National Institute for Health and Care Excellence

Final

Chronic heart failure in adults: diagnosis and management

[A] Evidence review for medicines for heart failure with reduced ejection fraction

NICE guideline NG106

Evidence review underpinning recommendations 1.4.1 to 1.4.4 and 1.7.3 to 1.7.8 in the NICE guideline

September 2025

Final

This evidence review was developed by NICE

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1.1. Review question

Is it clinically- and cost-effective to use a combination of some of the following first-line medicines in adults with chronic heart failure with reduced left ventricular ejection fraction:

- angiotensin converting enzyme I inhibitor
- angiotensin-receptor blocker
- angiotensin receptor neprilysin inhibitor
- beta blocker
- mineralocorticoid receptor antagonist
- sodium glucose cotransporter 2 inhibitor?

1.1.1. Introduction

Overarching principles:

In all types of heart failure, the specialist trained in heart failure and cardiac imaging should ascertains the phenotype of heart failure, looks for all potential causes of the patient's syndrome beyond heart failure, and addresses the co-morbidities associated with heart failure. It is important for the specialist in heart failure to look for the aetiology of heart failure and consider any required therapeutic interventions to treat the specific aetiology involved in the individual patient.

Chronic heart failure (CHF) with reduced ejection fraction (HFrEF) is defined by both the heart failure syndrome and a left ventricular ejection fraction <40%. The journey towards evidence-based pharmacological therapy for patients with HFrEF started in 1986, with the advent of combined hydralazine and nitrate therapy. Since then, evidence for treatment with angiotensin converting enzyme inhibitors (ACE inhibitor), beta-blockers (BB) and mineralocorticoid receptor antagonists (MRA) has emerged. These last three comprised triple therapy for HFrEF, which was the first step of therapy in those with symptomatic HFrEF in the NICE guidelines of 2018.

Traditionally, these patients are commenced on either an ACE inhibitor or a BB, which are up-titrated to the maximum tolerated doses, before they are commenced on an MRA if they remained symptomatic. The last NICE guidelines in 2018 proposed as a second stage one or more of the following interventions delivered by a specialist: angiotensin receptor/neprilysin antagonist (ARNI) instead of ACE inhibitor, ivabradine if in sinus rhythm with a heart rate >70 bpm, a combined hydralazine and nitrate if the patient is of Afro-Caribbean origin, and/or digoxin. Since these recommendations were implemented, sodium-glucose-co-transporter 2 inhibitors (SGLT2i) have become available. NICE provided two health technology appraisals for this new intervention: TA679 and TA773.

Beyond the need to integrate new evidence into the treatment pathway for patients with HFrEF, a new ethos in the treatment of patients with HFrEF has emerged. Many of the above-mentioned interventions reduce morbidity and mortality of patients with HFrEF by different pathways, and they tend to impact these outcomes at an early stage of commencing therapy. Thus, there is potential advantage of patients being commenced on no less than four agents. However, since these agents lower the patient's blood pressure, a pragmatic approach into the plan of therapy may need to be considered. The step-wise approach hitherto adopted not infrequently leads to patients being on maximal doses of two or may be three agents and unable to tolerate the third agent, and certainly not able to tolerate the

fourth. Therefore, using this pathway may have resulted in suboptimal treatment. Thus, the new approach that needs to be considered is the early introduction of all four modalities of therapy (ACEI+BB+MRA+SGLT2i) before up-titrating individual agents. For all these reasons, it was essential to re-consider the pharmacological therapy of patients with HFrEF in this iteration of the NICE guidelines.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	**Inclusion**: Adults diagnosed with heart failure due to left ventricular dysfunction with reduced ejection fraction (LVEF ≤40%). **Exclusions:** • Children • Acute heart failure in hospital • Heart failure due to right heart dysfunction • High output heart failure • Adult congenital heart disease • Primary heart valve disease • Acute MI (within 3 months of the event) • Isolated pulmonary hypertension • Treatment with chemotherapy • Heart failure with preserved EF (normal EF, diastolic dysfunction)
Interventions	**Inclusion**: Pharmacological agents as first-line treatment in combination with each other or with standard background therapy including diuretics when indicated: • 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) • SGLT2 inhibitor (sodium-glucose-cotransporter-2 inhibitors, dapagliflozin or empagliflozin) • Combinations of the above (e.g. ACE-I/ARB/ARNI + BB + MRA+ SGLT2i); including different initiation strategies At least 50% of the intervention group must be receiving more than one of the drugs listed above (either as the randomised intervention or as part of background treatment).

Comparisons	• Different approaches to initiation (e.g., sequential introduction with up-titration of each agent in turn vs more rapid introduction of all initial treatments).
	• Other active treatments in combination with each other or with standard background therapy:
	  ○ 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)
	  ○ SGLT2 inhibitor (sodium-glucose-cotransporter-2 inhibitors, dapagliflozin or empagliflozin)
	• Placebo + usual CHF care or usual CHF care alone

	At least 50% of the control group must be receiving more than one of the drugs listed above (either as the randomised comparator or as part of background treatment).
Outcomes	• 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) ○ all cause unplanned hospitalisation or visits will be included if HF-related is not reported in a study 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 Exclude if follow-up < 3 months
Study design	RCT or systematic reviews, individual participant data meta-analysis of network meta-analyses of RCTs.

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.

1.1.3.1. 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.

1.1.3.2. Review methods

Chronic heart failure is defined according to the following criteria:

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

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

Studies that were included and analysed in the previous update of the guideline and met the current protocol criteria are retained in this evidence review and pooled with newly identified studies where appropriate. The previously included studies were added to EPPI-reviewer and any data available for the additional outcomes that were not in the previous protocol were also extracted. All outcomes were reassessed for risk of bias according to the Cochrane Risk of Bias 2 checklist for consistency with current methods.

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

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

Twenty-eight RCTs, reported in 51 papers, were included in the review; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

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 Appendix F.

Populations

All of the included studies were in adults with symptomatic heart failure. Fourteen of the 23 trials 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 9 studies did not.

The age range of study participants across all studies was reported as mean or median from 59.2 to 70.0 years. Key co-morbidities that relate to inclusion and exclusion criteria in the trials are shown in Table 2. Details on type 2 diabetes, atrial fibrillation and eGFR of study participants are included in Appendix D.

Analyses were limited to including people with chronic heart failure with reduced ejection fraction, defined as LVEF ≤40%. One trial, STRONG-HF, was in a mixed ejection fraction population, so a paper reporting on the subgroup with LVEF ≤40% was used for analysis, in accordance with the protocol population. Two trials, STRONG-HF and EARLIER, recruited patients who were hospitalised for acute heart failure; however, they were eligible for inclusion because the trial assessed management and follow-up after discharge, beyond the acute phase.

Stratified data were presented for SGLT2 inhibitor trials according to the presence or absence of type 2 diabetes based on prespecified trial analyses. This is to determine if there are subgroup differences between those with and without type 2 diabetes for outcomes relevant to this review.

Interventions and comparisons

One trial, STRONG-HF, evaluated the efficacy and safety of rapid optimisation of heart failure therapy compared with usual heart failure therapy management.

