal of heart failure 16(3): 325-333	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Bohm, Michael, Anker, Stefan D, Butler, Javed et al. (2021) Empagliflozin Improves Cardiovascular and Renal Outcomes in Heart Failure Irrespective of Systolic Blood Pressure. Journal of the American College of Cardiology 78(13): 1337-1348	- Secondary publication of an included study that does not provide any additional relevant information
Bohm, Michael, Young, Robin, Jhund, Pardeep S et al. (2017) Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. European heart journal 38(15): 1132-1143	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis. No additional information*

Study	Exclusion reason
Bonet S, Agustí A, Arnau JM et al. (2000) Beta-adrenergic blocking agents in heart failure: benefits of vasodilating and non-vasodilating agents according to patients' characteristics: a meta-analysis of clinical trials. Archives of internal medicine 160(5): 621-627	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies
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	- Population not relevant to this review protocol *Preserved LVEF- LVEF ≥50%*
Bouzamondo, A, Hulot, JS, Sanchez, P et al. (2001) Beta-blocker treatment in heart failure. Fundamental & clinical pharmacology 15(2): 95-109	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *No reporting of a systematic search or assessment of quality of evidence*
Bouzamondo, Anissa, Hulot, Jean-Sebastien, Sanchez, Paola et al. (2003) Beta-blocker benefit according to severity of heart failure. European journal of heart failure 5(3): 281-9	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *No reporting of systematic search and assessment of quality of evidence*
Bowling CB, Sanders PW, Allman RM et al. (2013) Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. International journal of cardiology 167(1): 151-156	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Brahmbhatt, D.H., Ross, H.J., O'Sullivan, M. et al. (2024) The Effect of Using a Remote Patient Management Platform in Optimizing Guideline-Directed Medical Therapy in Heart Failure Patients: A Randomized Controlled Trial. JACC: Heart Failure 12(4): 678	- Study does not contain an intervention relevant to this review protocol *Remote medical therapy titration*
Brehm, Bernhard R, Wolf, Sabine C, Gorner, Sandra et al. (2002) Effect of nebivolol on left ventricular function in patients with chronic heart failure: a pilot study. European journal of heart failure 4(6): 757-63	- Study does not contain any outcome data relevant to this review protocol
Bristow, MR, Gilbert, EM, Abraham, WT et al. (1996) Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 94(11): 2807-2816	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Bristow, MR, O'Connell, JB, Gilbert, EM et al. (1994) Dose-response of chronic beta-blocker treatment in heart failure from either idiopathic	- Study does not contain an intervention relevant to this review protocol *Bucindolo*

Study	Exclusion reason
dilated or ischemic cardiomyopathy. Bucindolol Investigators. Circulation 89(4): 1632-1642	
Brophy JM; Joseph L; Rouleau JL (2001) Beta-blockers in congestive heart failure. A Bayesian meta-analysis. Annals of internal medicine 134(7): 550-560	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies
Brown, AJM, Lang, C, McCrimmon, R et al. (2017) Does dapagliflozin regress left ventricular hypertrophy in patients with type 2 diabetes? A prospective, double-blind, randomised, placebo-controlled study. BMC cardiovascular disorders 17(1): 229	- Population not relevant to this review protocol *Not CHF*
Bulluck, H., Frohlich, G.M., Nicholas, J.M. et al. (2019) Mineralocorticoid receptor antagonist pre-treatment and early post-treatment to minimize reperfusion injury after ST-elevation myocardial infarction: The MINIMIZE STEMI trial. American Heart Journal 211: 60-67	- Population not relevant to this review protocol *MI patients (patients with heart failure or LVEF ≤40% were excluded)*
Burnett, Heather, Earley, Amy, Voors, Adriaan A et al. (2017) Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta-Analysis. Circulation. Heart failure 10(1)	- Systematic review indirectly matches the review protocol: used as source of primary studies *Not all included studies meet protocol for LVEF (mixed LVEF) or follow-up*
Butler, J., Zannad, F., Fitchett, D. et al. (2019) Empagliflozin improves kidney outcomes in patients with or without heart failure insights from the Empa-Reg OUTCOME trial. Circulation: Heart Failure 12(6): e005875	- Population not relevant to this review protocol *LVEF not stated*
Butler, Javed, Anker, Stefan D, Filippatos, Gerasimos et al. (2021) Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. European heart journal 42(13): 1203-1212	- Population not relevant to this review protocol *Reduced LVEF*
Butler, Javed, Packer, Milton, Siddiqi, Tariq Jamal et al. (2023) Efficacy of Empagliflozin in Patients With Heart Failure Across Kidney Risk Categories. Journal of the American College of Cardiology 81(19): 1902-1914	- Secondary publication of an included study that does not provide any additional relevant information *HFrEF and HFpEF are pooled*
Butler, Javed, Usman, Muhammad Shariq, Khan, Muhammad Shahzeb et al. (2020) Efficacy and safety of SGLT2 inhibitors in heart failure: systematic review and meta-analysis. ESC heart failure 7(6): 3298-3309	- Study does not contain an intervention relevant to this review protocol *Specific SGLT2i not licensed in the UK*
Butler, Javed, Zannad, Faiez, Fitchett, David et al. (2019) Empagliflozin Improves Kidney Outcomes in Patients With or Without Heart Failure. Circulation. Heart failure 12(6): e005875	- Population not relevant to this review protocol *Provided HF definition was inadequate*

Study	Exclusion reason
Butt, Jawad H, Adamson, Carly, Docherty, Kieran F et al. (2021) Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to N-Terminal Pro-B-Type Natriuretic Peptide: Insights From the DAPA-HF Trial. Circulation. Heart failure 14(12): e008837	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis of DAPA-HF based on Baseline NT-proBNP Quartile. After cross-referenced with parent study now excluded as there are no extra outcomes/analyses of relevance to the protocol.*
Butt, Jawad H, Dewan, Pooja, DeFilippis, Ersilia M et al. (2022) Effects of Dapagliflozin According to the Heart Failure Collaboratory Medical Therapy Score: Insights From DAPA-HF. JACC. Heart failure 10(8): 543-555	- Secondary publication of an included study that does not provide any additional relevant information *No additional outcomes outside of parent study.*
Butt, Jawad H, Dewan, Pooja, Jhund, Pardeep S et al. (2022) Sacubitril/Valsartan and Frailty in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology 80(12): 1130-1143	- Secondary publication of an included study that does not provide any additional relevant information *PARAGON-HF: no HFmrEF subgroup data*
Butt, Jawad H, Dewan, Pooja, Merkely, Bela et al. (2022) Efficacy and Safety of Dapagliflozin According to Frailty in Heart Failure With Reduced Ejection Fraction : A Post Hoc Analysis of the DAPA-HF Trial. Annals of internal medicine 175(6): 820-830	- Secondary publication of an included study that does not provide any additional relevant information *Study evaluates the safety and efficacy of dapagliflozin according to the frailty status using Frailty index. Reports quality of life scores using KCCQ in relation to the frailty index. 8 months KCCQ scores are reported in supplemental data*
Butt, Jawad H, Docherty, Kieran F, Claggett, Brian L et al. (2023) Dapagliflozin in Black and White Patients With Heart Failure Across the Ejection Fraction Spectrum. JACC. Heart failure 11(4): 375-388	- Population not relevant to this review protocol *Pooled population with HFrEF and HFpEF participants*
Butt, Jawad H, Docherty, Kieran F, Petrie, Mark C et al. (2021) Efficacy and Safety of Dapagliflozin in Men and Women With Heart Failure With Reduced Ejection Fraction: A Prespecified Analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial. JAMA cardiology 6(6): 678-689	- Secondary publication of an included study that does not provide any additional relevant information
Butt, Jawad H, Henderson, Alasdair D, Jhund, Pardeep S et al. (2024) Finerenone, Obesity, and Heart Failure With Mildly Reduced/Preserved Ejection Fraction: Prespecified Analysis of FINEARTS-HF. Journal of the American College of Cardiology	- Population not relevant to this review protocol *Does not meet protocol defn for mrEF (30-40% with <50%LVEF)*
Butt, Jawad H, Jhund, Pardeep S, Docherty, Kieran F et al. (2024) Dapagliflozin and Timing of Prior Heart Failure Hospitalization: A Patient-Level Meta-Analysis of DAPA-HF and DELIVER. JACC. Heart failure 12(9): 1586-1599	- Population not relevant to this review protocol *No additional data that meets protocol (mixed reduced and preserved population)*

Study	Exclusion reason
Butt, Jawad H, McMurray, John J V, Claggett, Brian L et al. (2024) Therapeutic Effects of Heart Failure Medical Therapies on Standardized Kidney Outcomes: Comprehensive Individual Participant-Level Analysis of 6 Randomized Clinical Trials. Circulation 150(23): 1858-1868	- Population not relevant to this review protocol *Mixed LVEF studies* - Study does not contain any outcome data relevant to this review protocol *Does not meet protocol outcome definitions*
Butt, Jawad H, Nicolau, Jose C, Verma, Subodh et al. (2021) Efficacy and safety of dapagliflozin according to aetiology in heart failure with reduced ejection fraction: insights from the DAPA-HF trial. European journal of heart failure 23(4): 601-613	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis of DAPA-HF based on ischaemic or non-ischaemic aetiology. After cross-ref with parent study now excluded because no extra outcomes/analyses relevant to protocol.*
Butzner, Michael, Riello, Ralph J 3rd, Sarocco, Phil et al. (2022) Adverse drug effects across patients with heart failure: a systematic review. The American journal of managed care 28(3): e113-e120	- Systematic review indirectly matches the review protocol: used as source of primary studies
Cadrin-Tourigny, Julia, Shohoudi, Azadeh, Roy, Denis et al. (2017) Decreased Mortality With Beta-Blockers in Patients With Heart Failure and Coexisting Atrial Fibrillation: An AF-CHF Substudy. JACC. Heart failure 5(2): 99-106	- Study design not relevant to this review protocol *Not an RCT*
Cai, Ru-Ping; Xu, Yu-Li; Su, Qiang (2021) Dapagliflozin in Patients with Chronic Heart Failure: A Systematic Review and Meta-Analysis. Cardiology research and practice 2021: 6657380	- Systematic review indirectly matches the review protocol: used as source of primary studies *Studies included participants with mixed LVEF status*
Califf, Robert M, Lokhnygina, Yuliya, Velazquez, Eric J et al. (2009) Usefulness of beta blockers in high-risk patients after myocardial infarction in conjunction with captopril and/or valsartan (from the VALsartan In Acute Myocardial Infarction [VALIANT] trial). The American journal of cardiology 104(2): 151-7	- Population not relevant to this review protocol *Acute MI*
Camilli, Massimiliano, Lombardi, Marco, Chiabrando, Juan G et al. (2021) Sodium-Glucose Cotransporter Inhibitors Reduce Mortality and Morbidity in Patients With Heart Failure: Evidence From a Meta-Analysis of Randomized Trials. American journal of therapeutics 29(2): e199-e204	- Systematic review does not contain a protocol intervention *Sotaglifozin not specified in the protocol.*
Cannon, Jane A, Collier, Timothy J, Shen, Li et al. (2015) Clinical outcomes according to QRS duration and morphology in the Eplerenone in Mild Patients: Hospitalization and SurvIval Study	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
in Heart Failure (EMPHASIS-HF). European journal of heart failure 17(7): 707-16	
Cannon, Jane A, Shen, Li, Jhund, Pardeep S et al. (2016) Clinical outcomes according to QRS duration and morphology in the irbesartan in patients with heart failure and preserved systolic function (I-PRESERVE) trial. European journal of heart failure 18(8): 1021-31	- Population not relevant to this review protocol *Mixed LVEF* - Study does not contain an intervention relevant to this review protocol *Not licensed for CHF*
Cao, Yang, Li, Pengxiao, Li, Yi et al. (2022) Sodium-glucose cotransporter-2 inhibitors in heart failure: an updated meta-analysis. ESC heart failure 9(3): 1942-1953	- Systematic review does not contain a protocol intervention *Specific SGLT2i not licensed in the UK for HF*
Cardoso, Rhanderson, Graffunder, Fabrissio P, Ternes, Caique M P et al. (2021) SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis. EClinicalMedicine 36: 100933	- Systematic review indirectly matches the review protocol: used as source of primary studies *5 of the included studies use SGLT2i not licensed for CHF in UK, studies in a mixture of reduced and preserved LVEF patients*
Carson P, Ziesche S, Johnson G et al. (1999) Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. Journal of cardiac failure 5(3): 178-187	- Study does not contain an intervention relevant to this review protocol *Isosorbide dinitrate/hydralazine*
Carson, Peter, Massie, Barry M, McKelvie, Robert et al. (2005) The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial: rationale and design. Journal of cardiac failure 11(8): 576-85	- Comparator in study does not match that specified in this review protocol *Not licensed for CHF* - Population not relevant to this review protocol *Mixed LVEF*
Carson, Peter; Tognoni, Gianni; Cohn, Jay N (2003) Effect of Valsartan on hospitalization: results from Val-HeFT. Journal of cardiac failure 9(3): 164-71	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Castagno D, Jhund PS, McMurray JJ et al. (2010) Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. European journal of heart failure 12(6): 607-616	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Celutkiene, J., Cerlinskaite-Bajore, K., Cotter, G. et al. (2024) Impact of Rapid Up-Titration of Guideline-Directed Medical Therapies on Quality of Life: Insights from the STRONG-HF Trial. Circulation: Heart Failure 17(4): e011221	- Study does not contain any outcome data relevant to this review protocol *Identified in rerun. Reports on QoL from STRONG-HF but does not clearly provide*

Study	Exclusion reason
	additional info that's not already in evidence review.
Celutkiene, Jelena, Cerlinskaite-Bajore, Kamile, Cotter, Gad et al. (2024) Insights on prevalence and incidence of anemia and rapid up-titration of oral heart failure treatment from the STRONG-HF study. Clinical research in cardiology : official journal of the German Cardiac Society 113(11): 1589-1603	- Secondary publication of an included study that does not provide any additional relevant information *STRONG HF: no extra data and not stratified by LVEF*
Cerlinskaite-Bajore, K., Lam, C.S.P., Sliwa, K. et al. (2023) Sex-specific analysis of the rapid up-titration of guideline-directed medical therapies after a hospitalization for acute heart failure: Insights from the STRONG-HF trial. European Journal of Heart Failure 25(7): 1156-1165	- Secondary publication of an included study that does not provide any additional relevant information *HFrEF: STRONG-HF sub-study based on sex*
Cha, DH, Cha, YS, Kook, JH et al. (1998) Clinical Efficacy of Carvedilol in Patients with Moderate to Severe Congestive Heart Failure. Korean circulation journal 28(4): 523-531	- Study not reported in English *Non-English language study*
Chahoud, Georges and Joseph, Jacob (2003) Beta-blockade in chronic heart failure: does it work in everyone?. Current opinion in cardiology 18(5): 400-5	- Review article but not a systematic review *Narrative review*
Chambergo-Michilot, Diego; Tauma-Arrue, Astrid; Loli-Guevara, Silvana (2021) Effects and safety of SGLT2 inhibitors compared to placebo in patients with heart failure: A systematic review and meta-analysis. International journal of cardiology. Heart & vasculature 32: 100690	- Systematic review indirectly matches the review protocol: used as source of primary studies *Several included studies had baseline LVEF >40%, and HF with rEF or mrEF was not defined clearly as per the inclusion criteria*
Chan, Anna K Y, Sanderson, John E, Wang, Tian et al. (2007) Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. Journal of the American College of Cardiology 50(7): 591-6	- Population not relevant to this review protocol *Reduced LVEF*
Chandra, Alvin, Lewis, Eldrin F, Claggett, Brian L et al. (2018) Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of the PARADIGM-HF Trial. JAMA cardiology 3(6): 498-505	- Secondary publication of an included study that does not provide any additional relevant information
Chandra, Alvin, Polanczyk, Carisi A, Claggett, Brian L et al. (2022) Health-related quality of life outcomes in PARAGON-HF. European journal of heart failure 24(12): 2264-2274	- Population not relevant to this review protocol *Was considered for inclusion using the <57% LVEF subgroup, but another study Solomon 2020 includes a subgroup that meets the protocol more closely. So excluded based on population (LVEF too high to meet protocol)*

Study	Exclusion reason
Chandra, Alvin, Vaduganathan, Muthiah, Lewis, Eldrin F et al. (2019) Health-Related Quality of Life in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial. JACC. Heart failure 7(10): 862-874	- Secondary publication of an included study that does not provide any additional relevant information *PARAGON-HF baseline QoL data*
Charuel, Elodie, Menini, Thibault, Bedhomme, Sabrina et al. (2021) Benefits and adverse effects of sacubitril/valsartan in patients with chronic heart failure: A systematic review and meta-analysis. Pharmacology research & perspectives 9(5): e00844	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Study characteristics detail was limited and some trials were not relevant due to short follow up periods.*
Chatterjee, S., Biondi-Zoccai, G., Abbate, A. et al. (2013) Benefits of blockers in patients with heart failure and reduced ejection fraction: Network meta-analysis. BMJ (Online) 346(7893): f55	- Comparator in study does not match that specified in this review protocol *NMA of within-class comparisons*
Chatterjee, Saurav, Biondi-Zoccai, Giuseppe, Abbate, Antonio et al. (2013) Benefits of beta blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMJ (Clinical research ed.) 346: f55	- Systematic review in area where more recent reviews are available *Review from 2013*
Chatur, Safia, Beldhuis, Iris E, Claggett, Brian L et al. (2024) Sacubitril/Valsartan in Patients With Heart Failure and Deterioration in eGFR to <30 mL/min/1.73 m<ovid:sup>2</ovid:sup>. JACC. Heart failure 12(10): 1692-1703	- Secondary publication of an included study that does not provide any additional relevant information *Analysis of PARAGON-HF and PARADIGM-HF but no extra info*
Chatur, Safia, Claggett, Brian L, McCausland, Finnian R et al. (2023) Variation in Renal Function Following Transition to Sacubitril/Valsartan in Patients With Heart Failure. Journal of the American College of Cardiology 81(15): 1443-1455	- Secondary publication of an included study that does not provide any additional relevant information
Chatur, Safia, Neuen, Brendon L, Claggett, Brian L et al. (2024) Effects of Sacubitril/Valsartan Across the Spectrum of Renal Impairment in Patients With Heart Failure. Journal of the American College of Cardiology 83(22): 2148-2159	- Secondary publication of an included study that does not provide any additional relevant information
Chatur, Safia, Vaduganathan, Muthiah, Claggett, Brian L et al. (2023) Dapagliflozin in Patients With Heart Failure and Deterioration in Renal Function. Journal of the American College of Cardiology 82(19): 1854-1863	- Population not relevant to this review protocol *Combined HFrEF and HFpEF population*
Chen, Chengcong, Peng, Hong, Li, Mingzhu et al. (2021) Patients With Type 2 Diabetes Mellitus and Heart Failure Benefit More From Sodium-Glucose Cotransporter 2 Inhibitor: A Systematic Review and Meta-Analysis. Frontiers in endocrinology 12: 664533	- Systematic review indirectly matches the review protocol: used as source of primary studies *Study populations comprised of mixed LVEF status patients*

Study	Exclusion reason
Chen, Jiao, Jiang, Chunxia, Guo, Man et al. (2024) Effects of SGLT2 inhibitors on cardiac function and health status in chronic heart failure: a systematic review and meta-analysis. Cardiovascular diabetology 23(1): 2	- Systematic review does not contain a protocol comparison *Dose comparison*
Chen, KangYu, Nie, Zhiqiang, Shi, Rui et al. (2023) Time to Benefit of Sodium-Glucose Cotransporter-2 Inhibitors Among Patients With Heart Failure. JAMA network open 6(8): e2330754	- Data not reported in an extractable format or a format that can be analysed *Reported in time to benefit format*
Chen, Wen-Wen, Jiang, Juan, Gao, Jie et al. (2023) Efficacy and safety of low-dose sacubitril/valsartan in heart failure patients: A systematic review and meta-analysis. Clinical cardiology 46(3): 296-303	- Population not relevant to this review protocol *Participants not identified as either HFmrEF or HFrEF*
Chen, X., Wang, L., Li, H. et al. (2022) Clinical benefit of sodium-glucose transport protein-2 inhibitors in patients with heart failure: An updated meta-analysis and trial sequential analysis. Frontiers in Cardiovascular Medicine 9: 1067806	- Systematic review indirectly matches the review protocol: used as source of primary studies *Includes HFrEF and HFrEF and SGLTs not licenced in CHF*
Chen, Xiaogen, Jin, Chunna, Xie, Lan et al. (2020) LCZ696 and preservation of renal function in heart failure: A meta-analysis of 6 randomized trials. Reviews in cardiovascular medicine 21(1): 113-118	- Systematic review indirectly matches the review protocol: used as source of primary studies *Includes participants with HFrEF and HFpEF.*
Chen, Yan, He, Qian, Mo, Dun-Chang et al. (2022) The angiotensin receptor and neprilysin inhibitor, LCZ696, in heart failure: A meta-analysis of randomized controlled trials. Medicine 101(41): e30904	- Systematic review does not contain a protocol comparison
Chen, Zhi-Hao, Jiang, Yu-Rong, Peng, Jia-Qin et al. (2016) Clinical effects of combined treatment by optimal dose of furosemide and spironolactone on diastolic heart failure in elderly patients. Experimental and therapeutic medicine 11(3): 890-894	- Duration of follow up <3 months *Follow-up was 1 month*
Cheng, Judy W M and Nayar, Monica (2009) A review of heart failure management in the elderly population. The American journal of geriatric pharmacotherapy 7(5): 233-49	- Review article but not a systematic review *Narrative review*
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 17(11): e012437	- Population not relevant to this review protocol *Preserved LVEF*
Chimura, Misato, Wang, Xiaowen, Jhund, Pardeep S et al. (2024) Finerenone in Women and Men With Heart Failure With Mildly	- Population not relevant to this review protocol *LVEF too preserved*

Study	Exclusion reason
Reduced or Preserved Ejection Fraction: A Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial. JAMA cardiology	
Chin, Ken Lee, Collier, Timothy, Pocock, Stuart et al. (2019) Impact of eplerenone on major cardiovascular outcomes in patients with systolic heart failure according to baseline heart rate. Clinical research in cardiology : official journal of the German Cardiac Society 108(7): 806-814	- Study design not relevant to this review protocol *Post hoc analysis*
Chioncel O, Davison B, Adamo M et al. (2023) Non-cardiac comorbidities and intensive up-titration of oral treatment in patients recently hospitalized for heart failure: Insights from the STRONG-HF trial. European journal of heart failure 25(11): 1994-2006	- Secondary publication of an included study that does not provide any additional relevant information *HFrEF: STRONG-HF comorbidity subgroups*
Chizzola, Paulo Roberto, Goncalves de Freitas, Humberto Felicio, Marinho, Norma Vasconcelos Saldanha et al. (2006) The effect of beta-adrenergic receptor antagonism in cardiac sympathetic neuronal remodeling in patients with heart failure. International journal of cardiology 106(1): 29-34	- Study does not contain any outcome data relevant to this review protocol
Cice, G, Di Benedetto, A, D'Isa, S et al. (2006) Effect of telmisartan added to angiotensin converting enzyme inhibitors in reducing morbidity and mortality in haemodialysis patients with chronic heart failure. Journal of hypertension - supplement 24(suppl): 56	- Full text unavailable
Cice, Gennaro, Di Benedetto, Attilio, D'Isa, Salvatore et al. (2010) Effects of telmisartan added to Angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. Journal of the American College of Cardiology 56(21): 1701-8	- Population not relevant to this review protocol *Haemodialysis patients*
Cice, Gennaro, Ferrara, Luigi, D'Andrea, Antonello et al. (2003) Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. Journal of the American College of Cardiology 41(9): 1438-44	- Population not relevant to this review protocol *Population is dilated cardiomyopathy due to haemodialysis*
Cicoira, M, Zanolla, L, Rossi, A et al. (2002) Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. Journal of the American College of Cardiology 40(2): 304-310	- Population not relevant to this review protocol *Reduced LVEF*
Clark, Andrew L, Coats, Andrew J S, Krum, Henry et al. (2017) Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
COPERNICUS trial. Journal of cachexia, sarcopenia and muscle 8(4): 549-556	
Clark, Hannah; Krum, Henry; Hopper, Ingrid (2014) Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. European journal of heart failure 16(1): 41-8	- Systematic review indirectly matches the review protocol: used as source of primary studies *Combining ACEI, ARB and MRA interventions all together. Population of each included study does not meet population requirements of the protocol*
Clark, Katherine A A, Victoria-Castro, Angela M, Ghazi, Lama et al. (2024) Rationale, Design, and Patient Characteristics of a Cluster-Randomized Pragmatic Trial to Improve Mineralocorticoid Antagonist Use. JACC. Heart failure 12(2): 322-332	- Study does not contain an intervention relevant to this review protocol *Tailored best practice alert*
Cleland JG, Armstrong P, Horowitz JD et al. (1999) Baseline clinical characteristics of patients recruited into the assessment of treatment with lisinopril and survival study. European journal of heart failure 1(1): 73-79	- Comparator in study does not match that specified in this review protocol *Dose comparison*
Cleland JG, Tendera M, Adamus J et al. (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. European heart journal 27(19): 2338-2345	- Population not relevant to this review protocol *Preserved ejection fraction*
Cleland, J G F, Pennell, D J, Ray, S G et al. (2003) Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet (London, England) 362(9377): 14-21	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination therapy in both arms*
Cleland, JG, Tendera, M, Adamus, J et al. (1999) Perindopril for elderly people with chronic heart failure: the PEP-CHF study. The PEP investigators. European journal of heart failure 1(3): 211-217	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Cocco, Giuseppe; Kohn, Sophia; Sfrisi, Claudio (2003) Comparison of the Effects of Cilazapril and of the Combination of Cilazapril Plus Valsartan in Patients with Advanced Heart Failure. Heart Drug 2(6): 286-294	- Duration of follow up <3 months
Cohen Solal, Alain, Jondeau, Guillaume, Beauvais, Florence et al. (2004) Beneficial effects of carvedilol on angiotensin-converting enzyme activity and renin plasma levels in patients with chronic heart failure. European journal of heart failure 6(4): 463-6	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Cohen-Solal A, Kotecha D, van Veldhuisen DJ et al. (2009) Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
function: insights from the SENIORS trial. European journal of heart failure 11(9): 872-880	*HFrEF: not combination treatment in control group*
Cohen-Solal, Alain, McMurray, John J V, Swedberg, Karl et al. (2008) Benefits and safety of candesartan treatment in heart failure are independent of age: insights from the Candesartan in Heart failure--Assessment of Reduction in Mortality and morbidity programme. European heart journal 29(24): 3022-8	- Secondary publication of an included study that does not provide any additional relevant information
Cohen-Solal, Alain, Rouzet, Francois, Berdeaux, Alain et al. (2005) Effects of carvedilol on myocardial sympathetic innervation in patients with chronic heart failure. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 46(11): 1796-803	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Cohn JN, Archibald DG, Francis GS et al. (1987) Veterans Administration Cooperative Study on Vasodilator Therapy of Heart Failure: influence of prerandomization variables on the reduction of mortality by treatment with hydralazine and isosorbide dinitrate. Circulation 75(5 Pt 2): IV49	- Study does not contain an intervention relevant to this review protocol *Isosorbide dinitrate/hydralazine*
Cohn JN; Tognoni G; (2001) A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. The New England journal of medicine 345(23): 1667-1675	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Cohn, Jay N, Anand, Inder S, Latini, Roberto et al. (2003) Sustained reduction of aldosterone in response to the angiotensin receptor blocker valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial. Circulation 108(11): 1306-9	- Study does not contain any outcome data relevant to this review protocol
Cohn, JN, Fowler, MB, Bristow, MR et al. (1997) Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. Journal of cardiac failure 3(3): 173-179	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Cohn, JN, Johnson, G, Ziesche, S et al. (1991) A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. The New England journal of medicine 325(5): 303-310	- Comparator in study does not match that specified in this review protocol *Hydralazine-isosorbide*
Cohn, JN, Tognoni, G, Glazer, RD et al. (1999) Rationale and design of the Valsartan Heart Failure Trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. Journal of cardiac failure 5(2): 155-160	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
Collier TJ, Pocock SJ, McMurray JJ et al. (2013) The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASIS-HF trial. European heart journal 34(36): 2823-2829	- Study design not relevant to this review protocol *Non-randomised risk-tool derivation study*
Colucci, WS, Packer, M, Bristow, MR et al. (1996) Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. Circulation 94(11): 2800-2806	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Cotter G, Davison B, Metra M et al. (2021) Amended STRONG-HF study design. European journal of heart failure 23(11): 1981-1982	- Population not relevant to this review protocol *Reduced LVEF*
Cotter, G., Deniau, B., Davison, B. et al. (2024) Optimization of Evidence-Based Heart Failure Medications After an Acute Heart Failure Admission A Secondary Analysis of the STRONG-HF Randomized Clinical Trial. JAMA Cardiology 9(2): 165	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis of STRONG-HF focussing on doses*
Cowley AJ, Stainer K, Wynne RD et al. (1986) Symptomatic assessment of patients with heart failure: double-blind comparison of increasing doses of diuretics and captopril in moderate heart failure. Lancet (London, England) 2(8510): 770-772	- Duration of follow up <3 months
Crozier, I, Ikram, H, Awan, N et al. (1995) Losartan in heart failure. Hemodynamic effects and tolerability. Losartan Hemodynamic Study Group. Circulation 91(3): 691-697	- Study does not contain any outcome data relevant to this review protocol
Cunningham, Jonathan W, Claggett, Brian L, O'Meara, Eileen et al. (2020) Effect of Sacubitril/Valsartan on Biomarkers of Extracellular Matrix Regulation in Patients With HFpEF. Journal of the American College of Cardiology 76(5): 503-514	- Study does not contain any outcome data relevant to this review protocol
Curtain, James P, Adamson, Carly, Docherty, Kieran F et al. (2023) Prevalent and Incident Anemia in PARADIGM-HF and the Effect of Sacubitril/Valsartan. JACC. Heart failure 11(7): 749-759	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis. Subgroup based on anaemia status*
Curtain, James P, Docherty, Kieran F, Jhund, Pardeep S et al. (2021) Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. European heart journal 42(36): 3727-3738	- Study does not contain any outcome data relevant to this review protocol
Damman, Kevin, Gori, Mauro, Claggett, Brian et al. (2018) Renal Effects and Associated Outcomes During Angiotensin-Neprilysin	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
Inhibition in Heart Failure. JACC. Heart failure 6(6): 489-498	*Post hoc analysis, no additional information*
Damman, Kevin, Perez, Ana C, Anand, Inder S et al. (2014) Worsening renal function and outcome in heart failure patients with preserved ejection fraction and the impact of angiotensin receptor blocker treatment. Journal of the American College of Cardiology 64(11): 1106-13	- Population not relevant to this review protocol *Preserved LVEF*
Dargie HJ (2001) Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet (London, England) 357(9266): 1385-1390	- Population not relevant to this review protocol *Acute MI*
Dayi, Sennur Unal, Akbulut, Tamer, Akgoz, Haldun et al. (2005) Long-term combined therapy with losartan and an angiotensin-converting enzyme inhibitor improves functional capacity in patients with left ventricular dysfunction. Acta cardiologica 60(4): 373-7	- Study design not relevant to this review protocol *Non-randomised study*
de Boer, Rudolf A, Doehner, Wolfram, van der Horst, Iwan C C et al. (2010) Influence of diabetes mellitus and hyperglycemia on prognosis in patients > or =70 years old with heart failure and effects of nebivolol (data from the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure [SENIORS]). The American journal of cardiology 106(1): 78-86e1	- Secondary publication of an included study that does not provide any additional relevant information
de Boer, Rudolf A, Nunez, Julio, Kozlovski, Plamen et al. (2020) Effects of the dual sodium-glucose linked transporter inhibitor, licogliflozin vs placebo or empagliflozin in patients with type 2 diabetes and heart failure. British journal of clinical pharmacology 86(7): 1346-1356	- Population not relevant to this review protocol *Preserved LVEF*
De Marzo, Vincenzo, Savarese, Gianluigi, Tricarico, Lucia et al. (2022) Network meta-analysis of medical therapy efficacy in more than 90,000 patients with heart failure and reduced ejection fraction. Journal of internal medicine 292(2): 333-349	- Systematic review does not contain a protocol intervention
de Milliano, PA, de Groot, AC, Tijssen, JG et al. (2002) Beneficial effects of metoprolol on myocardial sympathetic function: evidence from a randomized, placebo-controlled study in patients with congestive heart failure. American heart journal 144(2): e3	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
de Simone, G, Chinali, M, Mureddu, G F et al. (2011) Effect of canrenone on left ventricular mechanics in patients with mild systolic heart failure and metabolic syndrome: the AREA-in-CHF study. Nutrition, metabolism, and cardiovascular diseases : NMCD 21(10): 783-91	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
De Tommasi, Elisabetta, Iacoviello, Massimo, Romito, Roberta et al. (2003) Comparison of the effect of valsartan and lisinopril on autonomic nervous system activity in chronic heart failure. American heart journal 146(5): e17	- Study does not contain any outcome data relevant to this review protocol
DE Vecchis, Renato and Ariano, Carmelina (2017) Aldosterone receptor antagonists decrease mortality and cardiovascular hospitalizations in chronic heart failure with reduced left ventricular ejection fraction, but not in chronic heart failure with preserved left ventricular ejection fraction: a meta-analysis of randomized controlled trials. Minerva cardioangiologica 65(4): 427-442	- Article retracted
De Vecchis, Renato and Ariano, Carmelina (2017) Differential efficacy profile of aldosterone receptor antagonists, depending on the type of chronic heart failure, whether with reduced or preserved left ventricular ejection fraction-results of a meta-analysis of randomized controlled trials. Cardiovascular diagnosis and therapy 7(3): 272-287	- Article retracted
De Vecchis, Renato, Cantatrione, Claudio, Mazzei, Damiana et al. (2017) The Impact Exerted on Clinical Outcomes of Patients With Chronic Heart Failure by Aldosterone Receptor Antagonists: A Meta-Analysis of Randomized Controlled Trials. Journal of clinical medicine research 9(2): 130-142	- Systematic review indirectly matches the review protocol: used as source of primary studies *Subgroup analyses by HFrEF and HFpEF but no definitions for these provided; not all included interventions clearly meet protocol. Included studies published 2014 or earlier.*
Deedwania PC, Gottlieb S, Ghali JK et al. (2004) Efficacy, safety and tolerability of beta-adrenergic blockade with metoprolol CR/XL in elderly patients with heart failure. European heart journal 25(15): 1300-1309	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Deedwania, Prakash C, Giles, Thomas D, Klibaner, Michael et al. (2005) Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. American heart journal 149(1): 159-67	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Demers, Catherine, McMurray, John J V, Swedberg, Karl et al. (2005) Impact of candesartan on nonfatal myocardial infarction and cardiovascular death in patients with heart failure. JAMA 294(14): 1794-8	- Publication type not relevant to review protocol *Brief report*
Desai AS, Lewis EF, Li R 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	- Population not relevant to this review protocol *LVEF ≥45% and mean not reported*