The remaining trials addressed direct comparisons of different intervention combinations. Trials comparing any intervention with monotherapy or placebo alone were excluded, although they were considered in previous versions of the guideline, because current practice in the people with heart failure with reduced ejection fraction now includes a minimum of dual therapy (ACEI + BB). A medicine class was listed as part of the intervention or comparator group if at least 50% of the participants in that trial arm were receiving an intervention from that class either as the randomised treatment or as part of stable, optimised background treatment. On this basis, the following comparisons were available for analysis, where the randomised agents are presented in bold text and background treatment is not bolded.

Placebo comparisons (with background treatment):

- **SGLT2i** + ACEI/ARB + BB + MRA *versus* ACEI/ARB + BB + MRA + **placebo** (9 trials)
- **MRA** + ACEI/ARB + BB *versus* ACEI/ARB + BB + **placebo** (7 trials)
- **MRA** + **ARB** + BB *versus* **ARB** + BB + **placebo** (1 trial)
- **ARB** + ACEI + BB *versus* ACEI + BB + **placebo** (2 trials)

Head-to-head comparisons (with background treatment):

- **ARNI** + MRA + BB *versus* **ARB** + MRA + BB (3 trials)
- **ARNI** + MRA + BB *versus* **ACEI** + MRA + BB (4 trials)
- **ARNI** + BB *versus* **ACEI** + BB (1 trial)

1.1.4.2. Excluded studies

Three potentially relevant Cochrane reviews were identified in the literature search but were excluded from the review for the reasons set out below:

- Lunney et al. (2020) Pharmacological interventions for heart failure in people with chronic kidney disease. The Cochrane database of systematic reviews 2: cd012466
  - The comparison presented is not relevant to the review protocol as this compares monotherapy with placebo.
- Heran et al. (2012) Angiotensin receptor blockers for heart failure. The Cochrane database of systematic reviews: cd003040
  - The searches were conducted in 2010 and have been superseded by more recent reviews presented in earlier versions of this NICE guideline. All included studies were cross-checked for inclusion in this review.
- Driscoll 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
  - The intervention is not relevant to this review protocol: Nurse-led titration.

Studies that were included in the previous update of the guideline but no longer met the current protocol criteria due to participants not receiving dual therapy (based on randomised and background treatment with a threshold of 50%) have been excluded. This was because less than dual therapy is considered sub-optimal treatment in current practice and so such trials are no longer relevant for decision making.

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

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
Rapid optimisation versus usual care				
Mebazaa 2022, Pagnesi 2023, Kimmoun 2019, Cotter 2021 **STRONG-HF** *Argentina, Austria, Bulgaria, Columbia, France, Hungary, Israel, Mozambique, Nigeria, Russia, Serbia, Slovakia, South Africa, and Tunisia*	Hospitalised for acute HF and had not been treated with optimal doses of oral HF therapies within 2 days before discharge *Assesses management and follow up after discharge* LVEF ≤40% subgroup: N=731 Mean (SD) age: 60.1 (14.02) years	Rapid optimisation: early up-titration of HF medical therapy (BB, ACEI/ARB or ARNI, and MRA) after hospitalisation for acute heart failure. Vs Usual care: discharged and followed up according to local practice	ACEI 39% ARB 17% ARNI 8% BB 36% MRA 95% Loop diuretic 96% SGLT2i (Jan 2021-Oct 2022): 10% and 5% of intervention and control group, respectively.	• All-cause mortality • Cardiovascular mortality • Health-related quality of life – EQ-5D VAS • Hospitalisation for heart failure • AKI • Hyperkalaemia • Falls Follow-up: 90 and 180 days
SGLT2i + ACEI/ARB + BB + MRA *versus* ACEI/ARB + BB + MRA + **placebo**				
Abraham 2021 **EMPERIAL-Reduced** *Australia, Europe and N. America*	Symptomatic HFrEF (NYHA class II-IV; LVEF ≤40%; NT-proBNP >600 pg/ml) stable on optimised pharma therapy and appropriate device therapy. 6MWTD of ≤350 m Acute MI excluded N=312 Median (IQR) age: 70 (62.5-77.0) years	Empagliflozin 10 mg daily Vs Placebo	BB 95% MRA 56% ACEI/ARB 55% ARNI 37%	• Health-related quality of life - KCCQ (overall summary score and clinical summary score) • Withdrawal due to drug-related adverse events Follow-up: 3 months

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
Jensen 2020, Jensen 2019 **EMPIRE-HF** *Denmark*	HFrEF (NYHA class I-III [<10% class I]; LVEF ≤40%) on optimised pharma therapy and appropriate device therapy. eGFR > 30 ml/min/1.73 m^2 N=190 Median (IQR) age: 64 (57-73) / 63 (55-72)	Empagliflozin 10 mg daily Vs Placebo	BB 95% ACEI/ARB/ARNI 96% MRA 66% ARNI 30%	• All-cause mortality • Cardiovascular mortality • Health-related quality of life - KCCQ (overall summary score and clinical summary score) • Hospitalisation for heart failure • Falls Follow-up: 3 months
Lee 2021 **SUGAR-DM-HF** *Scotland*	HFrEF (NYHA class II-IV; LVEF ≤40%) on stable pharma therapy and T2D. eGFR ≥30 ml/min/1.73 m2 Acute MI excluded N=105 Mean (SD) age: 68.7 (11.2) years	Empagliflozin 10 mg daily Vs Placebo	ACEI/ARB/ARNI 95% BB 91% MRA 60%	• All-cause mortality • Health-related quality of life - KCCQ (overall summary score) • AKI • Hyperkalaemia • Falls Follow-up: 9 months
Lin 2024 *China*	Patients ≥18 years with HFrEF and hyperuricemia with LVEF≤ 40%, NYHA class II-IV, serum uric acid level ≥ 7 mg/dL and stable medical therapy for CHF for at least 4 weeks. N=200 Mean (SD) age: 63 (10) years	Dapagliflozin (10mg/day) Vs Placebo	ACEI/ARB: 92/90% BB: 88/86% MRA: 72/70%	• All-cause mortality Follow-up: 24 months

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
McMurray 2019a, McMurray 2019b, McMurray 2019c, Petrie 2020, Shen 2021 **DAPA-HF** *N America, S America, Europe, Asia*	Symptomatic HFrEF (NYHA class II-IV; LVEF ≤40%; NT-proBNP ≥600 pg/ml (or ≥400 pg/ml if hospitalised for heart failure within the previous 12 months or ≥900 pg/ml for patients with atrial fibrillation) present for at least 2 months and stable on optimised pharmacological and/or device therapy. eGFR ≥30 ml/min/1.73 m^2 Acute MI excluded N=4744 Mean (SD) age: 66.2 (10.9) years	Dapagliflozin 10 mg daily Vs Placebo	BB 96% MRA 71% ACEI 56% ARB 27% ARNI 11%	• All-cause mortality • Cardiovascular mortality • Health-related quality of life - KCCQ (overall summary score) • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • AKI • Hyperkalaemia Follow-up: Median 18 months
Nassif 2019 **DEFINE-HF** *USA*	Established diagnosis of heart failure (NYHA class II–III; LVEF≤40%; NT pro-BNP ≥ 400 pg/mL) on GL-directed SoC. eGFR ≥30 ml/min/1.73 m^2 Acute MI excluded N=263 Mean (SD) age: 61.3 (11.5) years	Dapagliflozin 10 mg daily Vs Placebo	BB 93% MRA 61% ACEI/ARB 59% ARNI 32%	• All-cause mortality • Cardiovascular mortality • Health-related quality of life - KCCQ (overall summary score and clinical summary score) • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • AKI Follow-up: 3 months