Study	Exclusion reason
heart failure and preserved ejection fraction. American heart journal 162(6): 966-972.e10	
Desai AS, Swedberg K, McMurray JJ et al. (2007) Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. Journal of the American College of Cardiology 50(20): 1959-1966	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis using retrospective outcome definition for "clinically important hyperkalemia."*
Desai, Akshay S, Jhund, Pardeep S, Claggett, Brian L et al. (2022) Effect of Dapagliflozin on Cause-Specific Mortality in Patients With Heart Failure Across the Spectrum of Ejection Fraction: A Participant-Level Pooled Analysis of DAPA-HF and DELIVER. JAMA cardiology 7(12): 1227-1234	- Secondary publication of an included study that does not provide any additional relevant information *DAPA-HF*
Desai, Akshay S, McMurray, John J V, Packer, Milton et al. (2015) Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. European heart journal 36(30): 1990-7	- Secondary publication of an included study that does not provide any additional relevant information *PARADIGM-HF*
Desai, Akshay S, Solomon, Scott D, Shah, Amil M et al. (2019) Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA 322(11): 1077-1084	- Population not relevant to this review protocol *Reduced LVEF*
Desai, Akshay S, Solomon, Scott, Claggett, Brian et al. (2016) Factors Associated With Noncompletion During the Run-In Period Before Randomization and Influence on the Estimated Benefit of LCZ696 in the PARADIGM-HF Trial. Circulation. Heart failure 9(6)	- Study does not contain any outcome data relevant to this review protocol
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	- Population not relevant to this review protocol *LVEF too preserved*
Desai, Akshay S, Vaduganathan, Muthiah, Cleland, John G et al. (2021) Mode of Death in Patients With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF Trial. Circulation. Heart failure 14(12): e008597	- Secondary publication of an included study that does not provide any additional relevant information *PARAGON-HF*
Desai, Akshay S, Vardeny, Orly, Claggett, Brian et al. (2017) Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril: A Secondary Analysis of the PARADIGM-HF Trial. JAMA cardiology 2(1): 79-85	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis, no additional information*

Study	Exclusion reason
Dewan, Pooja, Shen, Li, Pedro Ferreira, Joao et al. (2024) Effect of Sacubitril/Valsartan on Cognitive Function in Patients With Heart Failure With Preserved Ejection Fraction: A Prespecified Analysis of PARAGON-HF. Circulation 150(4): 272-282	- Secondary publication of an included study that does not provide any additional relevant information *Not stratified by LVEF*
Dewan, Pooja, Solomon, Scott D, Jhund, Pardeep S et al. (2020) Efficacy and safety of sodium-glucose co-transporter 2 inhibition according to left ventricular ejection fraction in DAPA-HF. European journal of heart failure 22(7): 1247-1258	- Secondary publication of an included study that does not provide any additional relevant information
Di Lenarda, A, Sabbadini, G, Salvatore, L et al. (1999) Long-term effects of carvedilol in idiopathic dilated cardiomyopathy with persistent left ventricular dysfunction despite chronic metoprolol. The Heart-Muscle Disease Study Group. Journal of the American College of Cardiology 33(7): 1926-1934	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Dickstein K; Kjekshus J; (2002) Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet (London, England) 360(9335): 752-760	- Population not relevant to this review protocol *Unclear heart failure definition and LVEF; acute MI*
Dickstein, K, Chang, P, Willenheimer, R et al. (1995) Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure. Journal of the American College of Cardiology 26(2): 438-445	- Duration of follow up <3 months
Dimopoulos, Konstantinos, Salukhe, Tushar V, Coats, Andrew J S et al. (2004) Meta-analyses of mortality and morbidity effects of an angiotensin receptor blocker in patients with chronic heart failure already receiving an ACE inhibitor (alone or with a beta-blocker). International journal of cardiology 93(23): 105-11	- Systematic review in area where more recent reviews are available *Searches completed in 2003*
Ding, Yuanyuan, Wei, Zufa, Li, Jian et al. (2022) Effects of Metoprolol Succinate Combined with Entresto on Cardiac Function Indexes and Coagulation Function in Patients with Congestive Heart Failure. Computational and mathematical methods in medicine 2022: 9765884	- Article retracted
Dobre, Daniela, Haaijer-Ruskamp, Flora M, Voors, Adriaan A et al. (2007) beta-Adrenoceptor antagonists in elderly patients with heart failure: a critical review of their efficacy and tolerability. Drugs & aging 24(12): 1031-44	- Review article but not a systematic review *Narrative review*

Study	Exclusion reason
Dobre, Daniela, van Jaarsveld, Cornelia H M, deJongste, Mike J L et al. (2007) The effect of beta-blocker therapy on quality of life in heart failure patients: a systematic review and meta-analysis. Pharmacoepidemiology and drug safety 16(2): 152-9	- Systematic review indirectly matches the review protocol: used as source of primary studies *LVEF not reported*
Dobre, Daniela, van Veldhuisen, Dirk J, Goulder, Michael A et al. (2008) Clinical effects of initial 6 months monotherapy with bisoprolol versus enalapril in the treatment of patients with mild to moderate chronic heart failure. Data from the CIBIS III Trial. Cardiovascular drugs and therapy 22(5): 399-405	- Population not relevant to this review protocol *No information regarding EF status*
Dobre, Daniela, van Veldhuisen, Dirk J, Mordenti, Giacomo et al. (2007) Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. American heart journal 154(1): 109-15	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Docherty, Kieran F and McMurray, John J V (2021) SOLOIST-WHF and updated meta-analysis: sodium-glucose co-transporter 2 inhibitors should be initiated in patients hospitalized with worsening heart failure. European journal of heart failure 23(1): 27-30	- Publication type not relevant to review protocol *Commentary*
Docherty, Kieran F, Anand, Inder S, Chiang, Chern-En et al. (2022) Effects of Dapagliflozin in Asian Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. JACC. Asia 2(2): 139-153	- Secondary publication of an included study that does not provide any additional relevant information *Results focus on Asian patients from DAPA-HF trial*
Docherty, Kieran F, Campbell, Ross T, Brooksbank, Katriona J M et al. (2021) Effect of Neprilysin Inhibition on Left Ventricular Remodeling in Patients With Asymptomatic Left Ventricular Systolic Dysfunction Late After Myocardial Infarction. Circulation 144(3): 199-209	- Study does not contain any outcome data relevant to this review protocol
Docherty, Kieran F, Campbell, Ross T, Brooksbank, Katriona J M et al. (2021) Rationale and methods of a randomized trial evaluating the effect of neprilysin inhibition on left ventricular remodelling. ESC heart failure 8(1): 129-138	- Population not relevant to this review protocol *Patients at high risk of heart failure following MI*
Docherty, Kieran F, Henderson, Alasdair D, Jhund, Pardeep S et al. (2025) Efficacy and Safety of Finerenone Across the Ejection Fraction Spectrum in Heart Failure With Mildly Reduced or Preserved Ejection Fraction: A	- Duplicate reference

Study	Exclusion reason
Prespecified Analysis of the FINEARTS-HF Trial. Circulation 151(1): 45-58	
Docherty, Kieran F, Jhund, Pardeep S, Anand, Inder et al. (2020) Effect of Dapagliflozin on Outpatient Worsening of Patients With Heart Failure and Reduced Ejection Fraction: A Prespecified Analysis of DAPA-HF. Circulation 142(17): 1623-1632	- Secondary publication of an included study that does not provide any additional relevant information
Docherty, Kieran F, Jhund, Pardeep S, Bengtsson, Olof et al. (2020) Effect of Dapagliflozin in DAPA-HF According to Background Glucose-Lowering Therapy. Diabetes care 43(11): 2878-2881	- Data not reported in an extractable format or a format that can be analysed *Results reported by antihyperglycemic treatment*
Docherty, Kieran F, Jhund, Pardeep S, Claggett, Brian et al. (2021) Extrapolating Long-term Event-Free and Overall Survival With Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction: An Exploratory Analysis of a Phase 3 Randomized Clinical Trial. JAMA cardiology 6(11): 1298-1305	- Secondary publication of an included study that does not provide any additional relevant information *Exploratory analysis from DAPA-HF extrapolating the estimated long-term treatment effect of dapagliflozin over a patient's lifetime*
Docherty, Kieran F, Jhund, Pardeep S, Inzucchi, Silvio E et al. (2020) Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. European heart journal 41(25): 2379-2392	- Secondary publication of an included study that does not provide any additional relevant information *Subgroup analyses by background treatment in a post-hoc analysis.*
Docherty, Kieran F, Ogunniyi, Modele O, Anand, Inder S et al. (2022) Efficacy of Dapagliflozin in Black Versus White Patients With Heart Failure and Reduced Ejection Fraction. JACC. Heart failure 10(1): 52-64	- Secondary publication of an included study that does not provide any additional relevant information *DAPA-HF stratified by ethnicity*
Doehner, Wolfram, Anker, Stefan D, Butler, Javed et al. (2022) Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial. European heart journal 43(36): 3435-3446	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis exploring association of serum uric acid with study endpoints*
Doehner, Wolfram, Todorovic, Johanna, Kennecke, Cornelia et al. (2012) Improved insulin sensitivity by the angiotensin receptor antagonist irbesartan in patients with systolic heart failure: a randomized double-blinded placebo-controlled study. International journal of cardiology 161(3): 137-42	- Population not relevant to this review protocol *Mixed LVEF* - Study does not contain an intervention relevant to this review protocol *Not licensed for CHF*
Dos Santos, Marcelo Rodrigues, Alves, Maria-Janieire de Nazare Nunes, Jordao, Camila Paixao et al. (2021) Sacubitril/valsartan versus enalapril on exercise capacity in patients with heart failure with reduced ejection fraction: A	- Duration of follow up <3 months *Follow up for 6 weeks*

Study	Exclusion reason
randomized, double-blind, active-controlled study. American heart journal 239: 1-10	
Doughty, RN, Rodgers, A, Sharpe, N et al. (1997) Effects of beta-blocker therapy on mortality in patients with heart failure. A systematic overview of randomized controlled trials. European heart journal 18(4): 560-565	- Systematic review in area where more recent reviews are available *Systematic review published in 1997*
Doughty, RN, Whalley, GA, Gamble, G et al. (2000) Effects of carvedilol on left ventricular regional wall motion in patients with heart failure caused by ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. Journal of cardiac failure 6(1): 11-18	- Study does not contain any outcome data relevant to this review protocol
Doughty, Robert N, Whalley, Gillian A, Walsh, Helen A et al. (2004) Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation 109(2): 201-6	- Study does not contain any outcome data relevant to this review protocol
Driscoll, Andrea, Currey, Judy, Tonkin, Andrew et al. (2015) Nurse-led titration of angiotensin converting enzyme inhibitors, beta-adrenergic blocking agents, and angiotensin receptor blockers for people with heart failure with reduced ejection fraction. The Cochrane database of systematic reviews: cd009889	- Study does not contain an intervention relevant to this review protocol *Nurse-led titration*
Du, Haiping, Li, Xiao, Zhao, Weifang et al. (2022) The Difference between Sacubitril Valsartan and Valsartan on Vascular Endothelial Function, APN, MMP-9, and BNP Levels in Patients with Hypertension and Chronic Heart Failure. Journal of healthcare engineering 2022: 9494981	- Population not relevant to this review protocol *Mixed LVEF* - Study does not contain any outcome data relevant to this review protocol
Duan, Y.; Yu, M.; Xu, Y. (2023) Effect of sacubitril-valsartan on chronic systolic heart failure and its effect on LVEF, 6-MWT, NT proBNP and NT proBNP/BNP levels. Tropical Journal of Pharmaceutical Research 22(6): 1335-1340	- Population not relevant to this review protocol *Mixed LVEF (LVEF <50%; mean not stated); background Rx % not stated*
Dubach, P, Myers, J, Bonetti, P et al. (2002) Effects of bisoprolol fumarate on left ventricular size, function, and exercise capacity in patients with heart failure: analysis with magnetic resonance myocardial tagging. American heart journal 143(4): 676-683	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Ducharme, Anique, Swedberg, Karl, Pfeffer, Marc A et al. (2006) Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis describing the partcipants who had AF and factors asscoiated with AF. AF*

Study	Exclusion reason
Mortality and morbidity (CHARM) program. American heart journal 152(1): 86-92	*is not a subgroup or outcome relevant to the review protocol*
Ducharme, Anique, Swedberg, Karl, Pfeffer, Marc A et al. (2006) Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program. American heart journal 151(5): 985-91	- Duplicate reference
Dulin, Brian R, Haas, Steven J, Abraham, William T et al. (2005) Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. The American journal of cardiology 95(7): 896-8	- Review article but not a systematic review
Dunselman, PH (2001) Effects of the replacement of the angiotensin converting enzyme inhibitor enalapril by the angiotensin II receptor blocker telmisartan in patients with congestive heart failure. The replacement of angiotensin converting enzyme inhibition (REPLACE) investigators. International journal of cardiology 77(23): 131-8; discussion 139	- Study does not contain an intervention relevant to this review protocol *Intervention is a monotherapy*
Edelmann F, Schmidt AG, Gelbrich G 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): 874-882	- Population not relevant to this review protocol *Preserved ejection fraction*
Edelmann F, Wachter R, Schmidt AG 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): 781-791	- Population not relevant to this review protocol *Preserved ejection fraction*
Edelmann, Frank, Holzendorf, Volker, Wachter, Rolf et al. (2015) Galectin-3 in patients with heart failure with preserved ejection fraction: results from the Aldo-DHF trial. European journal of heart failure 17(2): 214-23	- Population not relevant to this review protocol *Overall population is preserved LVEF*
Edelmann, Frank, Jaarsma, Tiny, Comin-Colet, Josep et al. (2020) Rationale and study design of OUTSTEP-HF: a randomised controlled study to assess the effect of sacubitril/valsartan and enalapril on physical activity measured by accelerometry in patients with heart failure with reduced ejection fraction. European journal of heart failure 22(9): 1724-1733	- Population not relevant to this review protocol *Reduced LVEF*

Study	Exclusion reason
Edes I; Gasior Z; Wita K (2005) Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. European journal of heart failure 7(4): 631-639	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Eichhorn, EJ, Heesch, CM, Barnett, JH et al. (1994) Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. Journal of the American College of Cardiology 24(5): 1310-1320	- Study does not contain any outcome data relevant to this review protocol
Elkholey, K., Asad, Z.U.A., Shehata, E. et al. (2024) Association between atrial fibrillation and heart failure patient reported outcomes across the ejection fraction spectrum. American Heart Journal 273: 61	- Study does not contain an intervention relevant to this review protocol *Combines pharmacological and exercise interventions*
Emdin, Connor A, Callender, Tom, Cao, Jun et al. (2015) Meta-Analysis of Large-Scale Randomized Trials to Determine the Effectiveness of Inhibition of the Renin-Angiotensin Aldosterone System in Heart Failure. The American journal of cardiology 116(1): 155-61	- Systematic review indirectly matches the review protocol: used as source of primary studies *Combines multiple classes of drugs together as the intervention (RAAS inhibitors).*
Engelmeier, RS, O'Connell, JB, Walsh, R et al. (1985) Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. Circulation 72(3): 536-546	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment* - Study design not relevant to this review protocol *Cross-over RCT*
Erdmann E, Lechat P, Verkenne P et al. (2001) Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. European journal of heart failure 3(4): 469-479	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Erdmann, E, George, M, Voet, B et al. (2000) The safety and tolerability of candesartan cilexetil in CHF. Journal of the renin-angiotensin-aldosterone system : JRAAS 1suppl1: 31-36	- Systematic review indirectly matches the review protocol: used as source of primary studies *Time period of only 1 study exceeded 3 months*
Eschalier R, McMurray JJ, Swedberg K et al. (2013) Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). Journal of the American College of Cardiology 62(17): 1585-1593	- Population not relevant to this review protocol *Reduced LVEF*

Study	Exclusion reason
Faisal, Sana, Ahmad Ganaie, Zubair, Batool, Saima et al. (2022) The Efficacy of Various Pharmacological Agents on Long-Term Outcomes in Patients With Heart Failure With Preserved Ejection Fraction: A Meta-Analysis of Randomized Control Trials. Cureus 14(8): e28145	- Systematic review indirectly matches the review protocol: used as source of primary studies *Unclear definition for HFpEF / no LVEF specified. Only drug classes used as keywords in the literature search (individual drug names not included as key words). Follow up time ≥1 month.*
Falcao, Luiz Menezes, Pinto, Fausto, Ravara, Luciano et al. (2004) BNP and ANP as diagnostic and predictive markers in heart failure with left ventricular systolic dysfunction. Journal of the renin-angiotensin-aldosterone system : JRAAS 5(3): 121-9	- Study does not contain an intervention relevant to this review protocol *No combination therapy*
Fan, H, Zhang, L, Li, Y et al. (2020) Comparison of the efficacy of sacubitril/valsartan and valsartan in the treatment of patients with heart failure. Pharmaceutical care and research 20(4): 251-254	- Study not reported in English *Non English language study (Chinese)*
Faris R, Flather M, Purcell H et al. (2002) Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. International journal of cardiology 82(2): 149-158	- Systematic review does not contain a protocol intervention *Diuretics*
Farmakis, Dimitrios, Davison, Beth, Fountoulaki, Katerina et al. (2024) Rapid Uptitration of Guideline-Directed Medical Therapies in Acute Heart Failure With and Without Atrial Fibrillation. JACC. Heart failure 12(11): 1845-1858	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis of STRONG-HF focussing on AF*
Fatima Gilani, Syedah Fauzia, Ali, Shabana, Farhat, Kulsoom et al. (2024) Early initiation of Dapagliflozin and its effect on health related quality of life in acute heart failure: a randomised controlled trial. JPMA. The Journal of the Pakistan Medical Association 74(4): 621-625	- Population not relevant to this review protocol *Acute HF, mixed LVEF*
Feng, Yu, Yin, Yongmei, Deng, Rong et al. (2020) Renal safety and efficacy of angiotensin receptor-neprilysin inhibitor: A meta-analysis of randomized controlled trials. Journal of clinical pharmacy and therapeutics 45(6): 1235-1243	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Limited information available. Some included studies had a follow-up period of less than 3 months.*
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	- Population not relevant to this review protocol *Population defined as HFpEF*

Study	Exclusion reason
Ferreira, Joao Pedro, Abreu, Paula, McMurray, John J V et al. (2019) Renal function stratified dose comparisons of eplerenone versus placebo in the EMPHASIS-HF trial. European journal of heart failure 21(3): 345-351	- Secondary publication of an included study that does not provide any additional relevant information *EMPHASIS-HF: renal function stratification*
Ferreira, Joao Pedro, Anker, Stefan D, Butler, Javed et al. (2022) Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced. European journal of heart failure 24(4): 708-715	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis with irrelevant population*
Ferreira, Joao Pedro, Blatchford, Jonathan P, Teerlink, John R et al. (2023) Mineralocorticoid receptor antagonist use and the effects of empagliflozin on clinical outcomes in patients admitted for acute heart failure: Findings from EMPULSE. European journal of heart failure 25(10): 1797-1805	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis with irrelevant population*
Ferreira, Joao Pedro, Blatchford, Jonathan P, Teerlink, John R et al. (2024) Time from admission to randomization and the effect of empagliflozin in acute heart failure: A post-hoc analysis from EMPULSE. European journal of heart failure 26(9): 1976-1983	- Population not relevant to this review protocol *Recruited as acute HF and >30% not reduced LVEF*
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	- Secondary publication of an included study that does not provide any additional relevant information *Pooled analysis with the wrong population*
Ferreira, Joao Pedro, Packer, Milton, Sattar, Naveed et al. (2024) Insulin-like growth factor binding protein-7 concentrations in chronic heart failure: Results from the EMPEROR programme. European journal of heart failure 26(4): 806-816	- Study design not relevant to this review protocol *Primarily a prognostic study. Treatment effect elements not relevant to protocol*
Ferreira, Joao Pedro, Packer, Milton, Sattar, Naveed et al. (2024) Carbohydrate antigen 125 concentrations across the ejection fraction spectrum in chronic heart failure: The EMPEROR programme. European journal of heart failure 26(4): 788-802	- Population not relevant to this review protocol *Post hoc of subset from EMPEROR programme with CA-125 measured - mixed LVEF*
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	- Population not relevant to this review protocol *IPD analysis pooling a range of LVEF*
Ferreira, Joao Pedro, Rossello, Xavier, Pitt, Bertram et al. (2019) Eplerenone in patients with myocardial infarction and "mid-range" ejection fraction: An analysis from the EPHESUS trial. Clinical cardiology 42(11): 1106-1112	- Population not relevant to this review protocol *Acute MI*

Study	Exclusion reason
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	- Population not relevant to this review protocol *Population with preserved LVEF*
Ferreira, Joao Pedro, Zannad, Faiez, Pocock, Stuart J et al. (2021) Interplay of Mineralocorticoid Receptor Antagonists and Empagliflozin in Heart Failure: EMPEROR-Reduced. Journal of the American College of Cardiology 77(11): 1397-1407	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis*
Ferreira, JP, Butler, J, Anker, SD et al. (2023) Effects of empaglifozin on collagen biomarkers in patients with Heart Failure. Findings from the EMPEROR trials. European journal of heart failure	- Study does not contain any outcome data relevant to this review protocol
Filippatos, Gerasimos, Anker, Stefan D, Bohm, Michael et al. (2016) A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. European heart journal 37(27): 2105-14	- Comparator in study does not match that specified in this review protocol *Within class comparison (MRA)*
Filippatos, Gerasimos, Anker, Stefan D, Butler, Javed et al. (2022) Effects of empagliflozin on cardiovascular and renal outcomes in heart failure with reduced ejection fraction according to age: a secondary analysis of EMPEROR-Reduced. European journal of heart failure 24(12): 2297-2304	- Study design not relevant to this review protocol *Post hoc analysis*
Fisher, ML, Gottlieb, SS, Plotnick, GD et al. (1994) Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. Journal of the American College of Cardiology 23(4): 943-950	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Fitchett, David (2009) Results of the ONTARGET and TRANSCEND studies: an update and discussion. Vascular health and risk management 5(1): 21-9	- Publication type not relevant to review protocol *Commentary*
Fitchett, David, Inzucchi, Silvio E, Cannon, Christopher P et al. (2019) Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. Circulation 139(11): 1384-1395	- Population not relevant to this review protocol *Not comprised of HF patients*
Flather MD, Shibata MC, Coats AJ et al. (2005) Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). European heart journal 26(3): 215-225	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*