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
McMurray 2023 **DETERMINE-reduced** *Multicentre study*	Patients aged ≥18 years with HFrEF (LVEF≤40%), elevated NT-proBNP, in NYHA class II-IV. N=313 Median (IQR) age: 69 (60-76)	Dapagliflozin (10mg/day) Vs Placebo	BB (92.9/98.1%), ACEI/ARB (59.6/55.4%), MRA (57.1/59.9%)	• All-cause mortality • Withdrawal due to drug-related adverse events Follow-up: 16 weeks
Packer 2019, Packer 2020, Anker 2021, Butler 2021 **EMPEROR-Reduced** *N America, S America, Europe, Asia, S Africa, Australia*	Symptomatic HFrEF (NYHA class II-IV; LVEF ≤40%; elevated NT-proBNP with threshold varying by LVEF and atrial fibrillation status) stable on optimised pharma therapy and appropriate device therapy. eGFR ≥ 20 mL/min/1.73m^2 Acute MI excluded N=3730 Mean (SD): 66.9 (11.0) years	Empagliflozin 10 mg daily Vs Placebo	BB 95% ACEI/ARB without NI 70% ACEI/ARB with NI 19% MRA 71%	• All-cause mortality • Cardiovascular mortality • Health-related quality of life - KCCQ (overall summary score and clinical summary score) • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • Hyperkalaemia Follow-up: Median 16 months
Palau 2022 **DAPA-VO2** *Spain*	Stable symptomatic HFrEF (NYHA class II–III during the last 2 months; LVEF ≤40%; NT-proBNP ≥600 pg/ml) on optimised care eGFR ≥30 ml/min/1.73 m^2 N=90 Median (IQR) age: 69.8 (62.4-74.0) / 67.3 (60.8-75.1)	Dapagliflozin 10 mg daily Vs Placebo	BB 91% MRA 74% ACEI/ARB/ARNI 96% ARNI 89%	• All-cause mortality • Health-related quality of life - MLWHFQ (overall summary score) • Hospitalisation for heart failure

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
				Follow-up: 3 months
MRA + ACEI/ARB + BB *versus* ACEI/ARB + BB + **placebo**				
Asakura 2022, Asakura 2015 **EARLIER** *Japan*	Clinical evidence of acute decompensated HF: 1) de novo AHF, or 2) acute exacerbation of chronic heart failure, and/or 3) post-AMI heart failure. Signs of pulmonary congestion and LVEF ≤40% within 3 days of enrolment. N=300 Median (IQR) age: 69 (63-76) / 66 (56-76)	Early initiation of eplerenone: started at 25mg/d just after randomisation, and increased after 1 week to 50 mg/daily Vs Placebo	ACEI/ARB 90% BB 64%	• All-cause mortality • Cardiovascular mortality • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • Acute kidney injury • Hyperkalaemia Follow-up: 6 months
Berry 2007 *Not specified*	Mild-moderate HF (NYHA class I-III; 80% class II or III) and LVEF <40% N=40 Mean (SD) age: 62 (9) years	MRA (spironolactone): 25 mg/d for 12 weeks Vs Placebo	ACEI 85% ARB 15% BB 100%	• Health-related quality of life – EQ-VAS • AKI Follow-up: 12 weeks
Cicoira 2002 *Italy*	CHF and in stable clinical condition for at least 6 months, on an ACEI at the maximal tolerated dose and LVEF ≤45%. Patients in sinus rhythm. Mean (SD) NYHA: 2.2 (0.7) N=106 Mean (SD) age: 62.1 (8.3) years	MRA (spironolactone) 12.5 mg, 25 mg or 50 mg per day for 12 months Vs Usual care	ACEI 100% BB 65%	• All-cause mortality • Withdrawal due to drug-related adverse events • Hyperkalaemia Follow-up: 12 months
Tsutsui 2017a **J-EMPHASIS-HF** *Japan*	NYHA class II or higher and LVEF ≤30%; hospitalised for cardiovascular causes in previous 6 months or BNP ≥250 pg/mL (or NT-proBNP ≥500 pg/mL for men and ≥750 pg/mL for women).	MRA (eplerenone): starting at 25mg/d and increased to 50mg/d after 4 weeks.	ACEI 49.8% ARB 36.7% ACE/ARB 82.4% BB 86%	• All-cause mortality • Cardiovascular mortality

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
	N=221 Mean (SD) age: 68.7 (8.2) years	Vs Placebo		• Hospitalisation for heart failure • Hyperkalaemia Follow-up: 30 months
Vizzardi 2014 *Italy*	Diagnosis of CHF, NYHA class I or II (82% class II) symptoms, and LVEF <40% N=130 Mean (SD) age: 63 (16.2) years	MRA (spironolactone): starting at 25mg/d and increased to 50mg/d at 4 weeks Vs Placebo	ACEI/ ARB 99% BB 97%	• All-cause mortality • Cardiovascular mortality • Hospitalisation for heart failure • Hyperkalaemia Follow-up: 44 months
Zannad 2010, Zannad 2011, Rogers 2012, Eschalier 2013, **EMPHASIS-HF** *Sites in Australia, N America, S America, Europe, and Asia, plus South Africa and UAE*	NYHA class II and LVEF ≤30%; hospitalised for cardiovascular causes in previous 6 months or BNP ≥250 pg/mL (or NT-proBNP ≥500 pg/mL for men and ≥750 pg/mL for women). N=2737 Mean (SD) age: 68.7 (7.7) years	MRA (eplerenone): starting at 25mg/d and increased to 50mg/d after 4 weeks Vs Placebo	ACEI 77.5% ARB 19.2% BB 86.7%	• All-cause mortality • Cardiovascular mortality • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • Hyperkalaemia Follow-up: 21 months (median)
Udelson 2010 *US*	Symptomatic mild-to-moderate HF (NYHA class II and III) who had LVEF ≤35% and on stable ACEI and/or ARB (unless documented intolerance) N=226 Mean (SD) age: 62.7 (12.6) years	MRA (eplerenone): starting at 25mg/d and increased to 50mg/d after 4 weeks Vs Placebo	ACEI/ARB 96.5% BB 95.1%	• Hyperkalaemia Follow-up: 36 weeks

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
MRA + **ARB** + BB *versus* **ARB** + BB + **placebo**				
Chan, 2007	Participants with LVEF <40% (>80% NYHA class II or III) and receiving ACEI for more than 6 months. N=48 Mean (SD) age: 63.3 (8.7) years	ARB (candesartan) + MRA (spironolactone). Patients received 8 mg ARB + 25 mg MRA once daily for 52 weeks Vs ARB (candesartan) + placebo. Patients received 8 mg ARB and a matching placebo once daily for 52 weeks.	BB 71% (ACEI discontinued before randomisation)	• Withdrawal due to drug-related adverse events • Hyperkalaemia Follow-up: 52 weeks
ARB + ACEI + BB *versus* ACEI + BB + **placebo**				
McMurray 2003, Swedberg 1999 **CHARM-added** *Multicentre study in 26 countries*	HFrEF with LVEF ≤40%, NYHA class II–IV (if class II, patients had to have admission to hospital for a cardiac reason in the previous 6 months), and treatment with an ACEI at a constant dose for 30 days or longer. N=2548 Mean (SD) age: 64.1 (11.0) years	Candesartan initiated at 4 or 8 mg once daily; dose was doubled every 2 weeks, as tolerated, to the target dose of 32 mg once daily from 6 weeks onwards Vs Placebo	ACEI (100%) BB (55%)	• All-cause mortality • Cardiovascular mortality • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • AKI • Hyperkalaemia Follow-up: 41 months
White 2007 *Canada*	Symptomatic HF; LVEF <40%; on stable and optimal dose of ACEI for at least 3 months. NYHA class II = 57.5%, III = 41.3%. N=68	Candesartan initiated at either 4 or 8 mg once daily followed by 8 weeks of titration phase and 16 weeks of observation period.	ACEI (100%) BB (94%)	• Cardiovascular mortality • Withdrawal due to drug-related adverse events

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
	Mean (SD) age: 62.6 (8.5) years	The dose of candesartan was doubled every 2 weeks with goal to achieve 32mg/day Vs Placebo		• Hyperkalaemia • Falls Follow-up: 24 weeks
ARNI + MRA + BB *versus* **ARB** + MRA + BB				
Ghafur 2020 *Bangladesh*	HF with NYHA class II - IV and LVEF ≤40% and NT-proBNP ≥400 pg/mL N=100 Mean (SD) age: 61.4 (12.0) years	Sacubitril/valsartan initiated at 50 mg twice daily and titrated to 100 mg twice daily Vs Valsartan initiated at 40 mg twice daily and titrated to **80** mg twice daily.	BB 85% MRA 75% ACEI or ARB were discontinued	• Cardiovascular mortality • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • AKI • Hyperkalaemia Follow-up: 88 days
Mann 2022, Mann 2020 **LIFE trial** *US*	Advanced HFrEF defined as LVEF ≤35% documented during the preceding 12 months AND NYHA **class IV** symptomatology or patients who require **chronic inotropic therapy** AND minimum of 3 months guideline-directed medical therapy for HF and/or intolerant to therapy. Serum NT-proBNP ≥800 pg/mL OR BNP ≥250 pg/mL. N=336 Mean (SD) age: 59.2 (13.3) years	Sacubitril/valsartan orally twice per day titrated to target dose of 97 mg/103 mg twice per day Vs Valsartan orally twice per day titrated to target dose of **160** mg twice per day	BB 78% MRA 57%	• All-cause mortality • Cardiovascular mortality • Hospitalisation for heart failure • Hyperkalaemia Follow-up: 24 weeks

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
Nagele 2024 **VASCEND** *Switzerland*	Patients aged ≥18 years with HFrEF (LVEF ≤40%), in NYHA class II-IV. N=79 Mean (SD) age: 59.5 (11.6) years	Sacubitril/valsartan (50 mg twice daily up to the target dose of 200 mg twice daily) Vs Valsartan (40 mg twice daily up to the target dose of 160 mg twice daily)	BB (100/97.41%), MRA (74.4/76.9%)	• All-cause mortality • Withdrawal due to drug-related adverse events
ARNI + MRA + BB *versus* **ACEI** + MRA + BB				
Halle 2021 **ACTIVITY-HF** *Germany*	HFrEF (NYHA class III; LVEF ≤40%) taking an ACEI or ARB at a stable dose of/equivalent to at least enalapril 10mg/day. Reduced exercise capacity (peak VO_2 ≤ 18 mL/min/kg) Acute MI excluded N=201 Mean (SD) age: 66.8 (10.4) years	Sacubitril/valsartan initiated at 49/51 mg twice daily for 2 wks, up-titrated to 97/103 mg twice daily for 10 wks Vs Enalapril 5 mg twice daily for 2 wks, up-titrated to 10 mg twice daily for 10 weeks	BB 95% MRA 77% ARBs and ACEIs discontinued (36 hr washout for ACEI)	• All-cause mortality • Cardiovascular mortality • Health-related quality of life - KCCQ (overall summary score) and SF-36 (Physical and mental components) • Withdrawal due to drug-related adverse events • Hyperkalaemia Follow-up: 12 weeks
Piepoli 2021, Edelmann 2020 **OUTSTEP-HF** *Europe*	Symptomatic HF (NYHA class ≥II; LVEF ≤40%; NT-proBNP ≥300 pg/mL or BNP ≥100 pg/mL) On stable medication for heart failure with minimal daily dose of ACEI/ARB equivalent to at least 2.5 mg/d enalapril	Sacubitril/valsartan initiated at 24/26 mg twice daily and up-titrated to target dose of 97/103 mg twice daily by week 4	BB 91% MRA 67% ARBs and ACEIs discontinued (36 hr washout)	• All-cause mortality • Health-related quality of life – SF-12 (Physical and mental

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
	N=621 Mean (SD) age: 66.9 (10.8) years	Vs Enalapril initiated at 2.5 mg twice daily and up-titrated to target dose of 10 mg twice daily by week 4		components), EQ-5D, EQ-VAS • Hospitalisation for heart failure Follow-up: 12 weeks
McMurray 2013, McMurray 2014a, McMurray 2014b Lewis 2017 **PARADIGM-HF** *N America, S America, Europe, Asia, S Africa, Australia*	HFrEF (NYHA class II-IV; LVEF ≤35%; plasma NT-proBNP ≥600 pg/mL) taking an ACEI or ARB at a stable dose of/equivalent to at least enalapril 10mg/day (still symptomatic despite prior ACEI) Acute MI excluded N=8399 Mean (SD) age: 63.8 (11.4) years	Sacubitril/valsartan 200mg twice daily *Tolerability assessed and up-titration trialled in run-in period* *Vs* Enalapril 10 mg twice daily *Tolerability assessed in run-in period*	BB 93% MRA 56% ARBs and ACEIs discontinued	• All-cause mortality • Cardiovascular mortality • Health-related quality of life - KCCQ (overall summary score and clinical summary score) • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • AKI • Hyperkalaemia • Falls Follow-up: Median 27 months
Tsutsui 2017b, Tsutsui 2018, Tsutsui 2021 **PARALLEL-HF** *Japan*	HFrEF (NYHA class II-IV; LVEF ≤35%; plasma NT-proBNP ≥600 pg/mL) On stable medication for heart failure (including ACEI/ARB and BB when tolerated) Acute MI excluded	Sacubitril/valsartan 100mg twice daily for 4 wks and up-titrated to 200 mg twice daily if tolerated	BB 95% MRA 59% ARBs and ACEIs discontinued (36 hr washout)	• All-cause mortality • Cardiovascular mortality • Health-related quality of life -