Study	Exclusion reason
Flather MD, Yusuf S, Køber L et al. (2000) Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet (London, England) 355(9215): 1575-1581	- Systematic review indirectly matches the review protocol: used as source of primary studies
Florea, Viorel G, Rector, Thomas S, Anand, Inder S et al. (2016) Heart Failure With Improved Ejection Fraction: Clinical Characteristics, Correlates of Recovery, and Survival: Results From the Valsartan Heart Failure Trial. Circulation. Heart failure 9(7)	- Secondary publication of an included study that does not provide any additional relevant information *Subgroup analyses of only those with improved EF. All outcomes are biochemical, except survival curves for mortality (check this one does not add anything to Val-HeFT parent study if that is included)*
Foa, Alberto, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Sacubitril/Valsartan-Related Hypotension in Patients With Heart Failure and Preserved or Mildly Reduced Ejection Fraction. Journal of the American College of Cardiology 83(18): 1731-1739	- Population not relevant to this review protocol
Fonarow, GC, Chelimsky-Fallick, C, Stevenson, LW et al. (1992) Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C trial. Journal of the American College of Cardiology 19(4): 842-850	- Comparator in study does not match that specified in this review protocol *Hydralazine-isosorbide*
Fonseca, Candida, Brito, Dulce, Branco, Patricia et al. (2020) Hyperkalemia and management of renin-angiotensin-aldosterone system inhibitors in chronic heart failure with reduced ejection fraction: A systematic review. Revista portuguesa de cardiologia 39(9): 517-541	- Systematic review indirectly matches the review protocol: used as source of primary studies *SR includes observational studies*
Fowler, M.B. (2004) Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial: Carvedilol in severe heart failure. American Journal of Cardiology 93(9suppl1): 35-39	- Population not relevant to this review protocol *Randomisation occurred while the patients were hospitalised (likely acute setting).*
Fox, K M (2003) Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet (London, England) 362(9386): 782-8	- Population not relevant to this review protocol *Not chronic heart failure*
Fu, Qianyu, Zhou, Longhua, Fan, Yuqin et al. (2023) Effect of SGLT-2 inhibitor, dapagliflozin, on left ventricular remodeling in patients with type 2 diabetes and HFrEF. BMC cardiovascular disorders 23(1): 544	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
Fudim, Marat, Cyr, Derek D, Ward, Jonathan H et al. (2024) Association of Sacubitril/Valsartan vs Valsartan With Blood Pressure Changes and Symptomatic Hypotension: the PARAGLIDE-HF Trial. Journal of cardiac failure 30(12): 1568-1577	- Population not relevant to this review protocol *Does not meet population in protocol (preserved LVEF)*
Fukuta, Hidekatsu, Goto, Toshihiko, Wakami, Kazuaki et al. (2021) Effect of beta-blockers on heart failure severity in patients with heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Heart failure reviews 26(1): 165-171	- Systematic review indirectly matches the review protocol: used as source of primary studies
Funck-Brentano, Christian, van Veldhuisen, Dirk J, van de Ven, Louis L M et al. (2011) Influence of order and type of drug (bisoprolol vs. enalapril) on outcome and adverse events in patients with chronic heart failure: a post hoc analysis of the CIBIS-III trial. European journal of heart failure 13(7): 765-72	- Study does not contain an intervention relevant to this review protocol *Monotherapy*
Gager, Gloria M, Gelbenegger, Georg, Jilma, Bernd et al. (2021) Cardiovascular Outcome in Patients Treated With SGLT2 Inhibitors for Heart Failure: A Meta-Analysis. Frontiers in cardiovascular medicine 8: 691907	- Systematic review indirectly matches the review protocol: used as source of primary studies *Inclusion criteria for the studies did not match the protocol eg includes SGLT2i not licensed in CHF in UK, follow-up<3 months, unknown ejection fraction, not all 100% HF at baseline.*
Gallanagh, Siobhan, Castagno, Davide, Wilson, Ben et al. (2011) Evaluation of the functional status questionnaire in heart failure: a sub-study of the second cardiac insufficiency bisoprolol survival study (CIBIS-II). Cardiovascular drugs and therapy 25(1): 77-85	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Gandhi, Purvi S, Goyal, Ramesh K, Jain, Anil R et al. (2007) Beneficial effects of carvedilol as a concomitant therapy to angiotensin-converting enzyme inhibitor in patients with ischemic left ventricular systolic dysfunction. Canadian journal of physiology and pharmacology 85(2): 193-9	- Population not relevant to this review protocol *HF population not defined*
Gao, Juan, Zhao, Cong, Zhang, Wen-Zhong et al. (2023) Efficacy and safety profile of angiotensin receptor neprilysin inhibitors in the management of heart failure: a systematic review and meta-analysis of randomized controlled trials. Heart failure reviews 28(4): 905-923	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Unclear what background treatments were being taken; unclear how HFrEF and HFmrEF were defined*
Gao, Michael, Bhatia, Kirtipal, Kapoor, Arjun et al. (2024) SGLT2 Inhibitors, Functional Capacity, and Quality of Life in Patients With Heart Failure: A Systematic Review and Meta-Analysis. JAMA network open 7(4): e245135	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *SR: no new studies identified*

Study	Exclusion reason
Gao, Xiuren, Peng, Longyun, Adhikari, Chandra M et al. (2007) Spironolactone reduced arrhythmia and maintained magnesium homeostasis in patients with congestive heart failure. Journal of cardiac failure 13(3): 170-7	- Population not relevant to this review protocol *Possibly acute HF setting. LVEF mixed as threshold for reduced LVEF does not match the protocol*
Gasanin, E., Patyna, W., Tajdivand, M. et al. (2011) Exercise capacity, hemodynamic and neurohormonal effects of candesartan cilexetil as add-on therapy to ACE inhibitors in patients with moderate to severe symptomatic congestive heart failure. Perfusion 24(5): 162-170	- Study does not contain any outcome data relevant to this review protocol
Gasanin, Edis, Dragutinovic, Ivana, Bankovic, Dragic et al. (2013) Effects of combination of AT1-antagonist candesartan cilexetil and ACE-inhibitors in patients with congestive heart failure. Srpski arhiv za celokupno lekarstvo 141(12): 29-34	- Study does not contain any outcome data relevant to this review protocol
Gattis, Wendy A; O'Connor, Christopher M; Gheorghiade, Mihai (2002) The Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) Study: design and implications. Reviews in cardiovascular medicine 3suppl3: 48-54	- Population not relevant to this review protocol *Acute HF*
Gayathri, J. and Selvarajan Chettiar, K.P. (2024) Advances in Pharmacotherapy for Heart Failure: A Systematic Review. Research Journal of Pharmacology 18(3): 38	- Review article but not a systematic review *Review article but not a systematic review*
Ge, Ting; Yang, Yang; Zhao, Yanfang (2023) A study of the efficacy of sacubitril/valsartan plus dapagliflozin combination treatment in pulmonary arterial hypertension due to left heart disease. Perfusion 38(8): 1697-1704	- Population not relevant to this review protocol *Mixed LVEF*
Geng, Chang, Mao, Yu-Cheng, Qi, Su-Fen et al. (2023) Mineralocorticoid receptor antagonists for chronic heart failure: a meta-analysis focusing on the number needed to treat. Frontiers in cardiovascular medicine 10: 1236008	- Systematic review indirectly matches the review protocol: used as source of primary studies
Geng, Qiang, Li, Sufang, Wang, Zhengzhong et al. (2019) Efficacy and safety of combined neprilysin and RAS inhibition in heart failure: A meta-analysis of randomized controlled trials. International journal of cardiology 293: 159-164	- Population not relevant to this review protocol *Population characteristics not defined*
Genth-Zotz S, Zotz RJ, Sigmund M et al. (2000) MIC trial: metoprolol in patients with mild to moderate heart failure: effects on ventricular function and cardiopulmonary exercise testing. European journal of heart failure 2(2): 175-181	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
Gerstein, Hertzel C, Swedberg, Karl, Carlsson, Jonas et al. (2008) The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Archives of internal medicine 168(15): 1699-704	- Study does not contain any outcome data relevant to this review protocol
Ghafur, Shakil, Zahid, Md, Sarkar, Haripada et al. (2020) Effect of Angiotensin Receptor-Neprilysin Inhibitor versus Valsartan on Cardiac Status in Patients with Chronic Heart Failure with Reduced Ejection Fraction: A Randomized Clinical Trial in Rangpur Medical College Hospital, Bangladesh. Open Journal of Internal Medicine 10: 21-34	- Population not relevant to this review protocol *Reduced LVEF*
Ghali JK, Wikstrand J, Van Veldhuisen DJ et al. (2009) The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). Journal of cardiac failure 15(4): 310-318	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Ghali, J.K., Pina, I.L., Gottlieb, S.S. et al. (2002) Treating female heart failure patients with metoprolol CR/XL. Cardiology Review 19(12): 29-32	- Study does not contain any outcome data relevant to this review protocol
Ghali, JK, Piña, IL, Gottlieb, SS et al. (2002) Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). Circulation 105(13): 1585-1591	- Duplicate reference
Gheorghiade, Mihai, Gattis, Wendy A, Lukas, Mary Ann et al. (2003) Rationale and design of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study. American heart journal 145(2suppl): 60-1	- Study does not contain an intervention relevant to this review protocol
Gheorghiade, Mihai, Khan, Sadiya, Blair, John E A et al. (2009) The effects of eplerenone on length of stay and total days of heart failure hospitalization after myocardial infarction in patients with left ventricular systolic dysfunction. American heart journal 158(3): 437-43	- Population not relevant to this review protocol *Acute MI*
Ghio, Stefano, Magrini, Giulia, Serio, Alessandra et al. (2006) Effects of nebivolol in elderly heart failure patients with or without systolic left ventricular dysfunction: results of the SENIORS echocardiographic substudy. European heart journal 27(5): 562-8	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
Ghose, JC, Chakraborty, S, Mondal, M et al. (1993) Effect of vasodilator therapy on mortality in chronic congestive heart failure. The Journal of the Association of Physicians of India 41(5): 269-271	- Comparator in study does not match that specified in this review protocol *Hydralazine-isosorbide*
Ghosh-Swaby, Olivia R, Goodman, Shaun G, Leiter, Lawrence A et al. (2020) Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials. The lancet. Diabetes & endocrinology 8(5): 418-435	- Systematic review does not contain a protocol population
Girerd N, Collier T, Pocock S et al. (2015) Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial. European heart journal 36(34): 2310-2317	- Secondary publication of an included study that does not provide any additional relevant information *EMPHASIS-HF: post hoc analysis not relevant to protocol (time since qualifying event)*
Goldstein, S and Hjalmarson, A (1999) The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF Trial. Clinical cardiology 22suppl5: v30-5	- Full text paper not available
Goldstein, S, Fagerberg, B, Hjalmarson, A et al. (2001) Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. Journal of the American College of Cardiology 38(4): 932-938	- Study does not contain any outcome data relevant to this review protocol
Goldstein, S, Kennedy, HL, Hall, C et al. (1999) Metoprolol CR/XL in patients with heart failure: A pilot study examining the tolerability, safety, and effect on left ventricular ejection fraction. American heart journal 138(6pt1): 1158-1165	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Goldstein, Sidney, Deedwania, Prakash, Gottlieb, Stephen et al. (2003) Metoprolol CR/XL in black patients with heart failure (from the Metoprolol CR/XL randomized intervention trial in chronic heart failure). The American journal of cardiology 92(4): 478-80	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Gottlieb, SS, Fisher, ML, Kjekshus, J et al. (2002) Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Circulation 105(10): 1182-1188	- Study does not contain any outcome data relevant to this review protocol
Granger, C B, Ertl, G, Kuch, J et al. (2000) Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors. American heart journal 139(4): 609-17	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*

Study	Exclusion reason
Granger, Christopher B, McMurray, John J V, Yusuf, Salim et al. (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet (London, England) 362(9386): 772-6	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Greenberg, B.H., Mehra, M., Teerlink, J.R. et al. (2006) COMPARE: Comparison of the Effects of Carvedilol CR and Carvedilol IR on Left Ventricular Ejection Fraction in Patients with Heart Failure. American Journal of Cardiology 98(7suppl): 53-59	- Comparator in study does not match that specified in this review protocol *Within drug comparison (immediate release versus controlled release)*
Gremmler, Bernhard, Kisters, Klaus, Kunert, Matthias et al. (2007) Effects of different AT1-receptor antagonists in the therapy of severe heart failure pretreated with ACE inhibitors. Acta cardiologica 62(4): 321-8	- Study does not contain any outcome data relevant to this review protocol
Gremmler, Bernhard, Kunert, Matthias, Kisters, Klaus et al. (2002) Effects of AT1 receptor antagonist therapy in patients with severe heart failure pretreated with angiotensin-converting enzyme inhibitors. Experimental and clinical cardiology 7(4): 193-8	- Study does not contain any outcome data relevant to this review protocol
Groenning, BA; Nilsson, JC; Sondergaard, L (2001) Antiremodeling effects on the left ventricle during beta-blockage with metaprolol in the treatment of chronic heart failure. Congestive heart failure 7(1): 58	- Conference abstract *Abstract only*
Gruner Svealv, Bente, Tang, Margareta Scharin, Waagstein, Finn et al. (2007) Pronounced improvement in systolic and diastolic ventricular long axis function after treatment with metoprolol. European journal of heart failure 9(67): 678-83	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions* - Study does not contain any outcome data relevant to this review protocol
Guan, Xiangfeng, Zhang, Ju, Chen, Guangxin et al. (2023) MRAs may have lost their cornerstone position for heart failure treatment in the age of SGLT-2 inhibitors: A meta-analysis of randomized controlled trials. Heart failure reviews 28(6): 1427-1436	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis with no additional information*
Guazzi, M, Agostoni, P, Matturri, M et al. (1999) Pulmonary function, cardiac function, and exercise capacity in a follow-up of patients with congestive heart failure treated with carvedilol. American heart journal 138(3pt1): 460-467	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
Guo, Zhimin, Wang, Lingjiao, Yu, Jing et al. (2023) The role of SGLT-2 inhibitors on health-related quality of life, exercise capacity, and volume depletion in patients with chronic heart failure: a meta-analysis of randomized controlled trials. International journal of clinical pharmacy 45(3): 547-555	- Systematic review indirectly matches the review protocol: used as source of primary studies
Gupta, Kashvi, Spertus, John A, Birmingham, Mary et al. (2023) Racial Differences in Quality of Life in Patients With Heart Failure Treated With Sodium-Glucose Cotransporter 2 Inhibitors: A Patient-Level Meta-Analysis of the CHIEF-HF, DEFINE-HF, and PRESERVED-HF Trials. Circulation 148(3): 220-228	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included studies have a mixture of HFrEF or HFmrEF and one trial used SGLT2i not licenced for CHF*
Gupta, S.D., Butt, J.H., McMurray, E.G.M. et al. (2024) Effects of sacubitril/valsartan according to background beta-blocker therapy in patients with heart failure and reduced ejection fraction: Insights from PARADIGM-HF. European Journal of Heart Failure	- Secondary publication of an included study that does not provide any additional relevant information *PARADIGM-HF: results according to background BB use*
Haass, Markus, Kitzman, Dalane W, Anand, Inder S et al. (2011) Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circulation. Heart failure 4(3): 324-31	- Study does not contain an intervention relevant to this review protocol *Intervention not licensed for CHF and data licensed drug in this class available*
Halle, Martin, Schobel, Christoph, Winzer, Ephraim B et al. (2021) A randomized clinical trial on the short-term effects of 12-week sacubitril/valsartan vs. enalapril on peak oxygen consumption in patients with heart failure with reduced ejection fraction: results from the ACTIVITY-HF study. European journal of heart failure 23(12): 2073-2082	- Population not relevant to this review protocol *Reduced LVEF*
Hamaguchi, Sanae, Kinugawa, Shintaro, Tsuchihashi-Makaya, Miyuki et al. (2010) Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure. American heart journal 160(6): 1156-62	- Study design not relevant to this review protocol *Non-randomised study*
Hampton, JR, van Veldhuisen, DJ, Kleber, FX et al. (1997) Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Lancet (London, England) 349(9057): 971-977	- Study does not contain an intervention relevant to this review protocol *Ibopamine*
Hamroff, G, Katz, SD, Mancini, D et al. (1999) Addition of angiotensin II receptor blockade to maximal angiotensin-converting enzyme inhibition improves exercise capacity in patients	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
with severe congestive heart failure. Circulation 99(8): 990-992	*HFrEF: not combination treatment in control group*
Hansen, Morten Rix, Hrobjartsson, Asbjorn, Videbaek, Lars et al. (2020) Postponement of Death by Pharmacological Heart Failure Treatment: A Meta-Analysis of Randomized Clinical Trials. The American journal of medicine 133(6): e280-e289	- Systematic review indirectly matches the review protocol: used as source of primary studies *Includes Ivabradine as a drug treatment*
Harrington, Josephine, Fonarow, Gregg C, Khan, Muhammad Shahzeb et al. (2023) Medication-Attributable Adverse Events in Heart Failure Trials. JACC. Heart failure 11(4): 425-436	- Review article but not a systematic review
Hasan, Mohammed Tarek, Awad, Ahmed K, Shih, Mohamed et al. (2023) Meta-Analysis on the Safety and Efficacy of Sodium Glucose Cotransporters 2 Inhibitors in Patients With Heart Failure With and Without Diabetes. The American journal of cardiology 187: 93-99	- Systematic review indirectly matches the review protocol: used as source of primary studies
Haseeb, Muhammad Talha, Nouman Aslam, Muhammad, Avanteeka, Fnu et al. (2023) Comparison of Efficacy and Safety of Angiotensin Receptor-Neprilysin Inhibitors in Patients With Heart Failure With Reduced Ejection Fraction: A Meta-Analysis. Cureus 15(3): e36392	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Insufficient detail provided*
Hassan, Waleed, Nila, Shamima A, Ahmed, Muneeb et al. (2024) Comparative Efficacy and Long-Term Outcomes of Beta-Blockers Alone or in Combination With Angiotensin-Converting Enzyme (ACE) Inhibitors in Chronic Heart Failure: A Systematic Review. Cureus 16(11): e74329	- Systematic review indirectly matches the review protocol: used as source of primary studies *Mixed LVEF, no additional studies identified*
Hawkins, Nathaniel M, MacDonald, Michael R, Petrie, Mark C et al. (2009) Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: a randomized controlled trial. European journal of heart failure 11(7): 684-90	- Study does not contain any outcome data relevant to this review protocol
He, Yong-Ming, Yang, Xiang-Jun, Zhao, Xin et al. (2012) beta-Blockers in heart failure: benefits of beta-blockers according to varying male proportions of study patients. Clinical cardiology 35(8): 505-11	- Systematic review in area where more recent reviews are available *Publication from 2012*
He, Zheng, Sun, Yun, Gao, Hui et al. (2015) Efficacy and safety of supramaximal titrated inhibition of renin-angiotensin-aldosterone system in idiopathic dilated cardiomyopathy. ESC heart failure 2(4): 129-138	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
He, Zhiyu, Yang, Lin, Nie, Yutong et al. (2021) Effects of SGLT-2 inhibitors on health-related quality of life and exercise capacity in heart failure patients with reduced ejection fraction: A systematic review and meta-analysis. International journal of cardiology 345: 83-88	- Systematic review indirectly matches the review protocol: used as source of primary studies *1 of included studies does not meet definition of rEF but there is a QoL reported for relevant 6 studies only. Supplementary material not accessible to assess study quality information*
Heidenreich, P.A., Bozkurt, B., Aguilar, D. et al. (2022) 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. Journal of Cardiac Failure 28(5): e1-e167	- Publication type not relevant to review protocol *Clinical guideline*
Heran, Balraj S, Musini, Vijaya M, Bassett, Ken et al. (2012) Angiotensin receptor blockers for heart failure. The Cochrane database of systematic reviews: cd003040	- Systematic review in area where more recent reviews are available *Searches conducted in 2010*
Herlitz, J, Wikstrand, J, Denny, M et al. (2002) Effects of metoprolol CR/XL on mortality and hospitalizations in patients with heart failure and history of hypertension. Journal of cardiac failure 8(1): 8-14	- Study does not contain any outcome data relevant to this review protocol
Hernandez, Adrian V, Pasupuleti, Vinay, Scarpelli, Nancy et al. (2023) Efficacy and safety of sacubitril/valsartan in heart failure compared to renin-angiotensin-aldosterone system inhibitors: a systematic review and meta-analysis of randomised controlled trials. Archives of medical science : AMS 19(3): 565-576	- Population not relevant to this review protocol *Acute MI and range of chronic HF*
Hey, C.Y., Barra, S., Duehmke, R. et al. (2022) An updated systematic review on heart failure treatments for patients with renal impairment: the tide is not turning. Heart Failure Reviews 27(5): 1761-1777	- Review article but not a systematic review *Not a systematic review- articles from selected studies*
Hirai, R.; Hirai, T.; Fendler, T. (2020) Dapagliflozin improves cardiovascular outcomes in patients with heart failure and reduced ejection fraction. Journal of Clinical Outcomes Management 27(4): 159-160	- Publication type not relevant to review protocol *Commentary on an abstract*
Hjalmarson, A and Fagerberg, B (2000) MERIT-HF mortality and morbidity data. Basic research in cardiology 95suppl1: I98-103	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Hjalmarson, A, Goldstein, S, Fagerberg, B et al. (2000) Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 283(10): 1295-302	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*

Study	Exclusion reason
Hole, Torstein, Froland, Gisle, Gullestad, Lars et al. (2004) Metoprolol CR/XL improves systolic and diastolic left ventricular function in patients with chronic heart failure. Echocardiography (Mount Kisco, N.Y.) 21(3): 215-23	- Study does not contain any outcome data relevant to this review protocol
Hori, Masatsugu, Kitabatake, Akira, Tsutsui, Hiroyuki et al. (2005) Rationale and design of a randomized trial to assess the effects of beta-blocker in diastolic heart failure; Japanese Diastolic Heart Failure Study (J-DHF). Journal of cardiac failure 11(7): 542-7	- Publication type not relevant to review protocol *Protocol for RCT*
Hori, Masatsugu, Sasayama, Shigetake, Kitabatake, Akira et al. (2004) Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. American heart journal 147(2): 324-30	- Population not relevant to this review protocol *Patients who had ischemic and nonischemic cardiomyopathy with stable symptoms*
Houghton, A R, Harrison, M, Cowley, A J et al. (2000) Combined treatment with losartan and an ACE inhibitor in mild to moderate heart failure: results of a double-blind, randomized, placebo-controlled trial. American heart journal 140(5): e25	- Population not relevant to this review protocol *LVEF not clearly reported*
Houghton, AR; Harrison, M; Cowley, AJ (1999) Haemodynamic, neurohumoral and exercise effects of losartan vs. captopril in chronic heart failure: results of an ELITE trial substudy. Evaluation of Losartan in the Elderly. European journal of heart failure 1(4): 385-393	- Study does not contain an intervention relevant to this review protocol *Intervention is a monotherapy*
Houghton, T; Freemantle, N; Cleland, JG (2000) Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomised trials. European journal of heart failure 2(3): 333-340	- Systematic review indirectly matches the review protocol: used as source of primary studies *SR of trials for MI - some of the studies included a number of studies have no patients with HF*
Hryniewicz, Katarzyna, Dimayuga, Clarito, Hudaihed, Alhakam et al. (2005) Inhibition of angiotensin-converting enzyme and phosphodiesterase type 5 improves endothelial function in heart failure. Clinical science (London, England : 1979) 108(4): 331-8	- Comparator in study does not match that specified in this review protocol *Comparison was PDE5 inhibitor*
Hu, Li-jun, Chen, Yun-qing, Deng, Song-bai et al. (2013) Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: a systematic review and meta-analysis. British journal of clinical pharmacology 75(5): 1202-12	- Systematic review indirectly matches the review protocol: used as source of primary studies *Includes quasi RCTs*
Huang, Pingping, Song, Qingya, Wang, Yifei et al. (2022) Effect of arotinolol on chronic heart	- Systematic review does not contain a protocol intervention

Study	Exclusion reason
failure: A systematic review and meta-analysis of randomized controlled trials. Frontiers in cardiovascular medicine 9: 1071387	
Huang, Yun, Fang, Chongbo, Zhang, YuYu et al. (2023) Effectiveness and safety of angiotensin receptor-neprilysin inhibitor and sodium-glucose cotransporter-2 inhibitors for patients with heart failure with reduced ejection fraction: a meta-analysis. Journal of cardiovascular medicine (Hagerstown, Md.) 24(2): 123-131	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies
Hundertmark, Moritz J, Adler, Amanda, Antoniades, Charalambos et al. (2023) Assessment of Cardiac Energy Metabolism, Function, and Physiology in Patients With Heart Failure Taking Empagliflozin: The Randomized, Controlled EMPA-VISION Trial. Circulation 147(22): 1654-1669	- Study does not contain any outcome data relevant to this review protocol
Hundertmark, Moritz J, Agbaje, Olorunsola F, Coleman, Ruth et al. (2021) Design and rationale of the EMPA-VISION trial: investigating the metabolic effects of empagliflozin in patients with heart failure. ESC heart failure 8(4): 2580-2590	- Protocol for an excluded study *EMPA-VISION*
Jackson, Alice M, Dewan, Pooja, Anand, Inder S et al. (2020) Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. Circulation 142(11): 1040-1054	- Secondary publication of an included study that does not provide any additional relevant information
Jain, Anil Ranjeetmal, Aggarwal, Rakesh Kumar, Rao, Nanyam Srinivas et al. (2020) Efficacy and safety of sacubitril/valsartan compared with enalapril in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF India sub-study. Indian heart journal 72(6): 535-540	- Secondary publication of an included study that does not provide any additional relevant information *PARADIGM-HF*
Jain, Arpit, Meyur, Shourya, Wadhwa, Lovish et al. (2023) Effects of Angiotensin Receptor-Neprilysin Inhibitors Versus Enalapril or Valsartan on Patients With Heart Failure: A Systematic Review and Meta-Analysis. Cureus 15(7): e41566	- Systematic review indirectly matches the review protocol: used as source of primary studies *Not all included studies match the protocol.*
Jaiswal, Vikash, Latif, Fakhar, Naz, Sidra et al. (2024) Efficacy of finerenone in reducing heart failure outcomes in patients with history of heart failure: A meta-analysis of randomized controlled trials. International journal of cardiology. Heart & vasculature 55: 101548	- Systematic review indirectly matches the review protocol: used as source of primary studies *SR - not extra studies identified*
James, Stefan, Erlinge, David, Storey, Robert F et al. (2023) Rationale and design of the DAPA-MI trial: Dapagliflozin in patients without	- Population not relevant to this review protocol *Acute MI hospitalised patients.*

Study	Exclusion reason
diabetes mellitus with acute myocardial infarction. American heart journal 266: 188-197	
Janardhanan, Rajesh, Kenchaiah, Satish, Velazquez, Eric J et al. (2006) Extent of coronary artery disease as a predictor of outcomes in acute myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. American heart journal 152(1): 183-9	- Population not relevant to this review protocol *Acute MI patients*
Janosi, Andras, Ghali, Jalal K, Herlitz, Johan et al. (2003) Metoprolol CR/XL in postmyocardial infarction patients with chronic heart failure: experiences from MERIT-HF. American heart journal 146(4): 721-8	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Jansson, K, Dahlström, U, Karlberg, BE et al. (1999) The circulating renin-angiotensin system during treatment with metoprolol or captopril in patients with heart failure due to non-ischaemic dilated cardiomyopathy. Journal of internal medicine 245(5): 435-443	- Population not relevant to this review protocol *No EF details.*
Japp, D., Fisken, S., Japp, A. G. et al. (2014) 14 MINERALOCORTICOID RECEPTOR ANTAGONISTS IN ELDERLY PATIENTS WITH HEART FAILURE: A SYSTEMATIC REVIEW. Age & Ageing 43(suppl1): 4-4	- Conference abstract
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 indirectly matches the review protocol: used as source of primary studies *Unclear reporting. Exclusion criteria says <40% LVEF but the included studies have a range of LVEF that is a mix of rEF, pEFand mrEF.*
Jennings, Douglas L and Thompson, Melissa L (2009) Use of combination therapy with a beta-blocker and milrinone in patients with advanced heart failure. The Annals of pharmacotherapy 43(11): 1872-6	- Review article but not a systematic review *Narrative review*
Jensen, J, Omar, M, Kistorp, C et al. (2021) Metabolic Effects of Empagliflozin in Heart Failure: a Randomized, Double-Blind, and Placebo-Controlled Trial (Empire HF Metabolic). Circulation 143(22): 2208-2210	- Study does not contain any outcome data relevant to this review protocol
Jensen, Jesper, Omar, Massar, Ali, Mulham et al. (2022) The effect of empagliflozin on contractile reserve in heart failure: Prespecified sub-study of a randomized, double-blind, and placebo-controlled trial. American heart journal 250: 57-65	- Study does not contain any outcome data relevant to this review protocol
Jensen, Jesper, Omar, Massar, Kistorp, Caroline et al. (2019) Empagliflozin in heart failure patients with reduced ejection fraction: a	- Population not relevant to this review protocol *Reduced LVEF*