Author, year (trial name)	Population	Intervention and comparison	Background HF treatment	Outcomes
	N=225 Mean (SD) age: 67.8 (10.4) years	*Tolerability assessed trialled in run-in period* *Vs* Enalapril 10 mg twice daily *Tolerability assessed in run-in period*		KCCQ (clinical summary score) • Hospitalisation for heart failure • Withdrawal due to drug-related adverse events • Hyperkalaemia Follow-up: Median 33.6 months
ARNI + BB *versus* **ACEI** + BB				
Desai, 2019 **EVALUATE-HF** *US*	Participants aged 50 or older with LVEF ≤40% and NYHA class I-III. N=464 Mean (SD) age: 67.2 (9.2)	ARNI Sacubitril-Valsartan (started at 24/26 mg twice daily and then titrated to 97/ 103 mg twice daily) Vs ACEI Enalapril (started at 2.5 mg twice daily and then titrated to 10 mg twice daily)	ACEI/ARB 84% BB 87% MRA 25%	• All-cause mortality • Health-related quality of life - KCCQ (overall summary score) • Hospitalisation for heart failure • Acute kidney injury • Hyperkalaemia Follow-up: 12 weeks

6MWTD: 6 minute walk test; ACEI: Angiotensin converting enzyme inhibitor; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; BNP: B-type natriuretic peptides; CHF: Chronic heart failure; eGFR: estimated glomerular filtration rate; GL-directed SoC: ;EQ-5D: EuroQoL 5-dimensions questionnaire; EQ-VAS: EuroQoL visual analogue scale; HF: Heart Failure; HFrEF: Chronic heart failure due to left ventricular dysfunction with reduced ejection fraction of ≤40%; IPD: Individual participant data; IQR: Interquartile range; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; MRA: Mineralocorticoid receptor antagonist; NYHA: New York Health Association; SD: standard deviation; NT-proBNP: N-terminal pro-B-type natriuretic peptide level; SF-12: Short Form-12 health survey; SF-36: Short Form-36 health survey; SGLT2i: Sodium-glucose co-transporter 2 inhibitor; T2D: Type 2 diabetes; VO2: Volume of oxygen consumption

See Appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence

See Appendix F for full GRADE tables.

1.1.6.1. Rapid optimisation of combined treatments

Table 3: Clinical evidence summary: rapid optimisation versus usual care

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Rapid optimisation
All cause mortality (dichotomous) follow-up: 180 days	692 (1 RCT)	⊕◯◯◯ Very low[a,b]	RR 1.06 (0.67 to 1.70)	90 per 1,000	5 more per 1,000 (30 fewer to 63 more)
Cardiovascular mortality (dichotomous) follow-up: 180 days	692 (1 RCT)	⊕◯◯◯ Very low[a,b]	RR 0.97 (0.59 to 1.59)	84 per 1,000	3 fewer per 1,000 (34 fewer to 49 more)
Health-related quality of life (EQ-5D VAS, range 0-100, higher is better, change from baseline) follow-up: 90 days	731 (1 RCT)	⊕⊕⊕⊕ High	-	The mean EQ-5D VAS (change from baseline) was 8.29	MD 2.48 higher (2.34 higher to 2.62 higher)
Unplanned hospitalisation or visits (HF-related) (HF hospitalisation re-admission) (dichotomous) follow-up: 180 days	692 (1 RCT)	⊕⊕◯◯ Low[a,b]	RR 0.69 (0.46 to 1.03)	147 per 1,000	46 fewer per 1,000 (80 fewer to 4 more)
Acute kidney injury follow-up: 90 days	731 (1 RCT)	⊕◯◯◯ Very low[b,c]	Peto OR 7.45 (0.77 to 71.85)	0 per 1,000	0 fewer per 1,000 (0 fewer to 20 more)[d]
Hyperkalaemia follow-up: 90 days	731 (1 RCT)	⊕⊕◯◯ Low[b,c]	RR 2.61 (0.94 to 7.24)	14 per 1,000	22 more per 1,000 (1 fewer to 85 more)
Falls follow-up: 90 days	731 (1 RCT)	⊕◯◯◯ Very low[b,c]	Peto OR 7.41 (0.15 to 373.41)	0 per 1,000	0 fewer per 1,000 (0 fewer to 10 more)[d]

CI: confidence interval; EQ-5D VAS: EuroQoL 5-dimensions questionnaire visual analogue scale; HF: Heart failure; MD: Mean difference; OR: Odds ratio; RCT: Randomised controlled trial; RR: Relative risk

a) *Downgraded by 1 increment for outcome indirectness: time-to-event data not available for reduced EF subgroup*
b) *Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 x median of baseline SD of the intervention and control group for continuous outcomes; MID for EQ5D VAS = 9.37).*
c) *Downgraded by 1 increment for outcome indirectness: Outcome not defined*

d) Calculated from risk difference

1.1.6.2. Placebo comparisons

Table 4: Clinical evidence summary: SGLT2i + ACEI/ARB + BB + MRA *versus* ACEI/ARB + BB + MRA + placebo

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI/ARB + BB + MRA + placebo	Risk difference with SGLT2i + ACEI/ARB + BB + MRA
All-cause mortality (HR) follow-up: range 16 to 18 months	8474 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	HR 0.87 (0.77 to 0.98)	Not estimable	
All-cause mortality (dichotomous) follow-up: range 3 months to 24 months	9635 (8 RCTs)	⊕⊕⊕◯ Moderate[b]	RR 0.89 (0.80 to 0.99)	126 per 1,000	14 fewer per 1,000 (25 fewer to 1 fewer)
Cardiovascular mortality (HR) follow-up: range 16 to 18 months	8474 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	HR 0.86 (0.76 to 0.98)	Not estimable	
Cardiovascular mortality (dichotomous) follow-up: range 3 to 18 months	8927 (4 RCTs)	⊕⊕◯◯ Low[a,b]	RR 0.87 (0.77 to 0.99)	107 per 1,000	14 fewer per 1,000 (25 fewer to 1 fewer)
Health-related quality of life (KCCQ clinical summary score); change or final score Scale: 0 to 100, higher scores better follow-up: 3 months	4491 (4 RCTs)	⊕⊕⊕⊕ High	-	The mean health related quality of life (KCCQ clinical summary score); change or final score was 4.1	MD 1.7 higher (1.67 higher to 1.73 higher)
Health-related quality of life (KCCQ - overall summary score, change or final scores) Scale: 0 to 100, higher scores better follow-up: range 12 weeks to 52 weeks	765 (4 RCTs)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (KCCQ - overall summary score, change or final scores) was 3.75	MD 1.84 higher (0.78 higher to 2.91 higher)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI/ARB + BB + MRA + placebo	Risk difference with SGLT2i + ACEI/ARB + BB + MRA
Health-related quality of life (KCCQ total symptom score), change score Scale: 0 to 100, higher scores better follow-up: 8 months	4839 (2 RCTs)	⊕◯◯◯ Very low[a,c]	-	The mean health-related quality of life (KCCQ total symptom score), change score was 3.75	MD 0.47 higher (5.48 lower to 6.43 higher)
Unplanned hospitalisation or visits (HF-related); (first hospitalisation for heart failure, HR) follow-up: range 3 to 18 months	8737 (3 RCTs)	⊕⊕⊕⊕ High	HR 0.70 (0.62 to 0.78)	Not estimable	
Unplanned hospitalisation or visits (HF-related); (total hospitalisations for heart failure, rate ratio) follow-up: range 16 months to 18 months	8474 (2 RCTs)	⊕⊕⊕⊕ High	Rate ratio 0.72 (0.65 to 0.80)	21 per 1,000 patients per year	60 fewer per 1,000 patients per year (75 fewer to 43 fewer)[d]
Unplanned hospitalisation or visits (HF-related) (hospitalisation for heart failure, dichotomous) follow-up: range 3 months to 18 months	9017 (5 RCTs)	⊕⊕◯◯ Low[a,b]	RR 0.73 (0.65 to 0.81)	151 per 1,000	41 fewer per 1,000 (53 fewer to 29 fewer)
Withdrawal due to drug-related adverse events follow-up: range 3 months to 18 months	5631 (4 RCTs)	⊕⊕⊕◯ Moderate[a]	RR 0.93 (0.75 to 1.17)	53 per 1,000	4 fewer per 1,000 (13 fewer to 9 more)
Acute kidney injury follow-up: range 3 months to 18 months	5104 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	RR 0.54 (0.33 to 0.87)	18 per 1,000	8 fewer per 1,000 (12 fewer to 2 fewer)
Hyperkalaemia follow-up: range 3 to 18 months	8434 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	RR 0.90 (0.78 to 1.03)	94 per 1,000	9 fewer per 1,000 (21 fewer to 3 more)
Symptomatic hypotension (surrogate for falls) follow-up: range 12 weeks to 40 weeks	295 (2 RCTs)	⊕◯◯◯ Very low[a,e,f]	RR 0.92 (0.66 to 1.29)	216 per 1,000	17 fewer per 1,000 (74 fewer