Study	Exclusion reason
randomized clinical trial (Empire HF). Trials 20(1): 374	
Jensen, Jesper, Omar, Massar, Kistorp, Caroline et al. (2020) Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: A double-blinded, randomized, and placebo-controlled trial. American heart journal 228: 47-56	- Population not relevant to this review protocol *Reduced LVEF*
Jensen, Jesper, Omar, Massar, Kistorp, Caroline et al. (2021) Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF Renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. The lancet. Diabetes & endocrinology 9(2): 106-116	- Secondary publication of an included study that does not provide any additional relevant information
Jering, Karola S, Claggett, Brian, Pfeffer, Marc A et al. (2021) Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. European journal of heart failure 23(6): 1040-1048	- Population not relevant to this review protocol *Acute MI and prior HF*
Jering, Karola S, Zannad, Faiez, Claggett, Brian et al. (2021) Cardiovascular and Renal Outcomes of Mineralocorticoid Receptor Antagonist Use in PARAGON-HF. JACC. Heart failure 9(1): 13-24	- Population not relevant to this review protocol *Was considered for inclusion using the <57% LVEF subgroup, but another study Solomon 2020 includes a subgroup that meets the protocol more closely. So excluded based on population (LVEF too high to meet protocol)*
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 *Mixed LVEF and HF not defined*
Jhund, Pardeep S, Claggett, Brian, Packer, Milton et al. (2014) Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. European journal of heart failure 16(6): 671-7	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions*
Jhund, Pardeep S, Fu, Michael, Bayram, Edmundo et al. (2015) Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. European heart journal 36(38): 2576-84	- Secondary publication of an included study that does not provide any additional relevant information
Jhund, Pardeep S, Kondo, Toru, Butt, Jawad H et al. (2022) Dapagliflozin across the range of	- Population not relevant to this review protocol

Study	Exclusion reason
ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nature medicine 28(9): 1956-1964	*Mixed ejection fraction (pooled analysis of patient level data from DAPA-HF and DELIVER)*
Jhund, Pardeep S, Ponikowski, Piotr, Docherty, Kieran F et al. (2021) Dapagliflozin and Recurrent Heart Failure Hospitalizations in Heart Failure With Reduced Ejection Fraction: An Analysis of DAPA-HF. Circulation 143(20): 1962-1972	- Population not relevant to this review protocol *Reduced LVEF*
Jhund, Pardeep S, Solomon, Scott D, Docherty, Kieran F et al. (2021) Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. Circulation 143(4): 298-309	- Population not relevant to this review protocol *Reduced LVEF*
Jhund, PS, Talebi, A, Henderson, AD et al. (2024) Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. Lancet (London, England) 404(10458): 1119-1131	- Study does not contain any outcome data relevant to this review protocol *Considered for inclusion but only reports on a composite outcome for the relevant subgroup, that is not in the protocol. No need to include because review has other studies that report on relevant non-composite outcomes that directly meet the protocol.*
Ji, Peng-Juan, Zhang, Zhuo-Ya, Yan, Qi et al. (2023) The cardiovascular effects of SGLT2 inhibitors, RAS inhibitors, and ARN inhibitors in heart failure. ESC heart failure 10(2): 1314-1325	- Systematic review indirectly matches the review protocol: used as source of primary studies
Ji, Qing (2023) A meta-analysis investigating the efficacy and adverse events linked to sacubitril-valsartan in various heart failure subtypes. Clinical cardiology	- Systematic review indirectly matches the review protocol: used as source of primary studies *Not all studies meet the inclusion criteria*
Johnson, G, Carson, P, Francis, G S et al. (1993) Influence of prerandomization (baseline) variables on mortality and on the reduction of mortality by enalapril. Veterans Affairs Cooperative Study on Vasodilator Therapy of Heart Failure (V-HeFT II). V-HeFT VA Cooperative Studies Group. Circulation 87(6suppl): vi32-9	- Comparator in study does not match that specified in this review protocol *Hydralazine*
Jong, Philip, Demers, Catherine, McKelvie, Robert S et al. (2002) Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. Journal of the American College of Cardiology 39(3): 463-70	- Systematic review indirectly matches the review protocol: used as source of primary studies - Systematic review does not contain sufficient detail for included studies: used as source of primary studies

Study	Exclusion reason
Kalogeropoulos, Andreas P, Thankachen, Jincy, Butler, Javed et al. (2020) Diuretic and renal effects of spironolactone and heart failure hospitalizations: a TOPCAT Americas analysis. European journal of heart failure 22(9): 1600-1610	- Population not relevant to this review protocol *Preserved ejection fraction*
Kamath, Sandeep A and Yancy, Clyde W (2005) beta-Blocker therapy for congestive heart failure: clinical considerations. Postgraduate medicine 118(6supplbetablockers): 12-20	- Publication type not relevant to review protocol *Commentary*
Kang, Duk-Hyun, Park, Sung-Ji, Shin, Sung-Hee et al. (2019) Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation. Circulation 139(11): 1354-1365	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions*
Kang, Huaning, Zhang, Jinhua, Zhang, Xiaoting et al. (2020) Effects of sacubitril/valsartan in patients with heart failure and chronic kidney disease: A meta-analysis. European journal of pharmacology 884: 173444	- Systematic review indirectly matches the review protocol: used as source of primary studies
Kang, Yu, Yang, Zi-Xuan, Liu, Lu-Lu et al. (2022) ARNI or ARB Treats Residual Left Ventricular Remodelling after Surgery for Valvular Regurgitation: ReReRe study protocol. ESC heart failure 9(5): 3585-3592	- Population not relevant to this review protocol *Mixed LVEF and primary heart valve disease*
Kao, David P, Lewsey, James D, Anand, Inder S et al. (2015) Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. European journal of heart failure 17(9): 925-35	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions*
Kao, David P, Lowes, Brian D, Gilbert, Edward M et al. (2015) Therapeutic Molecular Phenotype of beta-Blocker-Associated Reverse-Remodeling in Nonischemic Dilated Cardiomyopathy. Circulation. Cardiovascular genetics 8(2): 270-83	- Study does not contain any outcome data relevant to this review protocol
Kasama, S, Toyama, T, Hatori, T et al. (2006) Comparative effects of valsartan and enalapril on cardiac sympathetic nerve activity and plasma brain natriuretic peptide in patients with congestive heart failure. Heart (British Cardiac Society) 92(5): 625-30	- Study does not contain any outcome data relevant to this review protocol
Kasama, Shu, Toyama, Takuji, Sumino, Hiroyuki et al. (2007) Additive effects of spironolactone and candesartan on cardiac sympathetic nerve activity and left ventricular remodeling in patients with congestive heart failure. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 48(12): 1993-2000	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions* - Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
Kato, Eri T, Silverman, Michael G, Mosenzon, Ofri et al. (2019) Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. Circulation 139(22): 2528-2536	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions and <80% symptomatic*
Katsiadas, Nikolaos, Xanthopoulos, Andrew, Giamouzis, Grigorios et al. (2022) The effect of SGLT-2i administration on red blood cell distribution width in patients with heart failure and type 2 diabetes mellitus: A randomized study. Frontiers in cardiovascular medicine 9: 984092	- Population not relevant to this review protocol *Mixed EF population*
Khan, Muhammad Shahzeb, Anker, Stefan D, Filippatos, Gerasimos et al. (2023) Vascular Disease Burden, Outcomes and Benefits with Empagliflozin in Heart Failure: Insights From the EMPEROR-Reduced Trial. Journal of cardiac failure 29(10): 1345-1354	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis, not relevant to the protocol.*
Khan, Muhammad Shahzeb, Butler, Javed, Anker, Stefan D et al. (2023) Impact of Empagliflozin in Heart Failure With Reduced Ejection Fraction in Patients With Ischemic Versus Nonischemic Cause. Journal of the American Heart Association 12(1): e027652	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis, not relevant to the protocol. No additional information of relevance.*
Khan, Muhammad Shahzeb, Fonarow, Gregg C, Ahmed, Ali et al. (2017) Dose of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and Outcomes in Heart Failure: A Meta-Analysis. Circulation. Heart failure 10(8)	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *No definition of LVrEF used. Some included studies do not report LVEF status.*
Khand, Aleem U, Chew, Pei G, Douglas, Homeyra et al. (2015) The effect of carvedilol on B-type natriuretic peptide and cardiac function in patients with heart failure and persistent atrial fibrillation. Cardiology 130(3): 153-8	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Khattar, RS, Senior, R, Soman, P et al. (2001) Regression of left ventricular remodeling in chronic heart failure: comparative and combined effects of captopril and carvedilol. American heart journal 142(4): 704-713	- Study design not relevant to this review protocol *Not randomised*
Khush, K.K. and Waters, D.D. (2006) Effects of Statin Therapy on the Development and Progression of Heart Failure: Mechanisms and Clinical Trials. Journal of Cardiac Failure 12(8): 664-674	- Review article but not a systematic review *Narrative review*
Kim, Yee Soo, Brar, Simerjeet, D'Albo, Natalie et al. (2022) Five Years of Sacubitril/Valsartan-a Safety Analysis of Randomized Clinical Trials and Real-World Pharmacovigilance. Cardiovascular drugs and therapy 36(5): 915-924	- Systematic review indirectly matches the review protocol: used as source of primary studies *Indirect match: Mixed population and comparison not in line with the protocol.*

Study	Exclusion reason
Kimmelstiel, C., Levine, D., Perry, K. et al. (2004) Randomized, controlled evaluation of short- and long-term benefits of heart failure disease management within a diverse provider network: The SPAN-CHF trial. Circulation 110(11): 1450-1455	- Population not relevant to this review protocol *Hospitalised HF (resulting from ischemic heart disease, dilated cardiomyopathy, valvular heart disease or hypertensive heart disease)*
Kimmoun, Antoine, Cotter, Gad, Davison, Beth et al. (2019) Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies (STRONG-HF): rationale and design for a multicentre, randomized, parallel-group study. European journal of heart failure 21(11): 1459-1467	- Population not relevant to this review protocol *Reduced LVEF*
Kitzman, Dalane W, Hundley, W Gregory, Brubaker, Peter H et al. (2010) A randomized double-blind trial of enalapril in older patients with heart failure and preserved ejection fraction: effects on exercise tolerance and arterial distensibility. Circulation. Heart failure 3(4): 477-85	- Population not relevant to this review protocol *HFpEF LVEF ≥50%*
Klein, Liviu, O'Connor, Christopher M, Gattis, Wendy A et al. (2003) Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials and practical considerations. The American journal of cardiology 91(9a): 18f-40f	- Review article but not a systematic review *Narrative review*
Klinge, R, Polis, A, Dickstein, K et al. (1997) Effects of angiotensin II receptor blockade on N-terminal proatrial natriuretic factor plasma levels in chronic heart failure. Journal of cardiac failure 3(2): 75-81	- Study does not contain any outcome data relevant to this review protocol - Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Kluger, A.Y., Tecson, K.M., Barbin, C.M. et al. (2018) Cardiorenal outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-ReG OutCome trials: A systematic review. Reviews in Cardiovascular Medicine 19(2): 41-49	- Population not relevant to this review protocol *Includes T2DM patients*
Ko, Dennis T, Hebert, Patricia R, Coffey, Christopher S et al. (2004) Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. Archives of internal medicine 164(13): 1389-94	- Population not relevant to this review protocol *No reported details on EF*
Kobayashi, Masatake, Ferreira, Joao Pedro, Matsue, Yuya et al. (2023) Effect of eplerenone on clinical stability of Japanese patients with acute heart failure. International journal of cardiology 374: 73-78	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
Kobayashi, Masatake, Yamashina, Akira, Satomi, Kazuhiro et al. (2024) Adverse events associated with early initiation of Eplerenone in patients hospitalized for acute heart failure. International journal of cardiology 415: 132477	- Secondary publication of an included study that does not provide any additional relevant information *No additional outcomes compared to main EARLIER paper*
Køber, L, Torp-Pedersen, C, Carlsen, JE et al. (1995) A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. The New England journal of medicine 333(25): 1670-1676	- Population not relevant to this review protocol *acute MI*
Kolwelter, Julie, Bosch, Agnes, Jung, Susanne et al. (2021) Effects of the sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function in patients with chronic heart failure. ESC heart failure 8(6): 5327-5337	- Study does not contain any outcome data relevant to this review protocol
Komajda, Michel, Bohm, Michael, Borer, Jeffrey S et al. (2018) Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. European journal of heart failure 20(9): 1315-1322	- Systematic review in area where more recent reviews are available *NMA does not include SGLT2i*
Komajda, Michel, Carson, Peter E, Hetzel, Scott et al. (2011) Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circulation. Heart failure 4(1): 27-35	- Population not relevant to this review protocol *Preserved LVEF*
Kommu, Sharath (2024) The Role of SGLT2 Inhibitors on Heart Failure Outcomes in Nondiabetic Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of cardiovascular pharmacology 83(2): 158-166	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Insufficient search strategy and small number of included studies matching the specified protocol. Not all protocol outcomes reported.*
Kommu, Sharath and Berg, Richard L (2024) The Efficacy and Safety of Sacubitril/Valsartan Compared to Valsartan in Patients with Heart Failure and Mildly Reduced and Preserved Ejection Fractions: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of clinical medicine 13(6)	- Systematic review indirectly matches the review protocol: used as source of primary studies *No new studies identified*
Kondo, Toru, Campbell, Ross, Jhund, Pardeep S et al. (2024) Low Natriuretic Peptide Levels and Outcomes in Patients With Heart Failure and Preserved Ejection Fraction. JACC. Heart failure 12(8): 1442-1455	- Study design not relevant to this review protocol *No treatment comparison*

Study	Exclusion reason
Kondo, Toru, Mogensen, Ulrik M, Talebi, Atefeh et al. (2024) Dapagliflozin and Days of Full Health Lost in the DAPA-HF Trial. Journal of the American College of Cardiology 83(20): 1973-1986	- Secondary publication of an included study that does not provide any additional relevant information *DAPA HF no extra data*
Kondo, Toru, Wang, Xiaowen, Yang, Mingming et al. (2023) Efficacy of Dapagliflozin According to Geographic Location of Patients With Heart Failure. Journal of the American College of Cardiology 82(10): 1014-1026	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis pooling 2 studies. Assessment by geographic region (not relevant to the review protocol).*
Konstam MA, Neaton JD, Dickstein K et al. (2009) Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet (London, England) 374(9704): 1840-1848	- Comparator in study does not match that specified in this review protocol *Dose comparison*
Konstam, Marvin A, Neaton, James D, Poole-Wilson, Philip A et al. (2005) Comparison of losartan and captopril on heart failure-related outcomes and symptoms from the losartan heart failure survival study (ELITE II). American heart journal 150(1): 123-31	- Study does not contain an intervention relevant to this review protocol *Intervention not in combination*
Kosiborod, Mikhail N, Angermann, Christiane E, Collins, Sean P et al. (2022) Effects of Empagliflozin on Symptoms, Physical Limitations, and Quality of Life in Patients Hospitalized for Acute Heart Failure: Results From the EMPULSE Trial. Circulation 146(4): 279-288	- Population not relevant to this review protocol *Includes participants with acute heart failure*
Kosiborod, Mikhail N, Jhund, Pardeep S, Docherty, Kieran F et al. (2020) Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. Circulation 141(2): 90-99	- Population not relevant to this review protocol *Adults hospitalised with a primary diagnosis of AHF with dyspnea on exertion or at rest*
Kosmala, Wojciech, Rojek, Aleksandra, Przewlocka-Kosmala, Monika et al. (2016) Effect of Aldosterone Antagonism on Exercise Tolerance in Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology 68(17): 1823-1834	- Population not relevant to this review protocol *All participants had LVEF >50%*
Kotecha D, Holmes J, Krum H et al. (2014) Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet (London, England) 384(9961): 2235-2243	- Systematic review indirectly matches the review protocol: used as source of primary studies *IPD meta-analysis for presence of atrial fibrillation vs sinus rhythm*

Study	Exclusion reason
Kotecha, Dipak, Manzano, Luis, Krum, Henry et al. (2016) Effect of age and sex on efficacy and tolerability of beta blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. BMJ (Clinical research ed.) 353: i1855	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies
Kotit, Susy (2023) Lessons from a pre-specified meta-analysis of sodium-glucose cotransporter-2 (SGLT2) inhibitors in heart failure: Time for new clinical recommendations. Global cardiology science & practice 2023(2): e202314	- Review article but not a systematic review
Kristensen, Soren L, Preiss, David, Jhund, Pardeep S et al. (2016) Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. Circulation. Heart failure 9(1)	- Secondary publication of an included study that does not provide any additional relevant information
Krum H, Shi H, Pitt B et al. (2013) Clinical benefit of eplerenone in patients with mild symptoms of systolic heart failure already receiving optimal best practice background drug therapy: analysis of the EMPHASIS-HF study. Circulation. Heart failure 6(4): 711-718	- Secondary publication of an included study that does not provide any additional relevant information *EMPHASIS-HF: sub-analysis based on dose of background medications*
Krum, H, Sackner-Bernstein, JD, Goldsmith, RL et al. (1995) Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. Circulation 92(6): 1499-1506	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Krum, Henry, Carson, Peter, Farsang, Csaba et al. (2004) Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. European journal of heart failure 6(7): 937-45	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Krum, Henry, Roecker, Ellen B, Mohacsi, Paul et al. (2003) Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. JAMA 289(6): 712-8	- Duration of follow up <3 months *8 weeks*
Krum, Henry, van Veldhuisen, Dirk J, Funck-Brentano, Christian et al. (2011) Effect on mode of death of heart failure treatment started with bisoprolol followed by Enalapril, compared to the opposite order: results of the randomized CIBIS III trial. Cardiovascular therapeutics 29(2): 89-98	- Study does not contain an intervention relevant to this review protocol *Monotherapy with background therapy of diuretic*
Kubo, T, Azevedo, ER, Newton, GE et al. (2001) Lack of evidence for peripheral alpha(1)-adrenoceptor blockade during long-term treatment of heart failure with carvedilol. Journal	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
of the American College of Cardiology 38(5): 1463-1469	
Kuenzli, Andrea, Bucher, Heiner C, Anand, Inder et al. (2010) Meta-analysis of combined therapy with angiotensin receptor antagonists versus ACE inhibitors alone in patients with heart failure. PloS one 5(4): e9946	- Systematic review in area where more recent reviews are available *SR published in 2010*
Kukin, ML, Kalman, J, Charney, RH et al. (1999) Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. Circulation 99(20): 2645-2651	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Kum, Leo Chi-Chiu, Yip, Gabriel Wai-Kwok, Lee, Pui-Wai et al. (2008) Comparison of angiotensin-converting enzyme inhibitor alone and in combination with irbesartan for the treatment of heart failure. International journal of cardiology 125(1): 16-21	- Population not relevant to this review protocol *Mixed EF*
Kumar, Kris, Kheiri, Babikir, Simpson, Timothy F et al. (2020) Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure: A Meta-Analysis of Randomized Clinical Trials. The American journal of medicine 133(11): e625-e630	- Review article but not a systematic review *Review article*
Kuno, Toshiki, Ueyama, Hiroki, Fujisaki, Tomohiro et al. (2020) Meta-Analysis Evaluating the Effects of Renin-Angiotensin-Aldosterone System Blockade on Outcomes of Heart Failure With Preserved Ejection Fraction. The American journal of cardiology 125(8): 1187-1193	- Population not relevant to this review protocol *HFpEF population*
Kurrelmeyer, Karla M, Ashton, Yelena, Xu, Jiaqiong et al. (2014) Effects of spironolactone treatment in elderly women with heart failure and preserved left ventricular ejection fraction. Journal of cardiac failure 20(8): 560-8	- Population not relevant to this review protocol *All participants had LVEF >50%*
Lakhdar, Rachid; Al-Mallah, Mouaz H; Lanfear, David E (2008) Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: a systematic review and meta-analysis of randomized controlled trials. Journal of cardiac failure 14(3): 181-8	- Population not relevant to this review protocol *Include participants with acute MI*
Lam, Carolyn S P, Ferreira, Joao Pedro, Pfarr, Egon et al. (2021) Regional and ethnic influences on the response to empagliflozin in patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. European heart journal 42(43): 4442-4451	- Population not relevant to this review protocol *Reduced LVEF*

Study	Exclusion reason
Lam, Phillip H, Dooley, Daniel J, Fonarow, Gregg C et al. (2018) Similar clinical benefits from below-target and target dose enalapril in patients with heart failure in the SOLVD Treatment trial. European journal of heart failure 20(2): 359-369	- Population not relevant to this review protocol *<80% were taking more than one therapy for HF*
Lam, Phillip H, Packer, Milton, Fonarow, Gregg C et al. (2020) Early Effects of Starting Doses of Enalapril in Patients with Chronic Heart Failure in the SOLVD Treatment Trial. The American journal of medicine 133(2): e25-e31	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Lan, Xiaohua, Zhu, Huijing, Cao, Yanjie et al. (2024) Effects of different sodium-glucose cotransporter 2 inhibitors in heart failure with reduced or preserved ejection fraction: a network meta-analysis. Frontiers in cardiovascular medicine 11: 1379765	- Comparator in study does not match that specified in this review protocol *Within class comparison*
Lang, RM, Elkayam, U, Yellen, LG et al. (1997) Comparative effects of losartan and enalapril on exercise capacity and clinical status in patients with heart failure. The Losartan Pilot Exercise Study Investigators. Journal of the American College of Cardiology 30(4): 983-991	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Larsen, Julie Hempel, Omar, Massar, Jensen, Jesper et al. (2023) Influence of angiotensin receptor-neprilysin inhibition on the efficacy of Empagliflozin on cardiac structure and function in patients with chronic heart failure and a reduced ejection fraction: The Empire HF trial. American heart journal plus : cardiology research and practice 26: 100264	- Study does not contain any outcome data relevant to this review protocol
Larstorp, Anne Cecilie K, Okin, Peter M, Devereux, Richard B et al. (2012) Regression of ECG-LVH is associated with lower risk of new-onset heart failure and mortality in patients with isolated systolic hypertension; The LIFE study. American journal of hypertension 25(10): 1101-9	- Population not relevant to this review protocol *Study is of hypertensive patients <80% have HF*
Lassen, Mats C H, Ostrominski, John W, Claggett, Brian L et al. (2024) Cardiovascular-kidney-metabolic overlap in heart failure with preserved ejection fraction: Cardiac structure and function, clinical outcomes, and response to sacubitril/valsartan in PARAGON-HF. European journal of heart failure 26(8): 1762-1774	- Population not relevant to this review protocol
Lavalle, Carlo, Mariani, Marco Valerio, Severino, Paolo et al. (2024) Efficacy of Modern Therapies for Heart Failure with Reduced Ejection Fraction in Specific Population Subgroups: A Systematic Review and Network Meta-Analysis. Cardiorenal medicine 14(1): 570-580	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *All included studies already identified and man relevant studies missing*

Study	Exclusion reason
Lee, M.M.Y., Gillis, K.A., Brooksbank, K.J.M. et al. (2022) Effect of Empagliflozin on Kidney Biochemical and Imaging Outcomes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF). Circulation 146(4): 364-367	- Publication type not relevant to review protocol *Letter only*
Lee, Matthew M Y, Brooksbank, Katriona J M, Wetherall, Kirsty et al. (2021) Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Circulation 143(6): 516-525	- Population not relevant to this review protocol *Reduced LVEF*
Lee, V., Zheng, Q., Toh, D.-F. et al. (2023) Sacubitril/valsartan versus valsartan in regressing myocardial fibrosis in hypertension: a prospective, randomized, open-label, blinded endpoint clinical trial protocol. Frontiers in Cardiovascular Medicine 10: 1248468	- Population not relevant to this review protocol *No HF population*
Lee, Victor C, Rhew, David C, Dylan, Michelle et al. (2004) Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Annals of internal medicine 141(9): 693-704	- Systematic review indirectly matches the review protocol: used as source of primary studies *Includes trials of patients on monotherapy with and without background therapy for a follow up minimum of 4 weeks.*
Lee, Wei-Chieh, Liao, Ting-Wei, Chen, Tien-Yu et al. (2023) Sacubitril/valsartan improves all-cause mortality in heart failure patients with reduced ejection fraction and chronic kidney disease. Cardiovascular drugs and therapy	- Study design not relevant to this review protocol *Cohort*
Lee, Young Soo, Kim, Kee Sik, Lee, Jin Bae et al. (2011) Effect of valsartan on N-terminal pro-brain natriuretic Peptide in patient with stable chronic heart failure: comparison with enalapril. Korean circulation journal 41(2): 61-7	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Leite, Marta, Sampaio, Francisco, Saraiva, Francisca A et al. (2023) The impact of heart failure therapy in patients with mildly reduced ejection fraction: a network meta-analysis. ESC heart failure 10(3): 1822-1834	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *HFmrEF:*
Leonetti Luparini, R, Celli, V, Piccirillo, G et al. (1999) Carvedilol in elderly patients with chronic heart failure, a 12 weeks randomized, placebo controlled open trial. Archives of gerontology and geriatrics 29(3): 275-82	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Lesogor A, Cohn JN, Latini R et al. (2013) Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: insights from the Val-	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*

Study	Exclusion reason
HeFT study. European journal of heart failure 15(11): 1236-1244	
Leung, M., Wong, V.W., Heritier, S. et al. (2013) Rationale and design of a randomized trial on the impact of aldosterone antagonism on cardiac structure and function in diabetic cardiomyopathy. Cardiovascular Diabetology 12(1): 139	- Publication type not relevant to review protocol *Protocol for a trial not yet completed*
Lewis EF, Kim HY, Claggett B 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	- Population not relevant to this review protocol *Preserved ejection fraction*
Lewis, Eldrin F, Claggett, Brian L, McMurray, John J V et al. (2017) Health-Related Quality of Life Outcomes in PARADIGM-HF. Circulation. Heart failure 10(8)	- Population not relevant to this review protocol *Reduced LVEF*
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	- Population not relevant to this review protocol *Participants all had HFpEF*
Li, Heng, Duan, Yuting, Chen, Benfa et al. (2020) New pharmacological treatments for heart failure with reduced ejection fraction (HFrEF): A Bayesian network meta-analysis. Medicine 99(5): e18341	- Study does not contain an intervention relevant to this review protocol *Interventions include Ivabradine, levosimendan, omega-3, tolvaptan, recombinant human B-type natriuretic peptide (rhBNP), isoorbide dinitrate and hydralazine (ISDN/HYD) and angiotensin-neprilysin inhibitor (LCZ696)*
Li, M J, Huang, C X, Okello, E et al. (2009) Treatment with spironolactone for 24 weeks decreases the level of matrix metalloproteinases and improves cardiac function in patients with chronic heart failure of ischemic etiology. The Canadian journal of cardiology 25(9): 523-6	- Study does not contain any outcome data relevant to this review protocol
Li, Weidong, Shen, Xuanyang, Zhang, Meiqi et al. (2024) Meta-analysis of the efficacy and impact on cardiac function of sodium-glucose cotransporter 2 inhibitor Empagliflozin in heart failure patients. Medicine 103(45): e40409	- Systematic review indirectly matches the review protocol: used as source of primary studies *All included (relevant) studies have been previously identified*
Li, XF; Cui, HY; YJ (2002) Eefficacy of valsartan in treatment of patients with chronic congestive heart failure. The journal of chinese cardiovascular 7(1): 41-43	- Full text unavailable

Study	Exclusion reason
Li, Xuexun, Zhang, Qian, Zhu, Lingming et al. (2021) Effects of SGLT2 inhibitors on cardiovascular, renal, and major safety outcomes in heart failure: A meta-analysis of randomized controlled trials. International journal of cardiology 332: 119-126	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included trials which used SGLT2i unlicensed for CHF in UK. No information on EF status.*
Li, Y., Wan, X., Yang, J. et al. (2022) Sarcobactrum Valsartan Sodium Tablets Prevent Heart Failure by Inhibiting Vasodilation and Cardiovascular Death. Latin American Journal of Pharmacy 41(6): 1149-1155	- Study does not contain any outcome data relevant to this review protocol
Li, YZ, Tan, BH, Luo, XT et al. (2002) The clinical efficacy of valsartan in combination with metoprolol in patients with congestive heart failure. South china journal of cardiovascular diseases 8(3): 193-195	- Study not reported in English *Non-English language*
Liao, Jia, Ebrahimi, Ramin, Ling, Zhiyu et al. (2024) Effect of SGLT-2 inhibitors on arrhythmia events: insight from an updated secondary analysis of > 80,000 patients (the SGLT2i-Arrhythmias and Sudden Cardiac Death). Cardiovascular diabetology 23(1): 78	- Systematic review indirectly matches the review protocol: used as source of primary studies *SR focussed on T2DM, CHF and CKD*
Lillyblad, Matthew P (2015) Dual Angiotensin Receptor and Neprilysin Inhibition with Sacubitril/Valsartan in Chronic Systolic Heart Failure: Understanding the New PARADIGM. The Annals of pharmacotherapy 49(11): 1237-51	- Review article but not a systematic review *Narrative review*
Lin, Jiezhong, Zhou, Jianyi, Xie, Guiting et al. (2021) Efficacy and safety of sacubitril-valsartan in patients with heart failure: a systematic review and meta-analysis of randomized clinical trials: A PRISMA-compliant article. Medicine 100(52): e28231	- Systematic review indirectly matches the review protocol: used as source of primary studies *LVEF ranges for each of the included 5 studies from mean of 32.7% (SD +/- 10.4) to 37.3 (SD +/-15.5)*
Lin, Meng-Jiao; Zou, Shu-Bin; Zhu, Bai-Xiang (2024) Effect of dapagliflozin on uric acid in patients with chronic heart failure and hyperuricemia. World journal of clinical cases 12(18): 3468-3475	- Population not relevant to this review protocol *Reduced LVEF*
Lin, Yanxia, Zhang, Huanrui, Zhao, Shijie et al. (2022) The Efficacy and Safety of the Combined Therapy of Sodium-Glucose Co-Transporter-2 Inhibitors and Angiotensin Receptor-Neprilysin Inhibitor in Patients With Heart Failure With Reduced Ejection Fraction: A Meta-Analysis of the EMPEROR-Reduced and DAPA-HF Sub-Analysis. Frontiers in cardiovascular medicine 9: 882089	- Systematic review indirectly matches the review protocol: used as source of primary studies *Meta-analysis of the EMPEROR-reduced and DAPA-HF sub-analysis*

Study	Exclusion reason
Lingyan, Z., Zijia, H., Ya, Z. et al. (2024) Cardiovascular outcomes of SGLT-2 Inhibitors Across BMI Spectrum in Heart Failure Patients: An Updated Systematic Review and Meta-Analysis. Journal of Cardiovascular Pharmacology: e001610	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included studies that had been previously identified*
Liu, Lang, Ding, Xiaofang, Han, Yaxiang et al. (2022) Effects and Safety of Sacubitril/Valsartan for Patients with Myocardial Infarction: A Systematic Review and Meta-Analysis. Journal of healthcare engineering 2022: 7840852	- Article retracted
Liu, Xue-Hui, Wang, Guan-Ling, Xu, Qiang et al. (2022) Effect of sacubitril/valsartan on the occurrence of cardiac arrhythmias and the risk of sudden cardiac death in heart failure: A meta-analysis of randomized controlled trials. Frontiers in cardiovascular medicine 9: 943377	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Included HFrEF and HFpEF threshold, not specified. Individualised medical therapy not a comparator or relevant to the review protocol.*
Liu, Xuyang, Zhong, Chengfu, Zhao, Pengtai et al. (2014) Analysis of therapeutic effect and safety of target-dose metoprolol in the treatment of patients with diabetes mellitus with chronic heart failure. Pakistan journal of medical sciences 30(1): 7-11	- Population not relevant to this review protocol *Background therapy unclear*
Lonn, Eva, Shaikholeslami, Roya, Yi, Qilong et al. (2004) Effects of ramipril on left ventricular mass and function in cardiovascular patients with controlled blood pressure and with preserved left ventricular ejection fraction: a substudy of the Heart Outcomes Prevention Evaluation (HOPE) Trial. Journal of the American College of Cardiology 43(12): 2200-6	- Population not relevant to this review protocol *Patients at risk of cardiovascular events but without left ventricular dysfunction or heart failure.*
Lopez-Usina, Almendra; Mantilla-Cisneros, Camila; Llerena-Velastegui, Jordan (2024) Comprehensive Benefits of Sodium-Glucose Cotransporter 2 Inhibitors in Heart Failure With Reduced Ejection Fraction: A Literature Review. Journal of clinical medicine research 16(10): 449-464	- Review article but not a systematic review
Lorenzo, Miguel, Minana, Gema, Palau, Patricia et al. (2023) Short-term Changes in Hemoglobin and Changes in Functional Status, Quality of Life and Natriuretic Peptides After Initiation of Dapagliflozin in Heart Failure With Reduced Ejection Fraction. Journal of cardiac failure 29(5): 849-854	- Study does not contain any outcome data relevant to this review protocol
Lu, Henri, Claggett, Brian L, Packer, Milton et al. (2024) Effects of Sacubitril/Valsartan on All-Cause Hospitalizations in Heart Failure: Post Hoc Analysis of the PARADIGM-HF and PARAGON-HF Randomized Clinical Trials. JAMA cardiology 9(11): 1047-1052	- Systematic review indirectly matches the review protocol: used as source of primary studies

Study	Exclusion reason
	IPD of PARADIGM-HF and PARAGON-HF but analyses LVEF as a continuous variable, not split by LVEF categories
Lu, Henri, Claggett, Brian L, Packer, Milton et al. (2024) Race in Heart Failure: A Pooled Participant-Level Analysis of the Global PARADIGM-HF and PARAGON-HF Trials. JACC. Heart failure	- Population not relevant to this review protocol *Mixed preserved/reduced LVEF so meets neither protocol on population*
Lu, Henri, Claggett, Brian L, Packer, Milton et al. (2024) Sacubitril/valsartan reduces incident anaemia and iron therapy utilization in heart failure: The PARAGON-HF trial. European journal of heart failure	- Population not relevant to this review protocol
Lu, Henri, Claggett, Brian L, Packer, Milton et al. (2024) Visit-to-visit changes in heart rate in heart failure: A pooled participant-level analysis of the PARADIGM-HF and PARAGON-HF trials. European journal of heart failure	- Systematic review indirectly matches the review protocol: used as source of primary studies *IPD of PARAGON-HF and PARADIGM-HF. No additional info*
Lu, Henri, Kondo, Toru, Claggett, Brian L et al. (2024) Systolic Blood Pressure and Pulse Pressure in Heart Failure: Pooled Participant-Level Analysis of 4 Trials. Journal of the American College of Cardiology	- Population not relevant to this review protocol
Lu, Yuan, Li, Fei, Fan, Yong et al. (2021) Effect of SGLT-2 inhibitors on cardiovascular outcomes in heart failure patients: A meta-analysis of randomized controlled trials. European journal of internal medicine 87: 20-28	- Systematic review indirectly matches the review protocol: used as source of primary studies *Includes mixed studies of HFrEF and HFpEF and a conference abstract. All interventions in line with the protocol.*
Lubsen, J, Chadha, D R, Yotof, Y T et al. (1996) Meta-analysis of morbidity and mortality in five exercise capacity trials evaluating ramipril in chronic congestive cardiac failure. The American journal of cardiology 77(14): 1191-6	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies
Lund, Lars H, James, Stefan, DeVore, Adam D et al. (2024) The Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRRIT-HFpEF): Rationale and design. European journal of heart failure 26(11): 2453-2463	- Publication type not relevant to review protocol *SPIRRIT-HFpEF rationale and design: results not yet published*
Lunney, Meaghan, Ruospo, Marinella, Natale, Patrizia et al. (2020) Pharmacological interventions for heart failure in people with chronic kidney disease. The Cochrane database of systematic reviews 2: cd012466	- Systematic review does not contain a protocol intervention *HFrEF: monotherapy versus placebo*
Ma, CY; Ma, X; Fu, BQ (2004) Therapeutic effect of carvedilol combined with enalapril on	- Full text unavailable

Study	Exclusion reason
chronic congestive heart failure. Chinese new medicine 5(14): 1265-1266	
Macdonald, J E; Kennedy, N; Struthers, A D (2004) Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. Heart (British Cardiac Society) 90(7): 765-70	- Study design not relevant to this review protocol *Cross-over RCT*
MacDonald, Michael R, Petrie, Mark C, Varyani, Fumi et al. (2008) Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. European heart journal 29(11): 1377-85	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Maeder, Micha T, Rickenbacher, Peter, Rickli, Hans et al. (2013) N-terminal pro brain natriuretic peptide-guided management in patients with heart failure and preserved ejection fraction: findings from the Trial of Intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF). European journal of heart failure 15(10): 1148-56	- Study does not contain an intervention relevant to this review protocol *NT-proBNP guided management*
Maggioni, Aldo P, Anand, Inder, Gottlieb, Sidney O et al. (2002) Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. Journal of the American College of Cardiology 40(8): 1414-21	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Maggioni, Aldo P, Latini, Roberto, Carson, Peter E et al. (2005) Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). American heart journal 149(3): 548-57	- Study does not contain any outcome data relevant to this review protocol
Majahalme, Silja K, Baruch, Lawrence, Aknay, Nora et al. (2005) Comparison of treatment benefit and outcome in women versus men with chronic heart failure (from the Valsartan Heart Failure Trial). The American journal of cardiology 95(4): 529-32	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Majani, Giuseppina, Giardini, Anna, Opasich, Cristina et al. (2005) Effect of valsartan on quality of life when added to usual therapy for heart failure: results from the Valsartan Heart Failure Trial. Journal of cardiac failure 11(4): 253-9	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
Makani, Harikrishna, Bangalore, Sripal, Desouza, Kavit A et al. (2013) Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ (Clinical research ed.) 346: f360	- Systematic review indirectly matches the review protocol: used as source of primary studies *Meta analysis of patients on 2 ACE inhibitors versus monotherapy and therefore not all patients have HF*
Mancini, GB (2000) Long-term use of angiotensin-converting enzyme inhibitors to modify endothelial dysfunction: a review of clinical investigations. Clinical and investigative medicine. Medecine clinique et experimentale 23(2): 144-161	- Systematic review indirectly matches the review protocol: used as source of primary studies *Not specific to heart failure*
Mann, Douglas L, Givertz, Michael M, Vader, Justin M et al. (2022) Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA cardiology 7(1): 17-25	- Population not relevant to this review protocol *Reduced LVEF*
Mann, Douglas L, Greene, Stephen J, Givertz, Michael M et al. (2020) Sacubitril/Valsartan in Advanced Heart Failure With Reduced Ejection Fraction: Rationale and Design of the LIFE Trial. JACC. Heart failure 8(10): 789-799	- Population not relevant to this review protocol *Reduced LVEF*
Marcy, Todd R and Ripley, Toni L (2006) Aldosterone antagonists in the treatment of heart failure. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 63(1): 49-58	- Review article but not a systematic review *Narrative review*
Martens, Pieter, Ferreira, Joao Pedro, Vincent, John et al. (2022) Serum sodium and eplerenone use in patients with a myocardial infarction and left ventricular dysfunction or heart failure: insights from the EPHESUS trial. Clinical research in cardiology : official journal of the German Cardiac Society 111(4): 380-392	- Population not relevant to this review protocol *Acute MI*
Martin, Nicole, Manoharan, Karthick, Davies, Ceri et al. (2021) Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. The Cochrane database of systematic reviews 5: cd012721	- Population not relevant to this review protocol *HFmrEF not reported separately*
Martinez, Felipe A, Serenelli, Matteo, Nicolau, Jose C et al. (2020) Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age: Insights From DAPA-HF. Circulation 141(2): 100-111	- Population not relevant to this review protocol *Reduced LVEF*
Massie BM, Armstrong PW, Cleland JG et al. (2001) Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
chronic heart failure: results from the ATLAS trial. The Assessment of Treatment with Lisinopril and Survival. Archives of internal medicine 161(2): 165-171	*Dose comparison*
Massie, Barry M, Carson, Peter E, McMurray, John J et al. (2008) Irbesartan in patients with heart failure and preserved ejection fraction. The New England journal of medicine 359(23): 2456-67	- Population not relevant to this review protocol *Low proportion in <59% LVEF subgroup likely to be in mrEF range* - Study does not contain an intervention relevant to this review protocol *Unlicensed ARB and data available for licensed ARB from another trial*
Masson, Serge, Latini, Roberto, Anand, Inder S et al. (2008) Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). Journal of the American College of Cardiology 52(12): 997-1003	- Study design not relevant to this review protocol *Retrospective cohort*
Matsumori, Akira (2003) Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. European journal of heart failure 5(5): 669-77	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions*
Matsumoto, Shingo, Henderson, Alasdair D, Shen, Li et al. (2024) Mineralocorticoid Receptor Antagonists in Patients With Heart Failure and Impaired Renal Function. Journal of the American College of Cardiology 83(24): 2426-2436	- Comparator in study does not match that specified in this review protocol *Pools 2 studies with different comparisons per our protocol (RALES is monotherapy)*
Matsumoto, Shingo, Kondo, Toru, Jhund, Pardeep S et al. (2023) Underutilization of Mineralocorticoid Antagonists in Patients With Heart Failure With Reduced Ejection Fraction. Journal of the American College of Cardiology 82(11): 1080-1091	- Study does not contain an intervention relevant to this review protocol *Eplerenone (aldosterone antagonist)*
Matsumoto, Shingo, Shen, Li, Henderson, Alasdair D et al. (2024) Asymptomatic vs Symptomatic Hypotension With Sacubitril/Valsartan in Heart Failure and Reduced Ejection Fraction in PARADIGM-HF. Journal of the American College of Cardiology 84(18): 1685-1700	- Secondary publication of an included study that does not provide any additional relevant information
Matsumoto, Shingo, Yang, Mingming, Shen, Li et al. (2024) Effects of sacubitril/valsartan according to polypharmacy status in PARAGON-HF. European journal of heart failure 26(5): 1125-1138	- Population not relevant to this review protocol *Secondary analysis of PARAGON-HF but on whole population that is preservedEF*

Study	Exclusion reason
	- Secondary publication of an included study that does not provide any additional relevant information
Mattumpuram, Jishanth, Maniya, Muhammad Talha, Fernandes, Craig Albert Luke et al. (2024) Angiotensin-Neprilysin inhibition in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Current problems in cardiology 49(1ptc): 102167	- Population not relevant to this review protocol *Population mostly comprised of individuals with HFpEF*
Mazayev, V P, Fomina, I G, Kazakov, E N et al. (1998) Valsartan in heart failure patients previously untreated with an ACE inhibitor. International journal of cardiology 65(3): 239-46	- Duration of follow up <3 months
Mazza, A., Townsend, D.M., Torin, G. et al. (2020) The role of sacubitril/valsartan in the treatment of chronic heart failure with reduced ejection fraction in hypertensive patients with comorbidities: From clinical trials to real-world settings. Biomedicine and Pharmacotherapy 130: 110596	- Study design not relevant to this review protocol *Open label study*
Mc Causland, Finnian R, Lefkowitz, Martin P, Claggett, Brian et al. (2020) Angiotensin-Neprilysin Inhibition and Renal Outcomes in Heart Failure With Preserved Ejection Fraction. Circulation 142(13): 1236-1245	- Population not relevant to this review protocol *>80% preserved ejection fraction*
Mc Causland, Finnian R, Vaduganathan, Muthiah, Claggett, Brian et al. (2024) Angiotensin Receptor Neprilysin Inhibition and Cardiovascular Outcomes Across the Kidney Function Spectrum: The PARAGON-HF Trial. JACC. Heart failure	- Population not relevant to this review protocol
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	- Secondary publication of an included study that does not provide any additional relevant information *FINEARTS-HF analysis: Outcome data not stratified by LVEF*
McAlister, Finlay A, Wiebe, Natasha, Ezekowitz, Justin A et al. (2009) Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Annals of internal medicine 150(11): 784-94	- Comparator in study does not match that specified in this review protocol *Placebo comparator*
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	- Population not relevant to this review protocol *No mrEF subgroup.*
McDowell, Kirsty, Welsh, Paul, Docherty, Kieran F et al. (2022) Dapagliflozin reduces uric acid concentration, an independent predictor of	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
adverse outcomes in DAPA-HF. European journal of heart failure 24(6): 1066-1076	*Secondary analysis, no additional data of analysis*
McKelvie, Robert S, Rouleau, Jean-Lucien, White, Michel et al. (2003) Comparative impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodelling in patients with congestive heart failure. European heart journal 24(19): 1727-34	- Comparator in study does not match that specified in this review protocol *Results include events in 2 randomisation periods with different interventions that cannot be analysed separately*
McKelvie, RS, Yusuf, S, Pericak, D et al. (1999) Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation 100(10): 1056-1064	- Comparator in study does not match that specified in this review protocol *Results include events in 2 randomisation periods with different interventions that cannot be analysed separately*
McKelvie, RS; Yusuf, S; Pericak, D (1999) Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. Congestive heart failure 5(6): 286-287	- Comparator in study does not match that specified in this review protocol *Results include events in 2 randomisation periods with different interventions that cannot be analysed separately*
McKenna, C, Burch, J, Suekarran, S et al. (2010) A systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for postmyocardial infarction heart failure. Health technology assessment (Winchester, England) 14(24): 1-162	- Publication type not relevant to review protocol *Cost-effectiveness analysis*
McMurray, John J V, Carson, Peter E, Komajda, Michel et al. (2008) Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. European journal of heart failure 10(2): 149-56	- Population not relevant to this review protocol *Preserved LVEF*
McMurray, John J V, DeMets, David L, Inzucchi, Silvio E et al. (2019) A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). European journal of heart failure 21(5): 665-675	- Population not relevant to this review protocol *Reduced LVEF*
McMurray, John J V, DeMets, David L, Inzucchi, Silvio E et al. (2019) The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. European journal of heart failure 21(11): 1402-1411	- Population not relevant to this review protocol *Reduced LVEF*
McMurray, John J V, Docherty, Kieran F, de Boer, Rudolf A et al. (2023) Effect of Dapagliflozin Versus Placebo on Symptoms and 6-Minute Walk Distance in Patients With Heart	- Population not relevant to this review protocol *Reduced LVEF*

Study	Exclusion reason
Failure: The DETERMINE Randomized Clinical Trials. Circulation	
McMurray, John J V, Ostergren, Jan, Swedberg, Karl et al. (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet (London, England) 362(9386): 767-71	- Population not relevant to this review protocol *Reduced LVEF*
McMurray, John J V, Packer, Milton, Desai, Akshay S et al. (2013) Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). European journal of heart failure 15(9): 1062-73	- Population not relevant to this review protocol *Reduced LVEF*
McMurray, John J V, Packer, Milton, Desai, Akshay S et al. (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England journal of medicine 371(11): 993-1004	- Population not relevant to this review protocol *Reduced LVEF*
McMurray, John J V, Packer, Milton, Desai, Akshay S et al. (2014) Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). European journal of heart failure 16(7): 817-25	- Population not relevant to this review protocol *Reduced LVEF*
McMurray, John J V, Pitt, Bertram, Latini, Roberto et al. (2008) Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. Circulation. Heart failure 1(1): 17-24	- Study does not contain an intervention relevant to this review protocol *Intervention is not a drug class of interest (aliskiren is a reinin inhibitor)*
McMurray, John J V, Solomon, Scott D, Docherty, Kieran F et al. (2021) The Dapagliflozin and Prevention of Adverse outcomes in Heart Failure trial (DAPA-HF) in context. European heart journal 42(13): 1199-1202	- Study design not relevant to this review protocol *Not RCT*
McMurray, John J V, Solomon, Scott D, Inzucchi, Silvio E et al. (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England journal of medicine 381(21): 1995-2008	- Population not relevant to this review protocol *Reduced LVEF*
McMurray, John J V, Young, James B, Dunlap, Mark E et al. (2006) Relationship of dose of background angiotensin-converting enzyme inhibitor to the benefits of candesartan in the Candesartan in Heart failure: Assessment of	- Population not relevant to this review protocol *Subgroup not of relevance to the protocol.*

Study	Exclusion reason
Reduction in Mortality and morbidity (CHARM)-Added trial. American heart journal 151(5): 985-91	
Mebazaa, Alexandre, Davison, Beth, Chioncel, Ovidiu et al. (2022) Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet (London, England) 400(10367): 1938-1952	- Population not relevant to this review protocol *Reduced LVEF*
Memon, Muhammad Mustafa, Yamani, Naser, Asmi, Nisar et al. (2020) Renin-angiotensin-aldosterone system inhibition in heart failure with mid-ranged ejection fraction: A systematic review and meta-analysis. European journal of preventive cardiology 27(19): 2371-2373	- Systematic review indirectly matches the review protocol: used as source of primary studies
Mentz, Robert J, Ward, Jonathan H, Hernandez, Adrian F et al. (2023) Rationale, Design and Baseline Characteristics of the PARAGLIDE-HF Trial: Sacubitril/Valsartan vs Valsartan in HFmrEF and HFpEF With a Worsening Heart Failure Event. Journal of cardiac failure 29(6): 922-930	- Population not relevant to this review protocol *78% preserved LVEF; 22% mildly reduced LVEF*
Mentz, Robert J, Ward, Jonathan H, Hernandez, Adrian F et al. (2023) Angiotensin-Neprilysin Inhibition in Patients With Mildly Reduced or Preserved Ejection Fraction and Worsening Heart Failure. Journal of the American College of Cardiology 82(1): 1-12	- Population not relevant to this review protocol *78% preserved LVEF; 22% mildly reduced LVEF*
Meredith, Peter A, Ostergren, Jan, Anand, Inder et al. (2008) Clinical outcomes according to baseline blood pressure in patients with a low ejection fraction in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Program. Journal of the American College of Cardiology 52(24): 2000-7	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis. No additional outcomes reported.*
Merrill, Miranda, Sweitzer, Nancy K, Lindenfeld, JoAnn et al. (2019) Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction: A Secondary Analysis of TOPCAT Trial. JACC. Heart failure 7(3): 228-238	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis with no extra information.*
Metra, M, Giubbini, R, Nodari, S et al. (2000) Differential effects of beta-blockers in patients with heart failure: A prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation 102(5): 546-551	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Metra, M, Nardi, M, Giubbini, R et al. (1994) Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
clinical conditions in patients with idiopathic dilated cardiomyopathy. Journal of the American College of Cardiology 24(7): 1678-1687	*HFrEF: not combination treatment in control group*
Miller, Robert J H, Howlett, Jonathan G, Exner, Derek V et al. (2015) Baseline Functional Class and Therapeutic Efficacy of Common Heart Failure Interventions: A Systematic Review and Meta-analysis. The Canadian journal of cardiology 31(6): 792-9	- Population not relevant to this review protocol *HFrEF definition does not meet either protocol.*
Mitchell, Gary F, Solomon, Scott D, Shah, Amil M et al. (2021) Hemodynamic Effects of Sacubitril-Valsartan Versus Enalapril in Patients With Heart Failure in the EVALUATE-HF Study: Effect Modification by Left Ventricular Ejection Fraction and Sex. Circulation. Heart failure 14(3): e007891	- Study does not contain any outcome data relevant to this review protocol *No outcomes of relevance*
Mitrovic, V, Willenbrock, R, Miric, M et al. (2003) Acute and 3-month treatment effects of candesartan cilexetil on hemodynamics, neurohormones, and clinical symptoms in patients with congestive heart failure. American heart journal 145(3): e14	- Population not relevant to this review protocol *Inadequate information on background treatments*
Mittal, Niti, Shafiq, Nusrat, Reddy, Sreenivas et al. (2017) Evaluation of efficacy of metoprolol in patients having heart failure with preserved ejection fraction: A randomized, double-blind, placebo-controlled pilot trial. Perspectives in clinical research 8(3): 124-131	- Population not relevant to this review protocol *Includes participants with LVEF greater than or equal to 50% (pEF)*
Mizutani, N. (2007) Combination therapy of an ACE inhibitor and an angiotensin II receptor blocker for patients with chronic heart failure. Therapeutic Research 28(11): 2243-2251	- Study does not contain any outcome data relevant to this review protocol
Mizutani, N.; Fukuta, M.; Itoh, T. (2007) Effects of combination therapy of an ACE inhibitor and an angiotensin II receptor blocker on QT dispersion. Therapeutic Research 28(11): 2235-2242	- Conference abstract
Mo, Xingchun; Lu, Ping; Yang, Xiaojing (2023) Efficacy of sacubitril-valsartan and SGLT2 inhibitors in heart failure with reduced ejection fraction: A systematic review and meta-analysis. Clinical cardiology 46(10): 1137-1145	- Systematic review indirectly matches the review protocol: used as source of primary studies *Systematic review pooled RCTs and retrospective cohort studies*
Mochizuki, Seibu, Dahlof, Bjorn, Shimizu, Mitsuyuki et al. (2007) Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. Lancet (London, England) 369(9571): 1431-1439	- Article retracted

Study	Exclusion reason
Mogensen, Ulrik M, Gong, Jianjian, Jhund, Pardeep S et al. (2018) Effect of sacubitril/valsartan on recurrent events in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). European journal of heart failure 20(4): 760-768	- Secondary publication of an included study that does not provide any additional relevant information
Montero-Perez-Barquero, Manuel, Flather, Marcus, Roughton, Michael et al. (2014) Influence of systolic blood pressure on clinical outcomes in elderly heart failure patients treated with nebivolol: data from the SENIORS trial. European journal of heart failure 16(9): 1009-15	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Monzo, Luca, Girerd, Nicolas, Duarte, Kevin et al. (2023) Time to clinical benefit of eplerenone among patients with heart failure and reduced ejection fraction: A subgroups analysis from the EMPHASIS-HF trial. European journal of heart failure 25(8): 1444-1449	- Secondary publication of an included study that does not provide any additional relevant information
Mooney, L., Hawkins, N.M., Jhund, P.S. et al. (2021) Impact of chronic obstructive pulmonary disease in patients with heart failure with preserved ejection fraction: Insights from paragon-hf. Journal of the American Heart Association 10(23): e021494	- Population not relevant to this review protocol *Preserved LVEF*
Morrow, David A, Velazquez, Eric J, Desai, Akshay S et al. (2024) Sacubitril/Valsartan in Patients Hospitalized With Decompensated Heart Failure. Journal of the American College of Cardiology 83(12): 1123-1132	- Population not relevant to this review protocol *Does not meet protocol population (IPD of a rEF and prEF trials)*
Mou, Y., Qin, L., Wang, L. et al. (2024) Effectiveness and Safety of Sacubitril/Valsartan in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. Alternative therapies in health and medicine 30(4): 190	- Duplicate reference
Mou, Yanhong, Qin, Lijun, Wang, Lili et al. (2023) Effectiveness and Safety of Sacubitril/Valsartan in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. Alternative therapies in health and medicine	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included studies do not meet protocol for population*
Mou, Yanhong, Qin, Lijun, Wang, Lili et al. (2024) Effectiveness and Safety of Sacubitril/Valsartan in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. Alternative therapies in health and medicine 30(4): 190-197	- Systematic review does not contain a protocol population
Mulder, Bart A, van Veldhuisen, Dirk J, Crijns, Harry J G M et al. (2012) Effect of nebivolol on outcome in elderly patients with heart failure and	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
atrial fibrillation: insights from SENIORS. European journal of heart failure 14(10): 1171-8	
Mustapic, Ivona, Bakovic, Darija, Susilovic Grabovac, Zora et al. (2022) Impact of SGLT2 Inhibitor Therapy on Right Ventricular Function in Patients with Heart Failure and Reduced Ejection Fraction. Journal of clinical medicine 12(1)	- Study does not contain any outcome data relevant to this review protocol
Myhre, Peder L, Claggett, Brian L, Shah, Amil M et al. (2022) Changes in cardiac biomarkers in association with alterations in cardiac structure and function, and health status in heart failure with reduced ejection fraction: the EVALUATE-HF trial. European journal of heart failure 24(7): 1200-1208	- Data not reported in an extractable format or a format that can be analysed *KCCQ scores are reported as relative changes to the outcomes. Does not report the overall quality of life score.*
Myhre, Peder Langeland, Vaduganathan, Muthiah, Claggett, Brian et al. (2019) B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. Journal of the American College of Cardiology 73(11): 1264-1272	- Secondary publication of an included study that does not provide any additional relevant information *PARADIGM-HF*
Nagele, Matthias P, Haider, Thomas, Kreysing, Leonie et al. (2024) Vascular Endothelial Effects of Sacubitril/Valsartan in Heart Failure With Reduced Ejection Fraction: Randomized Controlled Trial. JACC. Advances 3(12): 101392	- Population not relevant to this review protocol *Reduced LVEF*
Nakamura, Motoyuki, Saito, Seiichi, Yoshida, Hiroaki et al. (2002) Effects of chronic subdepressor dose of angiotensin II type 1 receptor antagonist on endothelium-dependent vasodilation in patients with congestive heart failure. Journal of cardiovascular pharmacology 40(3): 411-9	- Population not relevant to this review protocol *Does not meet the 80% threshold requirement of those receiving at least 2 of the listed interventions.*
Naser, Nabil, Durak-Nalbantic, Azra, Sabanovic-Bajramovic, Nirvana et al. (2023) The Effectiveness of Eplerenone vs Spironolactone on Left Ventricular Systolic Function, Hospitalization and Cardiovascular Death in Patients With Chronic Heart Failure-HFrEF. Medical archives (Sarajevo, Bosnia and Herzegovina) 77(2): 105-111	- Comparator in study does not match that specified in this review protocol *The comparison is two drugs within the same class*
Nassif, M.E., Windsor, S., Tang, F. et al. (2019) Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction. Circulation 140(18): 042929	- Duplicate reference
Nassif, Michael E, Qintar, Mohammed, Windsor, Sheryl L et al. (2021) Empagliflozin Effects on Pulmonary Artery Pressure in Patients With Heart Failure: Results From the EMBRACE-HF Trial. Circulation 143(17): 1673-1686	- Population not relevant to this review protocol *Mixed EF population with no details on proportion or data for either subgroup provided separately.*