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI/ARB + BB + MRA + placebo	Risk difference with SGLT2i + ACEI/ARB + BB + MRA
					to 63 more)

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; HF: Heart Failure; HR: Hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: Mean difference; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial; RR: Relative risk; SGLT2i: Sodium-glucose co-transporter 2 inhibitor; SUGAR-DM-HF: Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure
a. 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 (default MID=0.8 and 1.25 for dichotomous outcomes and 0.5 x median baseline SD of the intervention and control group for continuous outcomes, or 0.5 x control group SD if baseline values not reported; MID=5 for KCCQ).
b. Downgraded by 1 increment for outcome indirectness: dichotomous when time-to-event is the prespecified measure
c. Downgraded by 1 increment for inconsistency (unexplained heterogeneity was present that was too significant to permit pooling, resulting in single studies).
d. Absolute effect calculated using total event rates per 100 person years reported in the papers.
f. Downgraded by 1 increment for outcome indirectness (symptomatic hypotension used as a surrogate for falls in the protocol).
e. Downgraded by 2 increments for high risk of bias in >50% analysis weighting (missing data; no information about pre-specified analyses).

Table 5: Clinical evidence summary: MRA + ACEI/ARB + BB *versus* ACEI/ARB + BB + placebo

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI/ARB + BB +placebo	Risk difference with MRA +ACEI/ARB+ BB
All-cause mortality HR (Tsutsui, 2017) follow-up: 30 months	221 (1 RCT)	⊕⊕⊕◯ Very low[a,b]	HR 1.77 (0.81 to 3.87)	Not estimable	
All-cause mortality HR (Zannad, 2011) follow-up: median 21 months	2737 (1 RCT)	⊕⊕◯◯ Low[a,b]	HR 0.76 (0.62 to 0.93)	Not estimable	
All-cause mortality (dichotomous) follow-up: range 6 months to 44 months	3494 (5 RCTs)	⊕⊕⊕◯ Moderate[b]	RR 0.86 (0.72 to 1.02)	134 per 1,000	19 fewer per 1,000 (38 fewer to 3 more)
Cardiovascular mortality HR (Tsutsui, 2017) follow-up: 30 months	221 (1 RCT)	⊕⊕◯◯ Low[a,b]	HR 2.40 (0.92 to 6.26)	Not estimable	

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI/ARB + BB +placebo	Risk difference with MRA +ACEI/ARB+ BB
Cardiovascular mortality HR (Zannad, 2011) follow-up: median 21 months	2737 (1 RCT)	⊕⊕◯◯ Low[a,b]	HR 0.76 (0.61 to 0.94)	Not estimable	
Cardiovascular mortality (dichotomous) - Japan follow-up: range 6 months to 30 months	521 (2 RCTs)	⊕◯◯◯ Very low[b,c,d,e]	RR 2.47 (1.03 to 5.95)	23 per 1,000	34 more per 1,000 (1 more to 114 more)
Cardiovascular mortality (dichotomous) - Europe follow-up: range 21 months to 44 months	2867 (2 RCTs)	⊕⊕◯◯ Very low[b,d,e]	RR 0.79 (0.64 to 0.96)	134 per 1,000	28 fewer per 1,000 (48 fewer to 5 fewer)
Cardiovascular mortality (dichotomous) - total follow-up: range 6 months to 44 months	3388 (4 RCTs)	⊕◯◯◯ Very low[b,e,f]	RR 0.83 (0.68 to 1.01)	117 per 1,000	20 fewer per 1,000 (37 fewer to 1 more)
Health-related quality of life (EQ-VAS) Scale from: 0 to 100, higher scores better follow-up: 12 weeks	40 (1 RCT)	⊕◯◯◯ Very low[b,g]	-	The mean health-related quality of life (EQ-VAS) was 66	MD 3 higher (42.92 lower to 48.92 higher)
Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF, HR) follow-up: range 6 months to 30 months	3258 (3 RCTs)	⊕⊕⊕⊕ High	HR 0.60 (0.50 to 0.72)	Not estimable	
Unplanned hospitalisation or visits (HF-related) (HF-related hospitalisation) follow-up: range 6 months to 30 months	3258 (3 RCTs)	⊕⊕⊕◯ Moderate[e]	RR 0.67 (0.57 to 0.79)	182 per 1,000	60 fewer per 1,000 (78 fewer to 38 fewer)
Unplanned hospitalisation or visits (HF-related) (hospitalisation for	2737 (1 RCT)	⊕⊕⊕⊕ High	Rate ratio 0.53 (0.42 to 0.66)	Not estimable	Not estimable

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI/ARB + BB +placebo	Risk difference with MRA +ACEI/ARB+ BB
HF, including repeat events, total HHF) follow-up: median 25 months					
Withdrawal due to adverse events follow-up: range 6 months to 21 months	3132 (3 RCTs)	⊕⊕⊕◯ Moderate[b]	RR 0.88 (0.74 to 1.05)	149 per 1,000	18 fewer per 1,000 (39 fewer to 7 more)
Acute kidney injury follow-up: 12 weeks	40 (1 RCT)	⊕◯◯◯ Very low[g,h]	Risk Difference 0.00 (-0.09 to 0.09)	0 per 1,000	0 fewer per 1,000 (90 fewer to 90 more)
Hyperkalaemia follow-up: range 6 months to 44 months	3656 (6 RCTs)	⊕⊕⊕⊕ High	RR 1.69 (1.36 to 2.12)	61 per 1,000	42 more per 1,000 (22 more to 69 more)

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; EQ-VAS: EuroQoL visual analogue scale; HF: Heart Failure; HHF: Hospitalisation for heart failure; HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial; RR: Relative risk

a. Downgraded by 1 increment for inconsistency: Tsutsui and Zannad studies demonstrated opposite directions for the effect estimate so not appropriate to pool these trials.