Study	Exclusion reason
Nassif, Michael E, Windsor, Sheryl L, Gosch, Kensey et al. (2023) Dapagliflozin Improves Heart Failure Symptoms and Physical Limitations Across the Full Range of Ejection Fraction: Pooled Patient-Level Analysis From DEFINE-HF and PRESERVED-HF Trials. Circulation. Heart failure 16(7): e009837	- Secondary publication of an included study that does not provide any additional relevant information *Patient-level pooled analysis of DEFINE-HF and PRESERVED-HF trials, so a mix of population groups.*
Nassif, Michael E, Windsor, Sheryl L, Tang, Fengming et al. (2019) Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation 140(18): 1463-1476	- Population not relevant to this review protocol *Reduced LVEF*
Neal, B, MacMahon, S, Chapman, N et al. (2000) Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet (London, England) 356(9246): 1955-64	- Population not relevant to this review protocol *Not exclusively heart failure: mixed group using drugs for BP lowering*
Nesterov, Sergey V, Raty, Johanna, Nammas, Wail et al. (2023) Short-term effects of sacubitril/valsartan therapy on myocardial oxygen consumption and energetic efficiency of cardiac work in heart failure with reduced ejection fraction: A randomized controlled study. European journal of heart failure	- Duration of follow up <3 months *Duration of 9 weeks*
Nguyen, KN; Aursnes, I; Kjekshus, J (1997) Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). The American journal of cardiology 79(2): 115-119	- Population not relevant to this review protocol *Acute MI* - Comparator in study does not match that specified in this review protocol *Aspirin*
Nielsen, Emil Eik, Feinberg, Joshua Buron, Bu, Fan-Long et al. (2020) Beneficial and harmful effects of sacubitril/valsartan in patients with heart failure: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Open heart 7(2)	- Systematic review indirectly matches the review protocol: used as source of primary studies *Populations include HFrEF, HFpEF, mixed or unclear*
Nishioka, K, Nakagawa, K, Umemura, T et al. (2007) Carvedilol improves endothelium-dependent vasodilation in patients with dilated cardiomyopathy. Heart (British Cardiac Society) 93(2): 247-248	- Duration of follow up <3 months *Follow up was 4 weeks*
Oates, Connor P, Santos-Gallego, Carlos G, Smith, Alex et al. (2023) SGLT2 inhibitors reduce sudden cardiac death risk in heart failure: Meta-analysis of randomized clinical	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
trials. Journal of cardiovascular electrophysiology 34(5): 1277-1285	
Ohtsubo, Toshio, Shibata, Rei, Kai, Hisashi et al. (2019) Angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers in hypertensive patients with myocardial infarction or heart failure: a systematic review and meta-analysis. Hypertension research : official journal of the Japanese Society of Hypertension 42(5): 641-649	- Systematic review indirectly matches the review protocol: used as source of primary studies *Population: hypertension with either MI or HF*
Okumura, Naoki, Jhund, Pardeep S, Gong, Jianjian et al. (2016) Effects of Sacubitril/Valsartan in the PARADIGM-HF Trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) According to Background Therapy. Circulation. Heart failure 9(9)	- Secondary publication of an included study that does not provide any additional relevant information *PARADIGM-HF stratified by background therapy*
Olsen, SL, Gilbert, EM, Renlund, DG et al. (1995) Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. Journal of the American College of Cardiology 25(6): 1225-1231	- Secondary publication of an included study that does not provide any additional relevant information
Olsson, Lars G, Swedberg, Karl, Ducharme, Anique et al. (2006) Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. Journal of the American College of Cardiology 47(10): 1997-2004	- Secondary publication of an included study that does not provide any additional relevant information
Omar, Massar, Jensen, Jesper, Frederiksen, Peter H et al. (2020) Effect of Empagliflozin on Hemodynamics in Patients With Heart Failure and Reduced Ejection Fraction. Journal of the American College of Cardiology 76(23): 2740-2751	- Secondary publication of an included study that does not provide any additional relevant information
O'Meara, Eileen, Khairy, Paul, Blanchet, Malorie Chabot et al. (2012) Mineralocorticoid receptor antagonists and cardiovascular mortality in patients with atrial fibrillation and left ventricular dysfunction: insights from the Atrial Fibrillation and Congestive Heart Failure Trial. Circulation. Heart failure 5(5): 586-93	- Study design not relevant to this review protocol *Post hoc analysis includes non-randomisation of MRAs.*
O'Meara, Eileen, Lewis, Eldrin, Granger, Chris et al. (2005) Patient perception of the effect of treatment with candesartan in heart failure. Results of the candesartan in heart failure: assessment of reduction in mortality and	- Population not relevant to this review protocol *Population includes MI or HF with hypertension*

Study	Exclusion reason
morbidity (CHARM) programme. European journal of heart failure 7(4): 650-6	
O'Meara, Eileen, Solomon, Scott, McMurray, John et al. (2004) Effect of candesartan on New York Heart Association functional class. Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. European heart journal 25(21): 1920-6	- Secondary publication of an included study that does not provide any additional relevant information
Oriecuia, Chiara, Tomasoni, Daniela, Sala, Isabella et al. (2023) Sodium glucose co-transporter 2 inhibitors and quality of life in patients with heart failure: a comprehensive systematic review and meta-analysis of randomized controlled trials. European heart journal. Cardiovascular pharmacotherapy	- Systematic review indirectly matches the review protocol: used as source of primary studies *Patients with HF (stable chronic and acute or worsening HF)*
Osipova, OA, Gosteva, EV, Golivets, TP et al. (2021) Changes of myocardial fibrosis markers with the use of beta-blockers and mineralocorticoid receptor antagonists in patients with heart failure with mid-range ejection fraction of ischemic origin. Cardiovascular therapy and prevention (russian federation) 20(7): 32-40	- Study not reported in English *Non-English language study*
Osipova, OA, Mikhin, VP, Golovin, AI et al. (2022) Advantages of long-term combination pharmacotherapy with a beta-blocker and eplerenone in patients with ST-segment elevation acute coronary syndrome. Cardiovascular therapy and prevention (russian federation) 21(6): 71-77	- Study not reported in English *Non-English language study (Russian)*
Ostrominski, John W, Aggarwal, Rahul, Claggett, Brian L et al. (2024) Generalizability of the Spectrum of Kidney Risk in the FINEARTS-HF Trial to U.S. Adults With Heart Failure. Journal of cardiac failure 30(9): 1170-1174	- Secondary publication of an included study that does not provide any additional relevant information *Trial brief report*
Ostrominski, John W, Claggett, Brian L, Packer, Milton et al. (2023) Duration of Heart Failure With Preserved Ejection Fraction and Outcomes With Sacubitril/Valsartan: Insights From the PARAGON-HF Trial. Journal of cardiac failure 29(11): 1494-1503	- Population not relevant to this review protocol *No population subgroup data for HFmrEF*
Oyama, Kazuma, Raz, Itamar, Cahn, Avivit et al. (2022) Efficacy and Safety of Dapagliflozin According to Background Use of Cardiovascular Medications in Patients With Type 2 Diabetes: A Prespecified Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 7(9): 914-923	- Population not relevant to this review protocol *Not heart failure*
Ozdemir, Murat, Arslan, Ugur, Turkoglu, Sedat et al. (2007) Losartan improves heart rate variability and heart rate turbulence in heart	- Population not relevant to this review protocol

Study	Exclusion reason
failure due to ischemic cardiomyopathy. Journal of cardiac failure 13(10): 812-7	*Population not relevant- ischemic cardiomyopathy*
Packer M, Bristow MR, Cohn JN et al. (1996) The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. The New England journal of medicine 334(21): 1349-1355	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Packer M, Coats AJ, Fowler MB et al. (2001) Effect of carvedilol on survival in severe chronic heart failure. The New England journal of medicine 344(22): 1651-1658	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Packer, M, Antonopoulos, G V, Berlin, J A et al. (2001) Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta-analysis. American heart journal 141(6): 899-907	- Systematic review does not contain a protocol intervention *Within-class comparison*
Packer, M, Butler, J, Zannad, F et al. (2021) Empagliflozin and Major Renal Outcomes in Heart Failure. New England journal of medicine 385(16): 1531-1533	- Population not relevant to this review protocol *Pooled preserved and reduced LVEF*
Packer, M, Colucci, WS, Sackner-Bernstein, JD et al. (1996) Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation 94(11): 2793-2799	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Packer, M, Narahara, KA, Elkayam, U et al. (1993) Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. Principal Investigators of the REFLECT Study. Journal of the American College of Cardiology 22(1): 65-72	- Study does not contain an intervention relevant to this review protocol *Flosequinan*
Packer, M, Poole-Wilson, P A, Armstrong, P W et al. (1999) Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 100(23): 2312-8	- Comparator in study does not match that specified in this review protocol *Dose comparison*
Packer, M; Coats, AJ; Fowler, MB (2001) Carvedilol reduced mortality and hospitalisation in severe chronic heart failure. Evidence-based medicine 6(6): 173	- Study does not contain any outcome data relevant to this review protocol
Packer, Milton, Anker, Stefan D, Butler, Javed et al. (2020) Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The New England journal of medicine 383(15): 1413-1424	- Population not relevant to this review protocol *Reduced LVEF*

Study	Exclusion reason
Packer, Milton, Anker, Stefan D, Butler, Javed et al. (2021) Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. Circulation 143(4): 326-336	- Secondary publication of an included study that does not provide any additional relevant information *Reports renal outcomes and eGFR from patient level pooled analysis from EMPEROR-Reduced and EMPEROR-Preserved trial*
Packer, Milton, Anker, Stefan D, Butler, Javed et al. (2021) Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. Journal of the American College of Cardiology 77(11): 1381-1392	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis- no outcomes of interest reported*
Packer, Milton, Anker, Stefan D, Butler, Javed et al. (2021) Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. European heart journal 42(6): 671-680	- Secondary publication of an included study that does not provide any additional relevant information
Packer, Milton, Butler, Javed, Filippatos, Gerasimos et al. (2020) Design of a prospective patient-level pooled analysis of two parallel trials of empagliflozin in patients with established heart failure. European journal of heart failure 22(12): 2393-2398	- Population not relevant to this review protocol *Pooled preserved and reduced LVEF*
Packer, Milton, Butler, Javed, Filippatos, Gerasimos S et al. (2019) Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. European journal of heart failure 21(10): 1270-1278	- Population not relevant to this review protocol *Reduced LVEF*
Packer, Milton, Fowler, Michael B, Roecker, Ellen B et al. (2002) Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 106(17): 2194-9	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Packer, Milton, McMurray, John J V, Desai, Akshay S et al. (2015) Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 131(1): 54-61	- Secondary publication of an included study that does not provide any additional relevant information
Pagnesi, M., Vilamajo, O.A.G., Meirino, A. et al. (2024) Blood pressure and intensive treatment up-titration after acute heart failure hospitalization: Insights from the STRONG-HF trial. European Journal of Heart Failure 26(3): 638	- Population not relevant to this review protocol *Adults hospitalised with acute heart failure*

Study	Exclusion reason
Pagnesi, Matteo, Metra, Marco, Cohen-Solal, Alain et al. (2023) Uptitrating Treatment After Heart Failure Hospitalization Across the Spectrum of Left Ventricular Ejection Fraction. Journal of the American College of Cardiology 81(22): 2131-2144	- Population not relevant to this review protocol *Reduced LVEF*
Palau, Patricia, Amiguet, Martina, Dominguez, Eloy et al. (2022) Short-term effects of dapagliflozin on maximal functional capacity in heart failure with reduced ejection fraction (DAPA-VO2): a randomized clinical trial. European journal of heart failure 24(10): 1816-1826	- Population not relevant to this review protocol *Reduced LVEF*
Palazzuoli, A, Bruni, F, Puccetti, L et al. (2002) Effects of carvedilol on left ventricular remodeling and systolic function in elderly patients with heart failure. European journal of heart failure 4(6): 765-70	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Palazzuoli, A, Quatrini, I, Vecchiato, L et al. (2005) Effects of carvedilol on left ventricular diastolic function and chamber volumes in advanced heart failure. Minerva cardioangiologica 53(4): 321-8	- Data not reported in an extractable format or a format that can be analysed *Background treatment not reported sufficiently. Outcomes regarding mortality and timepoints are not clear.*
Palazzuoli, Alberto, Carrera, Arcangelo, Calabria, Paolo et al. (2004) Effects of carvedilol therapy on restrictive diastolic filling pattern in chronic heart failure. American heart journal 147(1): e2	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Palazzuoli, Alberto, Quatrini, Ilaria, Vecchiato, Lucia et al. (2005) Left ventricular diastolic function improvement by carvedilol therapy in advanced heart failure. Journal of cardiovascular pharmacology 45(6): 563-8	- Study does not contain an intervention relevant to this review protocol *Unclear number of participants receiving background medication.*
Pamporis, Konstantinos, Karakasis, Paschalis, Sagris, Marios et al. (2024) Mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: a systematic review and network meta-analysis of 32 randomized trials. Current problems in cardiology 49(7): 102615	- Systematic review does not contain a protocol comparison *Within class comparison and includes unlisted MRA*
Pan, Deng, Xu, Lin, Chen, Pengfei et al. (2021) Empagliflozin in Patients With Heart Failure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Frontiers in cardiovascular medicine 8: 683281	- Systematic review indirectly matches the review protocol: used as source of primary studies
Pandey, Arjun K, Dhingra, Nitish K, Hibino, Makoto et al. (2022) Sodium-glucose cotransporter 2 inhibitors in heart failure with reduced or preserved ejection fraction: a meta-analysis. ESC heart failure 9(2): 942-946	- Systematic review indirectly matches the review protocol: used as source of primary studies

Study	Exclusion reason
	Indirect population (mixed LVEF): not stratified for outcomes of interest
Pang, Zhihua, Pan, Chang, Yao, Zhuhua et al. (2021) A study of the sequential treatment of acute heart failure with sacubitril/valsartan by recombinant human brain natriuretic peptide: A randomized controlled trial. Medicine 100(16): e25621	- Study does not contain an intervention relevant to this review protocol *Recombinant human brain natriuretic peptide*
Paolisso, G, Gambardella, A, Marrazzo, G et al. (1992) Metabolic and cardiovascular benefits deriving from beta-adrenergic blockade in chronic congestive heart failure. American heart journal 123(1): 103-110	- Study design not relevant to this review protocol *Cross-over RCT*
Park, Dae Yong, An, Seokyung, Attanasio, Steve et al. (2023) Network Meta-Analysis Comparing Angiotensin Receptor-Neprilysin Inhibitors, Angiotensin Receptor Blockers, and Angiotensin-Converting Enzyme Inhibitors in Heart Failure With Reduced Ejection Fraction. The American journal of cardiology 187: 84-92	- Systematic review indirectly matches the review protocol: used as source of primary studies
Parker, Andrea B; Yusuf, Salim; Naylor, C David (2002) The relevance of subgroup-specific treatment effects: the Studies Of Left Ventricular Dysfunction (SOLVD) revisited. American heart journal 144(6): 941-7	- Secondary publication of an included study that does not provide any additional relevant information *Secondary publication of prevention and treatment trials. Research questions are prognostic.*
Parker, JO (1993) The effects of oral ibopamine in patients with mild heart failure--a double blind placebo controlled comparison to furosemide. The Ibopamine Study Group. International journal of cardiology 40(3): 221-227	- Population not relevant to this review protocol *Mixed LVEF not matching either reduced or mildly reduced ejection fraction definitions* - Study does not contain an intervention relevant to this review protocol *Ibopamine*
Pastore, Maria Concetta, Stefanini, Andrea, Mandoli, Giulia Elena et al. (2024) Dapagliflozin Effects on Cardiac Deformation in Heart Failure and Secondary Clinical Outcome. JACC. Cardiovascular imaging 17(12): 1399-1408	- Population not relevant to this review protocol *Mixed EF and results not stratified*
Patoulias, Dimitrios, Papadopoulos, Christodoulos, Kassimis, George et al. (2021) Updated Meta-Analysis Evaluating the Beneficial Effects of Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With Heart Failure. The American journal of cardiology 161: 118-120	- Systematic review indirectly matches the review protocol: used as source of primary studies *Does not include all relevant RCTs*
Patrianakos, Alexandros P, Parthenakis, Fragiskos I, Mavrakis, Hercules E et al. (2005) Effects of Nebivolol on left ventricular function	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
and exercise capacity in patients with non-ischaemic dilated cardiomyopathy. A randomised placebo-controlled study. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 46(3): 199-207	*No outcome data (0 events in only relevant outcomes/ underpowered and no TTE).*
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	- Study does not contain an intervention relevant to this review protocol *Finerenone not licensed for CHF*
Pelayo, Jerald, Lo, Kevin Bryan, Peterson, Eric et al. (2021) Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers and outcomes in patients with acute decompensated heart failure: a systematic review and meta-analysis. Expert review of cardiovascular therapy 19(11): 1037-1043	- Systematic review indirectly matches the review protocol: used as source of primary studies *Included non-randomised studies*
Pellicori, Pierpaolo, Ofstad, Anne Pernille, Fitchett, David et al. (2020) Early benefits of empagliflozin in patients with or without heart failure: findings from EMPA-REG OUTCOME. ESC heart failure 7(6): 3401-3407	- Population not relevant to this review protocol *Analysed populations includes patients with and without HF*
Penston, J. (2003) The CHARM programme. Lancet 362(9396): 1678-1679	- Publication type not relevant to review protocol *Letter/ commentary*
Persson, Hans, Lonn, Eva, Edner, Magnus et al. (2007) Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. Journal of the American College of Cardiology 49(6): 687-94	- Population not relevant to this review protocol *Mixed LVEF*
Petrie, Mark C, Udell, Jacob A, Anker, Stefan D et al. (2024) Empagliflozin in acute myocardial infarction in patients with and without type 2 diabetes: A pre-specified analysis of the EMPACT-MI trial. European journal of heart failure	- Population not relevant to this review protocol *Acute MI an exclusion*
Petrie, Mark C, Verma, Subodh, Docherty, Kieran F et al. (2020) Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. JAMA 323(14): 1353-1368	- Population not relevant to this review protocol *Reduced LVEF*
Pfeffer MA, Claggett B, Assmann SF 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	- Population not relevant to this review protocol *Population was comprised of patients with preserved ejection fraction*
Pfeffer MA, Swedberg K, Granger CB et al. (2003) Effects of candesartan on mortality and	- Publication type not relevant to review protocol

Study	Exclusion reason
morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet (London, England) 362(9386): 759-766	*Commentary article*
Pfeffer, MA, Braunwald, E, Moy?, LA et al. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. The New England journal of medicine 327(10): 669-677	- Population not relevant to this review protocol *Acute MI and no heart failure*
Pfeffer, Marc A, McMurray, John J V, Velazquez, Eric J et al. (2003) Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. The New England journal of medicine 349(20): 1893-906	- Population not relevant to this review protocol *Acute MI*
Piccirillo, Gianfranco, Quaglione, Raffaele, Nocco, Marialuce et al. (2002) Effects of long-term beta-blocker (metoprolol or carvedilol) therapy on QT variability in subjects with chronic heart failure secondary to ischemic cardiomyopathy. The American journal of cardiology 90(10): 1113-7	- Comparator in study does not match that specified in this review protocol *Within drug class comparison*
Piepoli, Massimo F, Hussain, Rizwan I, Comin-Colet, Josep et al. (2021) OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. European journal of heart failure 23(1): 127-135	- Population not relevant to this review protocol *Reduced LVEF*
Pierce, Jacob B, Mentz, Robert J, Sun, Jie-Lena et al. (2022) Titration of medical therapy and clinical outcomes among patients with heart failure with reduced ejection fraction: Findings from the HF-ACTION trial. American heart journal 251: 115-126	- Study does not contain any outcome data relevant to this review protocol *The study reports the association of dose trajectory of ACEI and beta-blockers with the outcomes. The original trial evaluated the effect of exercise therapy vs. usual care.*
Pieske, Burkert, Wachter, Rolf, Shah, Sanjiv J et al. (2021) Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial. JAMA 326(19): 1919-1929	- Population not relevant to this review protocol *Less than 80% trial population had HFmrEF (majority HFpEF)*
Pietschner, R, Kolwelter, J, Bosch, A et al. (2021) Effect of empagliflozin on ketone bodies in patients with stable chronic heart failure. Cardiovascular diabetology 20(1): 219	- Study does not contain any outcome data relevant to this review protocol
Pitt B, Zannad F, Remme WJ et al. (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure.	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine 341(10): 709-717	*HFrEF: not combination treatment in control group*
Pitt, B, Poole-Wilson, P A, Segal, R et al. (2000) Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet (London, England) 355(9215): 1582-7	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Pitt, B, Segal, R, Martinez, FA et al. (1997) Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet (London, England) 349(9054): 747-752	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Pitt, Bertram, Anker, Stefan D, Bohm, Michael et al. (2015) Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. European journal of heart failure 17(2): 224-32	- Study design not relevant to this review protocol *Design and rationale of a dose finding study*
Pitt, Bertram, Filippatos, Gerasimos, Gheorghiade, Mihai et al. (2012) Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. European journal of heart failure 14(6): 668-75	- Duration of follow up <3 months *Follow-up was 6 weeks*
Pitt, Bertram, Gheorghiade, Mihai, Zannad, Faiez et al. (2006) Evaluation of eplerenone in the subgroup of EPHESUS patients with baseline left ventricular ejection fraction <or=30%. European journal of heart failure 8(3): 295-301	- Population not relevant to this review protocol *Acute MI*
Pitt, Bertram, Kober, Lars, Ponikowski, Piotr et al. (2013) Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. European heart journal 34(31): 2453-63	- Duration of follow up <3 months *Follow up period was 4 weeks*
Pitt, Bertram, Remme, Willem, Zannad, Faiez et al. (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. The New England journal of medicine 348(14): 1309-21	- Population not relevant to this review protocol *Acute MI at randomisation*
Pitt, Bertram, White, Harvey, Nicolau, Jose et al. (2005) Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic	- Population not relevant to this review protocol *Population comprised of acute MI patients*

Study	Exclusion reason
dysfunction and heart failure. Journal of the American College of Cardiology 46(3): 425-31	
Pocock, Stuart, Wang, Duolao, Wilhelmsen, Lars et al. (2005) The data monitoring experience in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) program. American heart journal 149(5): 939-43	- Study design not relevant to this review protocol *Post hoc exploratory analysis*
Podzolkov, VI, Tarzimanova, AI, Bragina, AE et al. (2022) Effect of spironolactone therapy on the activity of the matrix metalloproteinase system in patients with heart failure after COVID-19. Cardiovascular therapy and prevention (russian federation) 21(10): 33-40	- Study not reported in English *Non-English language study (Russian)*
Poole-Wilson, Philip A, Cleland, John G F, Di Lenarda, Andrea et al. (2002) Rationale and design of the carvedilol or metoprolol European trial in patients with chronic heart failure: COMET. European journal of heart failure 4(3): 321-9	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Poole-Wilson, Philip A, Swedberg, Karl, Cleland, John G F et al. (2003) Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet (London, England) 362(9377): 7-13	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Pozzi, A, Cirelli, C, Merlo, A et al. (2023) Adverse effects of sodium-glucose cotransporter-2 inhibitors in patients with heart failure: a systematic review and meta-analysis. Heart failure reviews	- Systematic review indirectly matches the review protocol: used as source of primary studies *Background treatment not specified. Comparator was placebo.*
Preiss, David, van Veldhuisen, Dirk J, Sattar, Naveed et al. (2012) Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). European journal of heart failure 14(8): 909-15	- Secondary publication of an included study that does not provide any additional relevant information
Prisant, L Michael, Thomas, Kevin L, Lewis, Eldrin F et al. (2008) Racial analysis of patients with myocardial infarction complicated by heart failure and/or left ventricular dysfunction treated with valsartan, captopril, or both. Journal of the American College of Cardiology 51(19): 1865-71	- Population not relevant to this review protocol *Acute MI*
Prochaska, Jurgen H, Junger, Claus, Schulz, Andreas et al. (2023) Effects of empagliflozin on left ventricular diastolic function in addition to usual care in individuals with type 2 diabetes mellitus-results from the randomized, double-blind, placebo-controlled EmDia trial. Clinical	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
research in cardiology : official journal of the German Cardiac Society 112(7): 911-922	
Qin, Hailun, Dewan, Pooja, Santema, Bernadet T et al. (2024) Achieved dose and treatment discontinuation of candesartan in men and women with chronic heart failure: data from CHARM. ESC heart failure 11(4): 1880-1887	- Comparator in study does not match that specified in this review protocol *Pooled CHARM-added (which meets our protocol) with CHARM-alternative (which doesn't meet out protocol as it was ARB vs placebo with <50% on background BB)*
Qin, Jianbin, Wang, Weijian, Wei, Ping et al. (2022) Effects of sacubitril-valsartan on heart failure patients with mid-range ejection fractions: A systematic review and meta-analysis. Frontiers in pharmacology 13: 982372	- Systematic review indirectly matches the review protocol: used as source of primary studies *The systematic review included cohort studies and the follow-up period was variable (with no noted restrictions)*
Qin, S, Zhang, Z, Shi, J et al. (2021) Efficacy of sacubitril valsartan in treatment of chronic cardiac insufficiency. Drug evaluation research 44(6): 1270-1274	- Study not reported in English *Non-English language study (Chinese)*
Qiu, Mei; Ding, Liang-Liang; Zhou, Hai-Rong (2021) Factors affecting the efficacy of SGLT2is on heart failure events: a meta-analysis based on cardiovascular outcome trials. Cardiovascular diagnosis and therapy 11(3): 699-706	- Systematic review does not contain a protocol intervention *Includes studies of SGLT2i (not licensed in the UK), mixture of studies with rEF and pEF, population does not meet protocol.*
Qu, Wei; Li, Xia; Yu, Zhuxian (2019) The curative effect of carvedilol combined with conventional therapy in treatment of chronic heart failure. Pakistan journal of pharmaceutical sciences 32(3special): 1427-1430	- Study does not contain any outcome data relevant to this review protocol *Quality of life is reported, but it is not clear if a validated measure was used and if final values were reported.*
Radack, K and Deck, C (1991) Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. Archives of internal medicine 151(9): 1769-76	- Population not relevant to this review protocol *Peripheral arterial disease*
Rambarat, Paula and Newby, L Kristin (2024) RAS blocker effects on first HF hospitalization or CV death does not differ in Black and non-Black patients with HFrEF. Annals of internal medicine 177(10): jc112	- Review article but not a systematic review
Ramires, F J, Mansur, A, Coelho, O et al. (2000) Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. The American journal of cardiology 85(10): 1207-11	- Study does not contain any outcome data relevant to this review protocol
Rector, Thomas S, Carson, Peter E, Anand, Inder S et al. (2012) Assessment of long-term effects of irbesartan on heart failure with	- Population not relevant to this review protocol

Study	Exclusion reason
preserved ejection fraction as measured by the minnesota living with heart failure questionnaire in the irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial. Circulation. Heart failure 5(2): 217-25	*Less than 80% trial population had HFmrEF (majority HFpEF)*
Rector, TS, Johnson, G, Dunkman, WB et al. (1993) Evaluation by patients with heart failure of the effects of enalapril compared with hydralazine plus isosorbide dinitrate on quality of life. V-HeFT II. The V-HeFT VA Cooperative Studies Group. Circulation 87(6suppl): vi71	- Comparator in study does not match that specified in this review protocol *Hydralazine and isosorbide dinitrate*
Refsgaard, Jens, Thomsen, Claus, Andreasen, Frederik et al. (2002) Carvedilol does not alter the insulin sensitivity in patients with congestive heart failure. European journal of heart failure 4(4): 445-53	- Study does not contain any outcome data relevant to this review protocol *Reports insulin sensitivity*
Reis, Joao, Teixeira, Ana Rita, Goncalves, Antonio Valentim et al. (2022) Dapagliflozin Impact on the Exercise Capacity of Non-Diabetic Heart Failure with Reduced Ejection Fraction Patients. Journal of clinical medicine 11(10)	- Population not relevant to this review protocol *Comprised of a population with mixed EF status*
Remme, Willem J, Cleland, John G, Erhardt, Leif et al. (2007) Effect of carvedilol and metoprolol on the mode of death in patients with heart failure. European journal of heart failure 9(11): 1128-35	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Remme, Willem J, Riegger, Guenter, Hildebrandt, Per et al. (2004) The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor remodelling mild heart failure evaluation trial (CARMEN). Cardiovascular drugs and therapy 18(1): 57-66	- Comparator in study does not match that specified in this review protocol *Comparator not dual therapy*
Remme, Willem J, Torp-Pedersen, Christian, Cleland, John G F et al. (2007) Carvedilol protects better against vascular events than metoprolol in heart failure: results from COMET. Journal of the American College of Cardiology 49(9): 963-71	- Comparator in study does not match that specified in this review protocol *Within-class comparison*
Remme, WJ (2001) The Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure EvaluatioN trial (CARMEN)--rationale and design. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 15(1): 69-77	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Requena-Ibanez, Juan Antonio, Santos-Gallego, Carlos G, Rodriguez-Cordero, Anderly et al. (2021) Mechanistic Insights of Empagliflozin in Nondiabetic Patients With HFrEF: From the EMPA-TROPISM Study. JACC. Heart failure 9(8): 578-589	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
Reyaz, Ibrahim, Kaur, Avneet, Saad, Moyal Z et al. (2023) Comparison of Outcomes Between Sacubitril/Valsartan and Enalapril in Patients With Heart Failure: A Systematic Review and Meta-Analysis. Cureus 15(11): e48623	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Insufficient reporting of study characteristics and no risk of bias assessment*
Riegger, G A, Bouzo, H, Petr, P et al. (1999) Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexetil. Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) Investigators. Circulation 100(22): 2224-30	- Study does not contain an intervention relevant to this review protocol *Monotherapy only*
Rindone, Joseph P and Mellen, Chadwick K (2024) Sacubitril/valsartan compared to equivalent/sub-equivalent dose angiotensin receptor blocker or angiotensin-converting enzyme inhibitor in heart failure with reduced ejection fraction: a meta-analysis of randomized trials. European journal of clinical pharmacology 80(8): 1113-1120	- Systematic review indirectly matches the review protocol: used as source of primary studies *Checked this SR - no studies identified*
Rivera-Martinez, Juan Carlos, Sabina, Michael, Khanani, Aqeel et al. (2025) Effect of Finerenone in Cardiovascular and Renal Outcomes: A Systematic Review and Meta-analysis. Cardiovascular drugs and therapy	- Systematic review indirectly matches the review protocol: used as source of primary studies *Checked and no extra studies identified*
Rogers JK, McMurray JJ, Pocock SJ et al. (2012) Eplerenone in patients with systolic heart failure and mild symptoms: analysis of repeat hospitalizations. Circulation 126(19): 2317-2323	- Population not relevant to this review protocol *Reduced LVEF*
Rogers, Jennifer K, Pocock, Stuart J, McMurray, John J V et al. (2014) Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. European journal of heart failure 16(1): 33-40	- Population not relevant to this review protocol *Participants with LVEF >40%. No subgroup data for HFmrEF*
Rohde, Luis E, Claggett, Brian L, Wolsk, Emil et al. (2021) Cardiac and Noncardiac Disease Burden and Treatment Effect of Sacubitril/Valsartan: Insights From a Combined PARAGON-HF and PARADIGM-HF Analysis. Circulation. Heart failure 14(3): e008052	- Data not reported in an extractable format or a format that can be analysed *Pooled analysis of two trials, one HFrEF and one HFmrEF*
Rossignol P, Dobre D, McMurray JJ et al. (2014) Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and	- Secondary publication of an included study that does not provide any additional relevant information *EMPHASIS-HF: post hoc analysis of hyperkalaemia occurrence based on baseline characteristics*