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes; MID for EQ5D VAS = 33.5).

c. Downgrade by 1 increment because of some concerns about risk of bias due to the outcome assessment process being unblinded.

d. Subgroup analyses (by Europe/Japan) required to explain heterogeneity (not appropriate to pool).

e. Downgraded by 1 increment for indirectness due to outcome reported as number of events.

f. Downgraded by 2 increments for inconsistency due to the I^2 value of >60%.

g. Downgraded by 2 increments for risk of bias: limited information regarding randomisation, allocation concealment, the difference in attrition, unclear how the differences were accounted for, and no pre-specified plan.

h. Downgraded by two increments for imprecision (sample size <70).

Table 6: Clinical evidence summary: MRA + ARB + BB versus ARB + BB + placebo

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ARB +BB	Risk difference with MRA + ARB + BB
Withdrawal due to drug-related adverse events follow-up: 52 weeks	48 (1 RCT)	⊕◯◯◯ Very low[a,b]	RR 2.17 (0.21 to 22.40)	40 per 1,000	47 more per 1,000 (32 fewer to 856 more)
Hyperkalaemia follow-up: 52 weeks	48 (1 RCT)	⊕◯◯◯ Very low[a,b]	Peto OR 8.06 (0.16 to 407.60)	0 per 1,000	40 more per 1,000 (70 fewer to 50 more)[c]

ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; MRA: Mineralocorticoid receptor antagonist; OR: Odds ratio; RCT: Randomised controlled trial; RR: Relative risk

a) *Downgraded by 2 increments for risk of bias due to no details provided regarding randomisation, allocation concealment, attrition, or prespecified plan.*
b) *Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.*
c) *Calculated from risk difference.*

Table 7: Clinical evidence summary: ARB + ACEI + BB *versus* ACEI + BB + placebo

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI + BB + placebo	Risk difference with ARB + ACEI + BB
All-cause mortality (HR) follow-up: 41 months	2548 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.89 (0.77 to 1.02)	Not estimable	
All-cause mortality (dichotomous) follow-up: range 24 weeks to 41 months	2621 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	RR 0.91 (0.81 to 1.03)	315 per 1,000	28 fewer per 1,000 (60 fewer to 9 more)
Cardiovascular mortality (HR) follow-up: 41 months	2548 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.83 (0.71 to 0.97)	Not estimable	
Cardiovascular mortality (dichotomous) follow-up: 41 months	2548 (1 RCT)	⊕⊕◯◯ Low[a,b]	RR 0.87 (0.76 to 0.99)	273 per 1,000	35 fewer per 1,000 (65 fewer to 3 fewer)
Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, HR) follow-up: 41 months	2548 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.83 (0.71 to 0.97)	Not estimable	
Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, dichotomous) follow-up: 41 months	2548 (1 RCT)	⊕⊕◯◯ Low[a,b]	RR 0.87 (0.76 to 0.99)	280 per 1,000	36 fewer per 1,000 (67 fewer to 3 fewer)
Withdrawal due to drug-related adverse events follow-up: range 24 weeks to 41 months	2616 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	RR 1.32 (1.13 to 1.53)	182 per 1,000	58 more per 1,000 (24 more to 96 more)
Hyperkalaemia (causing discontinuation) follow-up: range 24 weeks to 41 months	2616 (2 RCTs)	⊕⊕⊕⊕ High	RR 4.97 (2.49 to 9.93)	7 per 1,000	27 more per 1,000 (10 more to 62 more)
Falls (symptomatic hypotension as a	68 (1 RCT)	⊕◯◯◯ Very low[a,c]	OR 7.19 (0.44 to 117.48)	0 per 1,000	60 more per 1,000

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI + BB + placebo	Risk difference with ARB + ACEI + BB
surrogate) follow-up: 24 weeks					(40 fewer to 150 more)[d]

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; HF: Heart Failure; HHF: Hospitalisation for heart failure; HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial; RR: Relative risk
a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.
b. Downgraded by 1 increment for outcome indirectness because events data is used rather than time-to-event data as pre-specified in the protocol.
c. Downgraded by 1 increment for outcome indirectness (symptomatic hypotension used as a surrogate for falls)
d. Absolute risk calculated from risk difference.

1.1.6.3. Head-to-head comparisons

Table 8: Clinical evidence summary: ARNI + MRA + BB versus ARB + MRA + BB

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ARB + MRA + BB	Risk difference with ARNI + MRA + BB
All-cause mortality (HR) follow-up: 24 weeks	336 (1 RCT)	⊕◯◯◯ Very low[a,b]	HR 1.63 (0.68 to 3.92)	Not estimable	
All-cause mortality (dichotomous) follow-up: range 12 to 24 weeks	414 (2 RCTs)	⊕◯◯◯ Very low[c,d]	RD 0.02 (-0.02 to 0.07)	39 per 1,000	20 more per 1,000 (20 fewer to 70 more)
Cardiovascular mortality (HR) - Ghafur 2020 follow-up: 88 days	100 (1 RCT)	⊕⊕◯◯ Low[e,f,g]	HR 0.37 (0.27 to 0.51)	Not estimable	
Cardiovascular mortality (HR) - Mann 2022 follow-up: 24 weeks	336 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	HR 1.58 (0.61 to 4.08)	Not estimable	
Cardiovascular mortality (dichotomous) - Ghafur 2020 follow-up: 88 days	100 (1 RCT)	⊕◯◯◯ Very low[b,e,f,g]	RR 0.36 (0.12 to 1.07)	220 per 1,000	141 fewer per 1,000 (194 fewer to 15 more)
Cardiovascular mortality (dichotomous) Mann 2022 follow-up: 24 weeks	335 (1 RCT)	⊕◯◯◯ Very low[b,c,f]	RR 1.58 (0.63 to 3.98)	42 per 1,000	24 more per 1,000 (15 fewer to 124 more)
Unplanned hospitalisation or visits HF-related	336 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	HR 1.24	Not estimable	