Study	Exclusion reason
Survival Study in Heart Failure (EMPHASIS-HF). Circulation. Heart failure 7(1): 51-58	
Rossignol, Patrick, Claggett, Brian Lee, Liu, Jiankang et al. (2018) Spironolactone and Resistant Hypertension in Heart Failure With Preserved Ejection Fraction. American journal of hypertension 31(4): 407-414	- Population not relevant to this review protocol *Participants with LVEF greater or equal to 45%. No subgroup data for HFmrEF reported*
Rossignol, Patrick, Girerd, Nicolas, Bakris, George et al. (2017) Impact of eplerenone on cardiovascular outcomes in heart failure patients with hypokalaemia. European journal of heart failure 19(6): 792-799	- Secondary publication of an included study that does not provide any additional relevant information
Rouleau, Jean L, Roecker, Ellen B, Tendera, Michal et al. (2004) Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. Journal of the American College of Cardiology 43(8): 1423-9	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Rujic, D., Schou, M., Madsen, P.L. et al. (2023) Echocardiographic Evaluation of Spironolactone on Myocardial Remodeling in Atrial Fibrillation with Preserved Ejection Fraction: the INSPIRE-AF randomized controlled trial. medRxiv	- Population not relevant to this review protocol *Study excluded population with heart failure NYHA functional class greater than or equal to II*
Rydén L, Armstrong PW, Cleland JG et al. (2000) Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. European heart journal 21(23): 1967-1978	- Comparator in study does not match that specified in this review protocol *Dose comparison*
Samir, Ahmad, Aboel-Naga, Salma, Shehata, Ahmed et al. (2023) Telmisartan versus EnalapRil In heart failure with redUced ejection fraction patients with Moderately impaired kidney Functions; randomized controlled trial: "TRIUMF trial". The Egyptian heart journal : (EHJ) : official bulletin of the Egyptian Society of Cardiology 75(1): 68	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Sanderson, J E, Chan, S K, Yip, G et al. (1999) Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. Journal of the American College of Cardiology 34(5): 1522-8	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Sanderson, JE, Chan, SK, Yu, CM et al. (1998) Beta blockers in heart failure: a comparison of a vasodilating beta blocker with metoprolol. Heart (British Cardiac Society) 79(1): 86-92	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*
Santos-Gallego, Carlos G, Garcia-Ropero, Alvaro, Mancini, Donna et al. (2019) Rationale and Design of the EMPA-TROPISM Trial (ATRU-4): Are the "Cardiac Benefits" of Empagliflozin Independent of its Hypoglycemic	- Protocol for an excluded study

Study	Exclusion reason
Activity?. Cardiovascular drugs and therapy 33(1): 87-95	
Santos-Gallego, Carlos G, Vargas-Delgado, Ariana P, Requena-Ibanez, Juan Antonio et al. (2021) Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. Journal of the American College of Cardiology 77(3): 243-255	- Population not relevant to this review protocol *<50% LVEF and baseline LVEF (36^ +/- 8%). Does not meet 80% threshold.*
Savage, Henry Oluwasefunmi, Dimarco, Anthony David, Li, Brian et al. (2023) Sequencing of medical therapy in heart failure with a reduced ejection fraction. Heart (British Cardiac Society) 109(7): 511-518	- Review article but not a systematic review *Non-systematic review regarding sequencing of medical therapy*
Savarese, Gianluigi, Uijl, Alicia, Lund, Lars H et al. (2021) Empagliflozin in Heart Failure With Predicted Preserved Versus Reduced Ejection Fraction: Data From the EMPA-REG OUTCOME Trial. Journal of cardiac failure 27(8): 888-895	- Study does not contain any outcome data relevant to this review protocol *Study used a predictive model to ascertain LVEF, LVmrEF or LVpEF*
Schoene, N, Keicher, C, Erbs, S et al. (2001) Influence of beta-blockage on endothelial dysfunction and haemodynamic parameters in congestive heart failure: a prospective randomised, placebo-controlled comparison of Carvedilol and Metoprolol. Zeitschrift fur Kardiologie 90(suppl2): 37	- Study not reported in English *Non-English language study*
Schou, Morten, Claggett, Brian, Miao, Zi Michael et al. (2023) Sacubitril/valsartan compared to ramipril in high-risk post-myocardial infarction patients stratified according to use of mineralocorticoid receptor antagonists: insight from the PARADISE MI trial. European journal of heart failure	- Conference abstract *Conference abstract*
Selvaraj, S., Claggett, B.L., Packer, M. et al. (2021) Effects of Sacubitril/Valsartan on Serum Lipids in Heart Failure With Preserved Ejection Fraction. Journal of the American Heart Association 10(17): e022069	- Population not relevant to this review protocol *preserved EF* - Study does not contain any outcome data relevant to this review protocol *Lipid outcomes*
Senni, Michele, McMurray, John J V, Wachter, Rolf et al. (2016) Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. European journal of heart failure 18(9): 1193-202	- Duration of follow up <3 months *Duration 11 weeks*
Senni, Michele, McMurray, John J V, Wachter, Rolf et al. (2018) Impact of systolic blood pressure on the safety and tolerability of initiating and up-titrating sacubitril/valsartan in	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
patients with heart failure and reduced ejection fraction: insights from the TITRATION study. European journal of heart failure 20(3): 491-500	*Post hoc analysis/ retrospective subgroup of RCT*
Serenelli, Matteo, Bohm, Michael, Inzucchi, Silvio E et al. (2020) Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). European heart journal 41(36): 3402-3418	- Secondary publication of an included study that does not provide any additional relevant information *Cross-referenced with parent study, no additional analyses of interest*
Serenelli, Matteo, Jackson, Alice, Dewan, Pooja et al. (2020) Mineralocorticoid Receptor Antagonists, Blood Pressure, and Outcomes in Heart Failure With Reduced Ejection Fraction. JACC. Heart failure 8(3): 188-198	- Study design not relevant to this review protocol *Post hoc/ retrospective subgroup*
Shah AM, Claggett B, Sweitzer NK 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): 740-751	- Population not relevant to this review protocol *Preserved ejection fraction*
Shah AM, Claggett B, Sweitzer NK et al. (2015) Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. Circulation 132(5): 402-414	- Population not relevant to this review protocol *Preserved ejection fraction*
Shah AM, Claggett B, Sweitzer NK 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): 1052-1058	- Population not relevant to this review protocol *Preserved ejection fraction*
Shah AM, Shah SJ, Anand IS 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): 104-115	- Study design not relevant to this review protocol *Cross sectional data from baseline assessment only*
Shah SJ, Heitner JF, Sweitzer NK 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): 184-192	- Population not relevant to this review protocol *Preserved ejection fraction*
Shah, Sanjiv J, Cowie, Martin R, Wachter, Rolf et al. (2021) Baseline characteristics of patients in the PARALLAX trial: insights into quality of life and exercise capacity in heart failure with preserved ejection fraction. European journal of heart failure 23(9): 1541-1551	- Population not relevant to this review protocol *>80% preserved LVEF*

Study	Exclusion reason
Shah, Yaksh R and Turgeon, Ricky D (2024) Impact of SGLT2 Inhibitors on Quality of Life in Heart Failure Across the Ejection Fraction Spectrum: Systematic Review and Meta-analysis. CJC open 6(4): 639-648	- Systematic review indirectly matches the review protocol: used as source of primary studies *No additional studies identified*
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 *Only includes participants with LVEF greater than or equal to 55%.*
Sharma, D, Buyse, M, Pitt, B et al. (2000) Meta-analysis of observed mortality data from all-controlled, double-blind, multiple-dose studies of losartan in heart failure. Losartan Heart Failure Mortality Meta-analysis Study Group. The American journal of cardiology 85(2): 187-92	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies - Systematic review indirectly matches the review protocol: used as source of primary studies *No restriction on length of follow-up*
Shen, Li, Kristensen, Soren Lund, Bengtsson, Olof et al. (2021) Dapagliflozin in HFrEF Patients Treated With Mineralocorticoid Receptor Antagonists: An Analysis of DAPA-HF. JACC. Heart failure 9(4): 254-264	- Population not relevant to this review protocol *Reduced LVEF*
Shettigar, U, Hare, T, Gelperin, K et al. (1999) Effects of fosinopril on exercise tolerance, symptoms, and clinical outcomes in patients with decompensated heart failure. Congestive heart failure 5(1): 27-34	- Study does not contain an intervention relevant to this review protocol *Monotherapy with background therapy of diuretic*
Shibata, M C; Flather, M D; Wang, D (2001) Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. European journal of heart failure 3(3): 351-7	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies - Systematic review indirectly matches the review protocol: used as source of primary studies
Shibata, M C; Tsuyuki, R T; Wiebe, N (2008) The effects of angiotensin-receptor blockers on mortality and morbidity in heart failure: a systematic review. International journal of clinical practice 62(9): 1397-402	- Systematic review does not contain a protocol intervention *Systematic review does not match the protocol*
Shibata, M.C., Flather, M.D., Bohm, M. et al. (2002) Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS). Rationale and design. International Journal of Cardiology 86(1): 77-85	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
Shim, C.Y., Seo, J., Cho, I. et al. (2021) Randomized, Controlled Trial to Evaluate the Effect of Dapagliflozin on Left Ventricular Diastolic Function in Patients With Type 2 Diabetes Mellitus: The IDDIA Trial. Circulation 143(5): 510-512	- Study does not contain any outcome data relevant to this review protocol *No outcomes of interest*
Shiraishi, J., Sawada, T., Kimura, S. et al. (2011) Enhanced cardiovascular protective effects of valsartan in high-risk hypertensive patients with left ventricular hypertrophy: Sub-analysis of the KYOTO HEART Study. Circulation Journal 75(4): 806-814	- Article retracted *Retracted from Circulation Journal*
Shirakabe, Akihiro, Matsushita, Masato, Kiuchi, Kazutaka et al. (2020) Empagliflozin Administration Can Decrease the Dose of Loop Diuretics and Prevent the Exacerbation of Renal Tubular Injury in Patients With Compensated Heart Failure Complicated by Diabetes. Circulation reports 2(10): 565-575	- Population not relevant to this review protocol *Participants with HF included acute and chronic HF.*
Shlipak MG, Smith GL, Rathore SS et al. (2004) Renal function, digoxin therapy, and heart failure outcomes: evidence from the digoxin intervention group trial. Journal of the American Society of Nephrology : JASN 15(8): 2195-2203	- Study does not contain an intervention relevant to this review protocol *Digoxin*
Shu, M., Xi, R., Zhang, P. et al. (2005) Short-term and long-term effects of bisoprolol on chronic heart failure related to rheumatic heart disease and atrial fibrillation. P and T 30(7): 400-407	- Population not relevant to this review protocol *Heart failure related to rheumatic heart disease and atrial fibrillation*
Silva, Alessandra Rodrigues, Martini, Alexandre Goes, Canto, Graziela De Luca et al. (2019) Effects of dual blockade in heart failure and renal dysfunction: Systematic review and meta-analysis. Journal of the renin-angiotensin-aldosterone system : JRAAS 20(4): 1470320319882656	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *LVEF not reported at all for included studies*
Silverman, Daniel N, Plante, Timothy B, Infeld, Margaret et al. (2019) Association of beta-Blocker Use With Heart Failure Hospitalizations and Cardiovascular Disease Mortality Among Patients With Heart Failure With a Preserved Ejection Fraction: A Secondary Analysis of the TOPCAT Trial. JAMA network open 2(12): e1916598	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis/ retrospective subgroup of RCT*
Singh, Jagdeep S S, Fathi, Amir, Vickneson, Keeran et al. (2016) Research into the effect Of SGLT2 inhibition on left ventricular remodelling in patients with heart failure and diabetes mellitus (REFORM) trial rationale and design. Cardiovascular diabetology 15: 97	- Protocol for an excluded study

Study	Exclusion reason
Singh, Jagdeep S S, Mordi, Ify R, Vickneson, Keeran et al. (2020) Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial. Diabetes care 43(6): 1356-1359	- Population not relevant to this review protocol *Unclear LVEF and 44% NYHA class I*
Singh, M., Shah, T., Adigopula, S. et al. (2011) Safety and efficacy of rennin-angiotensin system inhibitors in heart failure with preserved ejection fraction. International Journal of Collaborative Research on Internal Medicine and Public Health 3(4): 295-310	- Population not relevant to this review protocol *Participants with HFpEF*
Sitnikova, MIu and Shliakhto, EV (2003) Endothelial protection in patients with apparent cardiac failure in long-term therapy by carvedilol. Klinicheskaia meditsina 81(7): 44-47	- Study not reported in English *Non-English language study*
Skvortsov, AA, Mareev, VIu, Nasonova, SN et al. (2006) Is triple combination of different neurohormonal modulators recommended for treatment of mild-to-moderate congestive heart failure patients? (Results of SADKO-CHF study). Part 2. Terapevticheskii arkhiv 78(9): 61-71	- Study not reported in English *Study reported in Russian*
Skvortsov, AA, Nasonova, SN, Sychev, AV et al. (2006) Effects of long term therapy with angiotensin converting enzyme inhibitor quinapril, antagonist of receptors to angiotensin II valsartan, and combination of quinapril and valsartan in patients with moderate chronic heart failure. Main results of the SADKO-CHF study. Kardiologiia 46(7): 33-51	- Study not reported in English *Study reported in Russian*
Sliwa, K. (2005) Carvedilol before angiotensin-converting enzyme inhibitor therapy in heart failure. Cardiology Review 22(10): 24-27	- Population not relevant to this review protocol *Patients with idiopathic dilated cardiomyopathy*
Sliwa, Karen, Norton, Gavin R, Kone, Ngalulawa et al. (2004) Impact of initiating carvedilol before angiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure. Journal of the American College of Cardiology 44(9): 1825-30	- Study does not contain an intervention relevant to this review protocol *Monotherapy with background therapy of digoxin*
Solomon, Scott D, Claggett, Brian, Desai, Akshay S et al. (2016) Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. Circulation. Heart failure 9(3): e002744	- Secondary publication of an included study that does not provide any additional relevant information *PARADIGM-HF*
Solomon, Scott D, Claggett, Brian, Packer, Milton et al. (2016) Efficacy of Sacubitril/Valsartan Relative to a Prior	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
Decompensation: The PARADIGM-HF Trial. JACC. Heart failure 4(10): 816-822	
Solomon, Scott D, Jhund, Pardeep S, Claggett, Brian L et al. (2020) Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan: The DAPA-HF Trial. JACC. Heart failure 8(10): 811-818	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis comparing patients with/ without ARNI at baseline. Post hoc not mentioned in design paper.*
Solomon, Scott D, Wang, Duolao, Finn, Peter et al. (2004) Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 110(15): 2180-3	- Secondary publication of an included study that does not provide any additional relevant information *No additional information*
Spertus, John A, Tooley, Joseph, Jones, Phil et al. (2002) Expanding the outcomes in clinical trials of heart failure: the quality of life and economic components of EPHESUS (EPlerenone's neuroHormonal Efficacy and SUrvival Study). American heart journal 143(4): 636-42	- Population not relevant to this review protocol *Population comprised of acute MI participants*
Spinarova, L; Spinar, J; Vitovec, J (2014) Conclusions of the PARADIGM-HF study. Kardiologicka revue - interni medicina 16(5): 395-397	- Study not reported in English
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	- Review article but not a systematic review *Narrative*
Sturm B, Pacher R, Strametz-Juranek J et al. (2000) Effect of beta 1 blockade with atenolol on progression of heart failure in patients pretreated with high-dose enalapril. European journal of heart failure 2(4): 407-412	- Study does not contain an intervention relevant to this review protocol *Atenolol not licensed for CHF*
Suebsaicharoen, Thanakit, Chunekamrai, Puri, Yingchoncharoen, Teerapat et al. (2023) Comparative cardiovascular outcomes of novel drugs as an addition to conventional triple therapy for heart failure with reduced ejection fraction (HFrEF): a network meta-analysis of randomised controlled trials. Open heart 10(2)	- Systematic review does not contain a protocol intervention *Includes interventions not in review protocol*
Suzuki, Hiroshi, Geshi, Eiichi, Nanjyo, Shuji et al. (2009) Inhibitory effect of valsartan against progression of left ventricular dysfunction after myocardial infarction: T-VENTURE study. Circulation journal : official journal of the Japanese Circulation Society 73(5): 918-24	- Population not relevant to this review protocol *Patients with acute MI*

Study	Exclusion reason
Swedberg K, Komajda M, Böhm M et al. (2010) Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). European journal of heart failure 12(1): 75-81	- Study does not contain an intervention relevant to this review protocol *HFrEF: ivabradine*
Swedberg, K and Kjekshus, J (1988) Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The American journal of cardiology 62(2): 60a-66a	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
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	- Population not relevant to this review protocol *Preserved LVEF*
Tang, Huilin, Germinal, Kimberly, Milfort, Alexandra et al. (2024) The most effective combination of pharmacological therapy for heart failure with reduced ejection fraction: a network meta-analysis of randomized controlled trials. BMC cardiovascular disorders 24(1): 666	- Network meta-analysis does not include all relevant trials
Tang, Jia, Wang, Ping, Liu, Chenxi et al. (2024) Pharmacotherapy in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. Chinese medical journal	- Data not reported in an extractable format or a format that can be analysed
Tang, W H Wilson, Vagelos, Randall H, Yee, Yin Gail et al. (2002) Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. Journal of the American College of Cardiology 39(1): 70-8	- Comparator in study does not match that specified in this review protocol *Dose comparison*
Tatli, E., Kurum, T., Aktoz, M. et al. (2008) Effects of carvedilol on right ventricular ejection fraction and cytokines levels in patients with systolic heart failure. International Journal of Cardiology 125(2): 273-276	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Tatli, Ersan and Kurum, Turhan (2005) A controlled study of the effects of carvedilol on clinical events, left ventricular function and proinflammatory cytokines levels in patients with dilated cardiomyopathy. The Canadian journal of cardiology 21(4): 344-8	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Taylor, Anne L, Ziesche, Susan, Yancy, Clyde et al. (2004) Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. The New England journal of medicine 351(20): 2049-57	- Comparator in study does not match that specified in this review protocol *Hydralazine*

Study	Exclusion reason
Taylor, Anne L, Ziesche, Susan, Yancy, Clyde W et al. (2007) Early and sustained benefit on event-free survival and heart failure hospitalization from fixed-dose combination of isosorbide dinitrate/hydralazine: consistency across subgroups in the African-American Heart Failure Trial. Circulation 115(13): 1747-53	- Study does not contain an intervention relevant to this review protocol *Hydralazine nitrate*
Teo, Yao Neng, Teo, Yao Hao, Syn, Nicholas L et al. (2022) Comparing Sacubitril/Valsartan Against Sodium-Glucose Cotransporter 2 Inhibitors in Heart Failure: A Systematic Review and Network Meta-analysis. Clinical drug investigation 42(1): 1-16	- Systematic review does not contain a protocol population *HF not defined*
Tepper D (1999) Frontiers in congestive heart failure: Effect of Metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Congestive heart failure (Greenwich, Conn.) 5(4): 184-185	- Publication type not relevant to review protocol *Commentary*
ter Maaten, J.M., Mebazaa, A., Davison, B. et al. (2023) Early changes in renal function during rapid up-titration of guideline-directed medical therapy following an admission for acute heart failure. European Journal of Heart Failure 25(12): 2230-2242	- Secondary publication of an included study that does not provide any additional relevant information
Terzi, S, Dayi, SU, Akbulut, T et al. (2003) Assessment of the efficacy of bisoprolol administration by cardiopulmonary exercise testing in patients with heart failure. Anadolu kardiyoloji dergisi [Anatolian journal of cardiology] 3(4): 313-318	- Study not reported in English
Tillmann, HC, Sharpe, N, Sponer, G et al. (2001) Does intention-to-treat analysis answer all questions in long-term mortality trials? Considerations on the basis of the ANZ trial. International journal of clinical pharmacology and therapeutics 39(5): 205-212	- Study design not relevant to this review protocol *HFrEF: Post-hoc analysis of trial data*
Tiwari, Krishna, Deora, Surender, Choudhary, Rahul et al. (2024) Rationale and design of Dapagliflozin vErsus SacubiTrIl-valsartaN therapY in Heart Failure with reduced ejection fraction (DESTINY-HF): a pragmatic randomised controlled trial protocol. BMJ open 14(10): e089562	- Publication type not relevant to review protocol *Protocol (rationale and design paper)*
Tomasik, Andrzej, Jachec, Wojciech, Wojciechowska, Celina et al. (2015) Randomized placebo controlled blinded study to assess valsartan efficacy in preventing left ventricle remodeling in patients with dual chamber pacemaker--Rationale and design of the trial. Contemporary clinical trials 42: 239-43	- Protocol for an excluded study

Study	Exclusion reason
Tonkon, M, Awan, N, Niazi, I et al. (2000) A study of the efficacy and safety of irbesartan in combination with conventional therapy, including ACE inhibitors, in heart failure. Irbesartan Heart Failure Group. International journal of clinical practice 54(1): 11	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Totsuka, Nobuo, Awata, Nobuhisa, Takahashi, Katsuhito et al. (2003) A Single-Center, Open-Label, Randomized, Parallel-Group Study Assessing the Differences Between an Angiotensin II Receptor Antagonist and an Angiotensin-Converting Enzyme Inhibitor in Hypertensive Patients with Congestive Heart Failure: The Research for Efficacy of Angiotensin II Receptor Antagonist in Hypertensive Patients with Congestive Heart Failure Study. Current therapeutic research, clinical and experimental 64(2): 81-94	- Study does not contain any outcome data relevant to this review protocol
Toyama, Takuji, Hoshizaki, Hiroshi, Seki, Ryotaro et al. (2003) Efficacy of carvedilol treatment on cardiac function and cardiac sympathetic nerve activity in patients with dilated cardiomyopathy: comparison with metoprolol therapy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 44(10): 1604-11	- Study does not contain any outcome data relevant to this review protocol
Tromp, Jasper, Ponikowski, Piotr, Salsali, Afshin et al. (2021) Sodium-glucose co-transporter 2 inhibition in patients hospitalized for acute decompensated heart failure: rationale for and design of the EMPULSE trial. European journal of heart failure 23(5): 826-834	- Population not relevant to this review protocol *Acute heart failure patients*
Tsujimoto, Tetsuro and Kajio, Hiroshi (2018) Efficacy of renin-angiotensin system inhibitors for patients with heart failure with preserved ejection fraction and mild to moderate chronic kidney disease. European journal of preventive cardiology 25(12): 1268-1277	- Study design not relevant to this review protocol *Post hoc analysis/ retrospective subgroup of RCT*
Tsutsui H, Ito H, Kitakaze M 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 *Reduced LVEF*
Tsutsui, H., Momomura, S.-I., Saito, Y. et al. (2024) Incidence and risk factors of hypotension-related adverse events among Japanese patients with heart failure receiving sacubitril/valsartan or enalapril: Results from the PARALLEL-HF study. Journal of Cardiology	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
Tsutsui, Hiroyuki, Momomura, Shin-Ichi, Saito, Yoshihiko et al. (2018) Angiotensin Receptor Neprilysin Inhibitor in Japanese Patients With Heart Failure and Reduced Ejection Fraction - Baseline Characteristics and Treatment of PARALLEL-HF Trial. Circulation journal : official journal of the Japanese Circulation Society 82(10): 2575-2583	- Population not relevant to this review protocol *Reduced LVEF*
Tsutsui, Hiroyuki, Momomura, Shin-Ichi, Saito, Yoshihiko et al. (2021) Efficacy and Safety of Sacubitril/Valsartan in Japanese Patients With Chronic Heart Failure and Reduced Ejection Fraction - Results From the PARALLEL-HF Study. Circulation journal : official journal of the Japanese Circulation Society 85(5): 584-594	- Population not relevant to this review protocol *Reduced LVEF*
Tsutsui, Hiroyuki, Momomura, Shinichi, Saito, Yoshihiko et al. (2017) Efficacy and safety of sacubitril/valsartan (LCZ696) in Japanese patients with chronic heart failure and reduced ejection fraction: Rationale for and design of the randomized, double-blind PARALLEL-HF study. Journal of cardiology 70(3): 225-231	- Population not relevant to this review protocol *Reduced LVEF*
Udelson JE, Feldman AM, Greenberg B et al. (2010) Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. Circulation. Heart failure 3(3): 347-353	- Population not relevant to this review protocol *Reduced LVEF*
Uhlir, O, Dvorak, I, Gregor, P et al. (1997) Nebivolol in the treatment of cardiac failure: a double-blind controlled clinical trial. Journal of cardiac failure 3(4): 271-276	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment* - Study does not contain any outcome data relevant to this review protocol
Upadhya, Bharathi, Hundley, William G, Brubaker, Peter H 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	- Population not relevant to this review protocol *All participants have HFpEF*
Uretsky, B F, Young, J B, Shahidi, F E et al. (1993) Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. Journal of the American College of Cardiology 22(4): 955-62	- Comparator in study does not match that specified in this review protocol *Comparing withdrawal of digoxin vs continuation of digoxin*

Study	Exclusion reason
Usman, Muhammad Shariq, Bhatt, Deepak L, Hameed, Ishaque et al. (2024) Effect of SGLT2 inhibitors on heart failure outcomes and cardiovascular death across the cardiometabolic disease spectrum: a systematic review and meta-analysis. The lancet. Diabetes & endocrinology 12(7): 447-461	- Systematic review indirectly matches the review protocol: used as source of primary studies *Identified in re-run search: no new trials not already included in review*
Uzunhasan, I., Yildiz, A., Coskun, U. et al. (2009) Effects of aldosterone blockade on left ventricular function and clinical status during acute myocardial infarction. Scandinavian Journal of Clinical and Laboratory Investigation 69(5): 545-549	- Population not relevant to this review protocol *Population not HF, acute MI patients*
Vader, Justin M, Givertz, Michael M, Starling, Randall C et al. (2022) Tolerability of Sacubitril/Valsartan in Patients With Advanced Heart Failure: Analysis of the LIFE Trial Run-In. JACC. Heart failure 10(7): 449-456	- Population not relevant to this review protocol *Patient characteristics were noted during the run-in period from the original trial*
Vaduganathan, Muthiah, Claggett, Brian L, Chatterjee, Neal A et al. (2018) Sudden Death in Heart Failure With Preserved Ejection Fraction: A Competing Risks Analysis From the TOPCAT Trial. JACC. Heart failure 6(8): 653-661	- Population not relevant to this review protocol *No HFmrEF subgroup reported. Less than 80% of the patient population matches the protocol.*
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	- Population not relevant to this review protocol *Not specific to mrEF population* - Study does not contain any outcome data relevant to this review protocol *Further secondary outcomes not in protocol*
Vaduganathan, Muthiah, Claggett, Brian L, Jhund, Pardeep S et al. (2020) Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet (London, England) 396(10244): 121-128	- Publication type not relevant to review protocol *Comparative analysis of 3 RCTs.*
Vaduganathan, Muthiah, Claggett, Brian L, Kulac, Ian J et al. (2024) Effects of the Non-Steroidal MRA Finerenone with and without Concomitant SGLT2 Inhibitor Use in Heart Failure. Circulation	- Population not relevant to this review protocol *Population not relevant to the review protocol, subgroup not of interest*
Vaduganathan, Muthiah, Cunningham, Jonathan W, Claggett, Brian L et al. (2021) Worsening Heart Failure Episodes Outside a Hospital Setting in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial. JACC. Heart failure 9(5): 374-382	- Population not relevant to this review protocol *Was considered for inclusion using the <57% LVEF subgroup, but another study Solomon 2020 includes a subgroup that meets the protocol more closely. So excluded based on population (LVEF too high to meet protocol)*

Study	Exclusion reason
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 30(12): 3758-3764	- Population not relevant to this review protocol *Pooled 3 studies: majority of patient analysed did not have CHF and results not stratified by LVEF*
Vaduganathan, Muthiah, Mentz, Robert J, Claggett, Brian L et al. (2023) Sacubitril/valsartan in heart failure with mildly reduced or preserved ejection fraction: a pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF. European heart journal 44(31): 2982-2993	- Secondary publication of an included study that does not provide any additional relevant information
van Dissel, Alexandra C, Winter, Michiel M, van der Bom, Teun et al. (2019) Long-term clinical outcomes of valsartan in patients with a systemic right ventricle: Follow-up of a multicenter randomized controlled trial. International journal of cardiology 278: 84-87	- Population not relevant to this review protocol *Not CHF*
van Veldhuisen, D J, Man in 't Veld, A J, Dunselman, P H et al. (1993) Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMT). Journal of the American College of Cardiology 22(6): 1564-73	- Study does not contain an intervention relevant to this review protocol - Comparator in study does not match that specified in this review protocol
van Veldhuisen, Dirk J, Cohen-Solal, Alain, Bohm, Michael et al. (2009) Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). Journal of the American College of Cardiology 53(23): 2150-8	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Vardeny O, Claggett B, Anand I et al. (2014) Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. Circulation. Heart failure 7(4): 573-579	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Vardeny O, Wu DH, Desai A et al. (2012) Influence of baseline and worsening renal function on efficacy of spironolactone in patients With severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). Journal of the American College of Cardiology 60(20): 2082-2089	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Vardeny, Orly, Cavallari, Larisa H, Claggett, Brian et al. (2013) Race influences the safety and efficacy of spironolactone in severe heart failure. Circulation. Heart failure 6(5): 970-6	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
Vardeny, Orly, Claggett, Brian, Kachadourian, Jessica et al. (2019) Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. European journal of heart failure 21(3): 337-341	- Study does not contain any outcome data relevant to this review protocol
Vardeny, Orly, Claggett, Brian, Kachadourian, Jessica et al. (2018) Incidence, Predictors, and Outcomes Associated With Hypotensive Episodes Among Heart Failure Patients Receiving Sacubitril/Valsartan or Enalapril: The PARADIGM-HF Trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure). Circulation. Heart failure 11(4): e004745	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis/ retrospective subgroup of the RCT. No additional data of relevance.*
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	- Population not relevant to this review protocol *Less than 80% of the population matches the protocol criteria (HFrEF or HFmrEF).*
Vardeny, Orly, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Finerenone, Serum Potassium, and Clinical Outcomes in Heart Failure With Mildly Reduced or Preserved Ejection Fraction. JAMA cardiology	- Population not relevant to this review protocol *preserved LVEF*
Velazquez, Eric J, Morrow, David A, DeVore, Adam D et al. (2018) Rationale and design of the comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode (PIONEER-HF) trial. American heart journal 198: 145-151	- Duration of follow up <3 months
Velazquez, Eric J, Pfeffer, Marc A, McMurray, John V et al. (2003) VALsartan In Acute myocardial iNfarcTion (VALIANT) trial: baseline characteristics in context. European journal of heart failure 5(4): 537-44	- Population not relevant to this review protocol *Patients had either transient or persistent HF. Recruited within 3 months of acute MI.*
Velicki, Lazar, Popovic, Dejana, Okwose, Nduka C et al. (2024) Sacubitril/valsartan for the treatment of non-obstructive hypertrophic cardiomyopathy: An open label randomized controlled trial (SILICOFCM). European journal of heart failure 26(6): 1361-1368	- Population not relevant to this review protocol *Not a CHF population*
Verma, S., Dhingra, N.K., Butler, J. et al. (2022) Empagliflozin in the treatment of heart failure with reduced ejection fraction in addition to background therapies and therapeutic combinations (EMPEROR-Reduced): a post-hoc analysis of a randomised, double-blind trial. The Lancet Diabetes and Endocrinology 10(1): 35	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis of EMPEROR reduced; no additional data of relevance*

Study	Exclusion reason
Vizzardi, Enrico, Nodari, Savina, Caretta, Giorgio et al. (2014) Effects of spironolactone on long-term mortality and morbidity in patients with heart failure and mild or no symptoms. The American journal of the medical sciences 347(4): 271-6	- Population not relevant to this review protocol *Reduced LVEF*
Voors AA, van Veldhuisen DJ, Robertson M et al. (2014) The effect of heart rate reduction with ivabradine on renal function in patients with chronic heart failure: an analysis from SHIFT. European journal of heart failure 16(4): 426-434	- Study does not contain an intervention relevant to this review protocol *Ivabradine*
Voors, Adriaan A, Angermann, Christiane E, Teerlink, John R et al. (2022) The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nature medicine 28(3): 568-574	- Population not relevant to this review protocol *Acute HF*
Vorilhon, C., Jean, F., Mulliez, A. et al. (2016) Optimized management of heart failure patients aged 80 years or more improves outcomes versus usual care: The HF80 randomized trial. Archives of Cardiovascular Diseases 109(12): 667-678	- Study does not contain an intervention relevant to this review protocol *Intervention focused on management and frequency not drug treatment*
Waagstein F, Bristow MR, Swedberg K et al. (1993) Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet (London, England) 342(8885): 1441-1446	- Comparator in study does not match that specified in this review protocol *HFrEF: no combination treatment in control group*
Wachter, R., Shah, S.J., Cowie, M.R. et al. (2020) Angiotensin receptor neprilysin inhibition versus individualized RAAS blockade: design and rationale of the PARALLAX trial. ESC Heart Failure 7(3): 856-864	- Protocol for an excluded study
Wachter, Rolf, Senni, Michele, Belohlavek, Jan et al. (2019) Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. European journal of heart failure 21(8): 998-1007	- Duration of follow up <3 months *Follow-up period was 10 weeks*
Wang, J, Zhou, L, Xiao, X et al. (2023) The clinical effect of sacubitril valsartan combined with dapagliflozin in heart failure with reduced ejection fraction and non-diabetes patients. Journal of xi'an jiaotong university (medical sciences) 44(3): 415-420	- Study not reported in English *Not reported in English (Chinese)*
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	- Population not relevant to this review protocol *Less than 80% of the population matches the protocol.*

Study	Exclusion reason
Wang, Xianghong, He, Meihong, Jin, Donghua et al. (2024) Effect of SGLT-2 inhibitors on acute kidney injury in patients with heart failure: a systematic review and meta-analysis. Diabetology & metabolic syndrome 16(1): 207	- Systematic review indirectly matches the review protocol: used as source of primary studies *No new studies identified*
Wang, Xiaowen, Vardeny, Orly, Claggett, Brian et al. (2024) Effect of sacubitril/valsartan in heart failure with preserved ejection fraction across the age spectrum in PARAGON-HF. European journal of heart failure	- Population not relevant to this review protocol *Mixed LVEF*
Wang, Z, Chen, L, Chen, J et al. (2024) Impact of sacubitril/valsartan and valsartan on cardiac structure in heart failure patients with mildly reduced ejection fraction. Chinese journal of medical imaging technology 40(3): 361-365	- Secondary publication of an included study that does not provide any additional relevant information *PARAGON HF: results stratified by age and not by LVEF*
Wanner, C., Lachin, J.M., Inzucchi, S.E. et al. (2018) Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation 137(2): 119-129	- Population not relevant to this review protocol *The population was people with established cardiovascular disease. Only 11% had heart failure (unclear definition of heart failure).*
Wedel, H, Demets, D, Deedwania, P et al. (2001) Challenges of subgroup analyses in multinational clinical trials: experiences from the MERIT-HF trial. American heart journal 142(3): 502-511	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Wei, Fang-Fei, Pellicori, Pierpaolo, Ferreira, Joao Pedro et al. (2024) Effects of spironolactone on exercise blood pressure in patients at increased risk of developing heart failure: report from the HOMAGE trial. Hypertension research : official journal of the Japanese Society of Hypertension 47(11): 3225-3236	- Population not relevant to this review protocol *Population does not fit protocol (at risk of CHF)*
Wei, Fang-Fei, Xue, Ruicong, Thijs, Lutgarde et al. (2020) Associations of Left Ventricular Structure and Function With Blood Pressure in Heart Failure With Preserved Ejection Fraction: Analysis of the TOPCAT Trial. Journal of the American Heart Association 9(15): e016009	- Population not relevant to this review protocol *Less than 80% of the population matches either protocol*
Weir, R A P, McMurray, John J V, Puu, Margareta et al. (2008) Efficacy and tolerability of adding an angiotensin receptor blocker in patients with heart failure already receiving an angiotensin-converting inhibitor plus aldosterone antagonist, with or without a beta blocker. Findings from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial. European journal of heart failure 10(2): 157-63	- Publication type not relevant to review protocol *Subgroup by baseline background treatment*

Study	Exclusion reason
White, Harvey D, Aylward, Philip E G, Huang, Zhen et al. (2005) Mortality and morbidity remain high despite captopril and/or Valsartan therapy in elderly patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction: results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Circulation 112(22): 3391-9	- Population not relevant to this review protocol *Acute MI*
White, Michel, Lepage, Serge, Lavoie, Joel et al. (2007) Effects of combined candesartan and ACE inhibitors on BNP, markers of inflammation and oxidative stress, and glucose regulation in patients with symptomatic heart failure. Journal of cardiac failure 13(2): 86-94	- Population not relevant to this review protocol *Reduced LVEF*
Whorlow, S L and Krum, H (2000) Meta-analysis of effect of beta-blocker therapy on mortality in patients with New York Heart Association class IV chronic congestive heart failure. The American journal of cardiology 86(8): 886-9	- Systematic review indirectly matches the review protocol: used as source of primary studies - Systematic review does not contain sufficient detail for included studies: used as source of primary studies
Wijkman, Magnus O, Claggett, Brian, Vaduganathan, Muthiah et al. (2022) Effects of sacubitril/valsartan on glycemia in patients with diabetes and heart failure: the PARAGON-HF and PARADIGM-HF trials. Cardiovascular diabetology 21(1): 110	- Study does not contain any outcome data relevant to this review protocol
Wikstrand, J (2000) MERIT-HF--description of the trial. Basic research in cardiology 95suppl1: I90-7	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
Wikstrand, J, Wedel, H, Castagno, D et al. (2014) The large-scale placebo-controlled beta-blocker studies in systolic heart failure revisited: results from CIBIS-II, COPERNICUS and SENIORS-SHF compared with stratified subsets from MERIT-HF. Journal of internal medicine 275(2): 134-43	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination therapy*
Wiley, G. and Cole, C. (2004) Candesartan reduces cardiovascular death in CHF patients on ACE inhibitor. Journal of Family Practice 53(2): 93-94	- Publication type not relevant to review protocol *Commentary/ summary of CHARM-Added trial*
Willenheimer, Ronnie, Erdmann, Erland, Follath, Ferenc et al. (2004) Comparison of treatment initiation with bisoprolol vs. enalapril in chronic heart failure patients: rationale and design of CIBIS-III. European journal of heart failure 6(4): 493-500	- Study does not contain an intervention relevant to this review protocol *The intervention is a monotherapy followed by both arms receiving the same therapies.*

Study	Exclusion reason
Willenheimer, Ronnie, Helmers, Claes, Pantev, Emil et al. (2002) Safety and efficacy of valsartan versus enalapril in heart failure patients. International journal of cardiology 85(23): 261-70	- Population not relevant to this review protocol *Mixed LVEF; mean not reported*
Willenheimer, Ronnie, van Veldhuisen, Dirk J, Silke, Bernard et al. (2005) Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 112(16): 2426-35	- Comparator in study does not match that specified in this review protocol *Order of introducing beta blocker and ACEI*
Wisenbaugh, T, Katz, I, Davis, J et al. (1993) Long-term (3-month) effects of a new beta-blocker (nebivolol) on cardiac performance in dilated cardiomyopathy. Journal of the American College of Cardiology 21(5): 1094-1100	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Witchitz, S, Cohen-Solal, A, Dartois, N et al. (2000) Treatment of heart failure with celiprolol, a cardioselective beta blocker with beta-2 agonist vasodilatory properties. The CELICARD Group. American journal of cardiology 85(12): 1467-1471	- Study does not contain an intervention relevant to this review protocol *Unlicensed beta blockers*
Wiviott, SD, Raz, I, Bonaca, MP et al. (2019) Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine 380(4): 347-357	- Population not relevant to this review protocol *Diabetes, not chronic heart failure (LVEF not reported for CHF subgroup outcomes)*
Wiviott, Stephen D, Raz, Itamar, Bonaca, Marc P et al. (2018) The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. American heart journal 200: 83-89	- Population not relevant to this review protocol *People with type 2 diabetes with ASCVD or risk factors for ASCVD. A proportion could have heart failure.*
Wong, M, Staszewsky, L, Latini, R et al. (2002) Valsartan benefits left ventricular structure and function in heart failure: val-HeFT echocardiographic study. Journal of the American College of Cardiology 40(5): 970-975	- Study does not contain any outcome data relevant to this review protocol
Wu, Z., Cui, W., Li, G. et al. (2024) Effect of sacubitril and valsartan combined with conventional therapy on patients with heart failure. Tropical Journal of Pharmaceutical Research 23(9): 1541	- Data not reported in an extractable format or a format that can be analysed *Poorly reported. no LVEF entry criterion; insufficient detail on background treatment; FUP not reported*
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 a protocol population *NMA pools preserved and mildly reduced LVEF*

Study	Exclusion reason
Xiang, Boyang; Yu, Zongliang; Zhou, Xiang (2021) Comparative Efficacy of Medical Treatments for Chronic Heart Failure: A Network Meta-Analysis. Frontiers in cardiovascular medicine 8: 787810	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Network meta analysis, which did not include all recent trials and included some interventions not relevant to the protocol. Drug class comparisons look relevant but a 50% threshold used to identify concomitant drugs.*
Xie, Liang, Li, Shengnan, Yu, Xiaojin et al. (2024) DAHOS Study: Efficacy of dapagliflozin in treating heart failure with reduced ejection fraction and obstructive sleep apnea syndrome - A 3-month, multicenter, randomized controlled clinical trial. European journal of clinical pharmacology 80(5): 771-780	- Population not relevant to this review protocol *Considered for exclusion but participants have sleep apnea as well as CHF. QoL outcomes likely affected by the sleep apnea. Excluded after consultation with topic advisor.*
Xin, Yan-Guo, Chen, Xin, Zhao, Yi-Nan et al. (2019) Outcomes of spironolactone treatment in patients in Northeast China suffering from heart failure with mid-range ejection fraction. Current medical research and opinion 35(4): 561-568	- Study design not relevant to this review protocol *Retrospective cohort study*
Yabe, Daisuke, Shiki, Kosuke, Homma, Gosuke et al. (2023) Efficacy and safety of the sodium-glucose co-transporter-2 inhibitor empagliflozin in elderly Japanese adults (>=65 years) with type 2 diabetes: A randomized, double-blind, placebo-controlled, 52-week clinical trial (EMPA-ELDERLY). Diabetes, obesity & metabolism 25(12): 3538-3548	- Population not relevant to this review protocol *Type 2 diabetes and CHF not specified*
Yamamoto, Kazuhiro, Origasa, Hideki, Hori, Masatsugu et al. (2013) Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). European journal of heart failure 15(1): 110-8	- Population not relevant to this review protocol *Preserved LVEF*
Yan, Qingkai, Chen, Xinrao, Yu, Changqing et al. (2024) Long-term surrogate cardiovascular outcomes of SGLT2 inhibitor empagliflozin in chronic heart failure: a systematic review and meta-analysis. BMC cardiovascular disorders 24(1): 663	- Systematic review indirectly matches the review protocol: used as source of primary studies *Checked and no further studies identified*
Yan, Yuling, Liu, Bin, Du, Jun et al. (2021) SGLT2i versus ARNI in heart failure with reduced ejection fraction: a systematic review and meta-analysis. ESC heart failure 8(3): 2210-2219	- Systematic review indirectly matches the review protocol: used as source of primary studies *Mix of HFrEF and HFpEF participants, intervention on drug and inappropriate follow-up period.*
Yang, Da-Ya, He, Xin, Liang, Hui-Wei et al. (2019) Comparative outcomes of heart failure among existent classes of anti-diabetic agents: a network meta-analysis of 171,253 participants	- Study does not contain an intervention relevant to this review protocol *Diabetic drugs for people with T2DM.*

Study	Exclusion reason
from 91 randomized controlled trials. Cardiovascular diabetology 18(1): 47	
Yang, Hua-Rong, Xu, Xiao-di, Shaikh, Abdul Sami et al. (2023) Efficacy and Safety of Sacubitril/Valsartan Compared With ACEI/ARB on Health-Related Quality of Life in Heart Failure Patients: A Meta-Analysis. The Annals of pharmacotherapy 57(8): 907-917	- Population not relevant to this review protocol *Subgroup analysis was by HFpEF and HFrEF but EF was not defined. The background treatment was unclear.*
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
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 does not meet either specified protocol (ejection fraction less than or equal to 45%).*
Yang, S and Wang, D (2022) Effects of sakubatril valsartan combined with dagliflozin in the treatment of patients with HFrEF and the effect on serum cTn I and BNP levels. Chinese journal of clinical pharmacology and therapeutics 27(9): 1010-1015	- Study not reported in English *Not reported in English (Chinese)*
Yang, Zhao, Ma, Huayu, Yin, Delu et al. (2024) Impact of Sacubitril/Valsartan on Cardiac Structure and Blood Levels of miRNA-328 and NT-proBNP in Patients with CHD and Chronic Heart Failure. Alternative therapies in health and medicine	- Secondary publication of an included study that does not provide any additional relevant information *Secondary paper: no extra information*
Yasumura, Yoshio, Miyatake, Kunio, Okamoto, Hiroshi et al. (2004) Rationale for the use of combination angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker therapy in heart failure. Circulation journal : official journal of the Japanese Circulation Society 68(4): 361-6	- Study does not contain any outcome data relevant to this review protocol
Yoshihara, Fumiki, Imazu, Miki, Hamasaki, Toshimitsu et al. (2018) An Exploratory Study of Dapagliflozin for the Attenuation of Albuminuria in Patients with Heart Failure and Type 2 Diabetes Mellitus (DAPPER). Cardiovascular drugs and therapy 32(2): 183-190	- Population not relevant to this review protocol *Unable to allocate to HFrEF or HFmEF based on inclusion criteria and baseline characteristics.*
Yoshihara, Fumiki, Imazu, Miki, Sakuma, Ichiro et al. (2023) DAPagliflozin for the attenuation of albuminuria in Patients with hEaRt failure and type 2 diabetes (DAPPER study): a multicentre, randomised, open-label, parallel-group, standard treatment-controlled trial. EClinicalMedicine 66: 102334	- Population not relevant to this review protocol *People with preserved ejection fraction (based on baseline characteristics)*

Study	Exclusion reason
Young, James B, Dunlap, Mark E, Pfeffer, Marc A et al. (2004) Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 110(17): 2618-26	- Study does not contain an intervention relevant to this review protocol *Patients received monotherapy whilst not clear if 80% patients received approved background therapy*
Yu, Li-Tian, Zhu, Jun, Tan, Hui-Qiong et al. (2011) Telmisartan, ramipril, or both in high-risk Chinese patients: analysis of ONTARGET China data. Chinese medical journal 124(12): 1763-8	- Population not relevant to this review protocol *Mixture of high risk patients - not necessarily with HF. No details given on EF status*
Yu, Yu-Ling, Siwy, Justyna, An, De-Wei et al. (2024) Urinary proteomic signature of mineralocorticoid receptor antagonism by spironolactone: evidence from the HOMAGE trial. Heart (British Cardiac Society) 110(19): 1180-1187	- Population not relevant to this review protocol *At risk of CHF*
Yuheng, Jiao, Yanyan, Li, Song, Zhang et al. (2022) The effects of sacubitril/valsartan on heart failure with preserved ejection fraction: a meta-analysis. Acta cardiologica 77(6): 471-479	- Population not relevant to this review protocol *The study included participants with HFpEF. No subgroup for HFmrEF noted.*
Yusuf, S and Lonn, E (1998) Anti-ischaemic effects of ACE inhibitors: review of current clinical evidence and ongoing clinical trials. European heart journal: j36	- Publication type not relevant to review protocol *Erratum only*
Yusuf, S, Pitt, B, Davis, CE et al. (1992) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The New England journal of medicine 327(10): 685-691	- Study does not contain an intervention relevant to this review protocol *HFrEF: not combination treatment*
Yusuf, S, Sleight, P, Pogue, J et al. (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The New England journal of medicine 342(3): 145-53	- Population not relevant to this review protocol *Not chronic heart failure*
Yusuf, Salim, Pfeffer, Marc A, Swedberg, Karl et al. (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet (London, England) 362(9386): 777-81	- Population not relevant to this review protocol *preserved ejection fraction*
Zafeiropoulos, Stefanos, Farmakis, Ioannis T, Milioglou, Ioannis et al. (2023) Pharmacological Treatments in Heart Failure With Mildly Reduced and Preserved Ejection Fraction: Systematic Review and Network Meta-Analysis. JACC. Heart failure	- Network meta-analysis does not include all relevant trials
Zannad F, McMurray JJ, Drexler H et al. (2010) Rationale and design of the Eplerenone in Mild	- Population not relevant to this review protocol

Study	Exclusion reason
Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF). European journal of heart failure 12(6): 617-622	*Reduced LVEF*
Zannad F, McMurray JJ, Krum H et al. (2011) Eplerenone in patients with systolic heart failure and mild symptoms. The New England journal of medicine 364(1): 11-21	- Population not relevant to this review protocol *Reduced LVEF*
Zannad, Faiez, Ferreira, Joao Pedro, Gregson, John et al. (2022) Early changes in estimated glomerular filtration rate post-initiation of empagliflozin in EMPEROR-Reduced. European journal of heart failure 24(10): 1829-1839	- Study design not relevant to this review protocol *Post hoc analysis*
Zannad, Faiez, Ferreira, Joao Pedro, Pocock, Stuart J et al. (2020) SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet (London, England) 396(10254): 819-829	- Secondary publication of an included study that does not provide any additional relevant information
Zannad, Faiez, Ferreira, Joao Pedro, Pocock, Stuart J et al. (2021) Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. Circulation 143(4): 310-321	- Population not relevant to this review protocol *Reduced LVEF*
Zelniker, Thomas A, Raz, Itamar, Mosenzon, Ofri et al. (2021) Effect of Dapagliflozin on Cardiovascular Outcomes According to Baseline Kidney Function and Albuminuria Status in Patients With Type 2 Diabetes: A Prespecified Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 6(7): 801-810	- Population not relevant to this review protocol *Population not HFrEF or HFmrEF*
Zeng, Jianping, Zhu, Yunlong, Zhao, Wenjiao et al. (2022) Rationale and Design of the ADIDAS Study: Association Between Dapagliflozin-Induced Improvement and Anemia in Heart Failure Patients. Cardiovascular drugs and therapy 36(3): 505-509	- Study design not relevant to this review protocol
Zeng, Y.-W., Zhang, M., Huang, D.-D. et al. (2018) Observation of efficacy of combined medication of bisoprolol and irbesartan on chronic congestive heart failure. Acta Medica Mediterranea 34(3): 827-830	- Study does not contain any outcome data relevant to this review protocol *No protocol outcomes reported.*
Zhang, Shuai, Xu, Panpan, Wei, Tianhao et al. (2024) Novel Adiposity Indices Are Associated With Poor Prognosis in Heart Failure With Preserved Ejection Fraction Without the Obesity Paradox. Journal of the American Heart Association 13(22): e035430	- Data not reported in an extractable format or a format that can be analysed
Zhang, Zefeng, Mahoney, Elizabeth M, Kolm, Paul et al. (2010) Cost effectiveness of eplerenone in patients with heart failure after	- Population not relevant to this review protocol *Patients recruited post MI.*

Study	Exclusion reason
acute myocardial infarction who were taking both ACE inhibitors and beta-blockers: subanalysis of the EPHESUS. American journal of cardiovascular drugs : drugs, devices, and other interventions 10(1): 55-63	
Zhao, Lingyue, Guo, Wenqin, Huang, Weichao et al. (2022) Benefit of sodium-glucose cotransporter-2 inhibitors on survival outcome is related to the type of heart failure: A meta-analysis. Diabetes research and clinical practice 187: 109871	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies *Includes SGLT2 not licenced in CHF and insufficient detail of included study characteristics*
Zhao, X-D, Gao, B-B, Deng, L et al. (2023) Impact of Sacubitril Valsartan Treatment on Cardiac Function and Psychological Status in Eldly Patients of Heart Failure with Reduced Ejection Fraction. Chinese pharmaceutical journal 58(14): 1339-1342	- Study not reported in English *Non-English language study (Chinese)*
Zhao, Ying, Tian, Li-Guo, Zhang, Li-Xin et al. (2022) The comparative effects of sacubitril/valsartan versus enalapril on pulmonary hypertension due to heart failure with a reduced ejection fraction. Pulmonary circulation 12(3): e12034	- Study does not contain an intervention relevant to this review protocol *Sacubitril valsartan dose not optimised and aim is to treat pulmonary hypertension not heart failure*
Zhou, Jingmin, Shi, Haiming, Zhang, Jian et al. (2010) Rationale and design of the beta-blocker in heart failure with normal left ventricular ejection fraction (beta-PRESERVE) study. European journal of heart failure 12(2): 181-5	- Population not relevant to this review protocol *Patients included with only LVEF greater than or equal to 50%*
Zhou, Lingyan, Huang, Zijia, Zeng, Ya et al. (2024) Cardiovascular Outcomes of Sodium-Glucose Cotransporter 2 Inhibitors Across Body Mass Index Spectrum in Patients With Heart Failure: An Updated Systematic Review and Meta-Analysis. Journal of cardiovascular pharmacology 84(4): 400-409	- Systematic review indirectly matches the review protocol: used as source of primary studies *References check complete and relevant rEF studies already included*
Zhu, Doreen and Herrington, William G (2024) In HF, T2D, CKD, or atherosclerotic CVD, SGLT2 inhibitors reduce HF hospitalizations and CV mortality. Annals of internal medicine 177(11): jc123	- Review article but not a systematic review *Commentary paper*
Zhu, WL (2003) Carvedilol in chronic heart failure: a single-blind, randomized, placebo-controlled trial. Chinese journal of cardiology 31(1): 7-10	- Study not reported in English *Non-English language*
Zi, Min; Carmichael, Neil; Lye, Michael (2003) The effect of quinapril on functional status of elderly patients with diastolic heart failure. Cardiovascular drugs and therapy 17(2): 133-9	- Population not relevant to this review protocol *LVEF not stated*
Zile, Michael R, Gaasch, William H, Anand, Inder S et al. (2010) Mode of death in patients	- Study design not relevant to this review protocol

Study	Exclusion reason
with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. Circulation 121(12): 1393-405	*Retrospective cohort study*
Zinman, B, Wanner, C, Lachin, JM et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22): 2117-2128	- Population not relevant to this review protocol *Diabetes, not chronic heart failure (LVEF not reported for CHF subgroup outcomes)*

J.2 Health Economic studies

Table 23: Studies excluded from the health economic review

Study	Exclusion reason
Arbel, Ronen, Azab, Abed N, Oberoi, Mansi et al. (2024) Dapagliflozin <ovid:i>versus</ovid:i> sacubitril-valsartan for heart failure with mildly reduced or preserved ejection fraction. Frontiers in pharmacology 15: 1357673	- Wrong intervention/comparator – SGLT2 inhibitor
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-	- Wrong intervention/comparator – SGLT2 inhibitor

Study	Exclusion reason
Preserved Clinical Trial. PharmacoEconomics - open 8(1): 19-30	
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
Tan, Yi Jing; Linden, Stephan; Ong, Siew Chin (2024) Cost-effectiveness of empagliflozin in the treatment of Malaysian patients with chronic heart failure and preserved or mildly reduced ejection fraction. PloS one 19(8): e0305257	- 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