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ARB + MRA + BB	Risk difference with ARNI + MRA + BB
(HR) - Mann 2022 follow-up: 24 weeks			(0.80 to 1.93)		
Unplanned hospitalisation or visits HF-related (HR) - Ghafur 2020 follow-up: 88 days	100 (1 RCT)	⊕◯◯◯ Very low[b,e,f]	HR 0.80 (0.63 to 1.02)	Not estimable	
Unplanned hospitalisation or visits HF related (dichotomous) - Ghafur 2020 follow-up: 88 days	100 (1 RCT)	⊕◯◯◯ Very low[b,e,f,g]	RR 0.20 (0.05 to 0.87)	200 per 1,000	160 fewer per 1,000 (190 fewer to 26 fewer)
Unplanned hospitalisation or visits HF related (dichotomous) - Mann 2022 follow-up: 24 weeks	335 (1 RCT)	⊕◯◯◯ Very low[b,c,f]	RR 1.23 (0.84 to 1.81)	214 per 1,000	49 more per 1,000 (34 fewer to 174 more)
Withdrawal due to drug-related adverse events – Nagele 2024 follow-up: 3 months	79 (1 RCT)	⊕◯◯◯ Very low[b,h]	RR 0.49 (0.05-5.16)	51 for 1,000	26 fewer per 1,000 (49 fewer to 213 more)
Hyperkalaemia follow-up: range 88 days to 24 weeks	435 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	RR 1.82 (1.03 to 3.24)	73 per 1,000	60 more per 1,000 (2 more to 164 more)

ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin; BB: Beta-blocker; CI: Confidence interval; HF: Heart Failure; HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial; RD: Risk difference; RR: Relative risk

a) Downgraded by 1 increment for intervention indirectness because only 78% received combination therapy
b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.
c) Downgraded by 2 increments for indirectness (outcome indirectness because not time-to-event outcome and intervention indirectness because only 78% received combination therapy)
d) Downgraded by 2 increments for imprecision (calculated using OIS)
e) Downgraded by 1 increment because of some concerns about risk of bias (no information about allocation concealment)
f) Downgraded by 1 increment for inconsistency: Ghafur and Mann studies demonstrated opposite directions for the effect estimate so not appropriate to pool these trials.
g) Downgraded by 1 increment for outcome indirectness because not time-to-event outcome as specified in the protocol
h) Downgraded by 1 increment because of some concerns about risk of bias (adverse events not pre-specified outcome)

Table 9: Clinical evidence summary: ARNI + MRA + BB versus ACEI + MRA + BB

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI+MRA+BB	Risk difference with ARNI+MRA+BB
All-cause mortality (HR) follow-up: median 27 months	8399 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.84 (0.76 to 0.93)	Not estimable	
All-cause mortality (dichotomous) follow-up: range 12 weeks to 33.6 months	9442 (4 RCTs)	⊕⊕◯◯ Low[a,b]	RR 0.86 (0.78 to 0.94)	178 per 1,000	25 fewer per 1,000 (39 fewer to 11 fewer)
Cardiovascular mortality (HR) follow-up: range 27 months to 33.6 months	8622 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	HR 0.81 (0.72 to 0.90)	Not estimable	
Cardiovascular mortality (dichotomous) follow-up: range 12 weeks to 33.6 months	8823 (3 RCTs)	⊕⊕◯◯ Low[a,b]	RR 0.82 (0.74 to 0.91)	159 per 1,000	29 fewer per 1,000 (41 fewer to 14 fewer)
Health-related quality of life (KCCQ- CSS, change score) Scale from: 0 to 100, higher scores better follow-up: range 3 months to 8 months	8823 (3 RCTs)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (KCCQ- CSS, change score) was 4.92	MD 1.66 higher (0.72 higher to 2.61 higher)
Health-related quality of life (KCCQ overall summary score, change score) Scale from: 0 to 100, higher scores better follow-up: range 3 months to 8 months	7824 (2 RCTs)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (KCCQ overall summary score, change score) was 2.84	MD 1.3 higher (0.61 higher to 1.98 higher)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI+MRA+BB	Risk difference with ARNI+MRA+BB
Health-related quality of life (EQ-5D, change score) Scale from: 0 to 1, higher scores better follow-up: 12 weeks	604 (1 RCT)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (EQ-5D, change score) was 0.02	MD 0.01 higher (0.01 lower to 0.03 higher)
Health-related quality of life (EQ-VAS, change score) Scale from: 0 to 100, higher scores better follow-up: 12 weeks	604 (1 RCT)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (EQ-VAS, change score) was 4.01	MD 0.49 higher (2.08 lower to 3.06 higher)
Health-related quality of life (SF-12, mental component summary, change score) Scale from: 0 to 100, higher scores better follow-up: 12 weeks	604 (1 RCT)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (SF-12, mental component summary, change score) was 1.79	MD 0.34 lower (1.69 lower to 1.01 higher)
Health-related quality of life (SF-12 physical component summary, change score) Scale from: 0 to 100, higher scores better follow-up: 12 weeks	604 (1 RCT)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (SF-12 physical component summary, change score) was 1.65	MD 0.93 higher (0.17 lower to 2.03 higher)
Health-related quality of life (SF-36 mental component score, change score) Scale from: 0 to 100, higher scores better follow-up: 12 weeks	201 (1 RCT)	⊕⊕⊕⊕ High	-	The mean health-related quality of life (SF-36 mental component score, change score) was 1.75	MD 0.97 lower (2.99 lower to 1.05 higher)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI+MRA+BB	Risk difference with ARNI+MRA+BB
Health-related quality of life (SF-36 physical component score, change score) Scale from: 0 to 100, higher scores better follow-up: 12 weeks	201 (1 RCT)	⊕⊕⊕◯ Moderate[a]	-	The mean health-related quality of life (SF-36 physical component score, change score) was 1.87	MD 0.45 higher (1.15 lower to 2.05 higher)
Unplanned hospitalisation or visits (HF-related) (first unplanned hospitalisation or visits HF related, HR) - McMurray 2014 follow-up: 27 months	8399 (1 RCT)	⊕⊕◯◯ Low[a,c]	HR 0.79 (0.71 to 0.88)	Not estimable	
Unplanned hospitalisation or visits (HF-related) (first unplanned hospitalisation or visits HF related, HR) - Tsutsui 2021 follow-up: 33.6 months	223 (1 RCT)	⊕◯◯◯ Very low[a,c,d]	HR 1.27 (0.70 to 2.29)	Not estimable	
Unplanned hospitalisations or visits, HF-related (dichotomous) - McMurray 2014 follow-up: median 27 months	8399 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	RR 0.82 (0.74 to 0.91)	156 per 1,000	28 fewer per 1,000 (41 fewer to 14 fewer)
Unplanned hospitalisations or visits, HF-related (dichotomous) - Tsutsui 2021 follow-up:	223 (1 RCT)	⊕◯◯◯ Very low[a,b,c,d]	RR 1.26 (0.75 to 2.13)	179 per 1,000	46 more per 1,000 (45 fewer to 202 more)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI+MRA+BB	Risk difference with ARNI+MRA+BB
median 33.6 months					
Withdrawal due to drug-related adverse events follow-up: range 3 months to 34 months	8823 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	RR 0.86 (0.77 to 0.97)	121 per 1,000	17 fewer per 1,000 (28 fewer to 4 fewer)
Acute kidney injury (renal failure acute) follow-up: median 27 months	8432 (1 RCT)	⊕⊕◯◯ Low[a]	RR 1.03 (0.77 to 1.36)	22 per 1,000	1 more per 1,000 (5 fewer to 8 more)
Hyperkalaemia - Elevated serum potassium >5.5 mmol/l follow-up: median 27 months	8399 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.89 (0.82 to 0.97)	229 per 1,000	25 fewer per 1,000 (41 fewer to 7 fewer)
Hyperkalaemia - Hyperkalaemia measurement undefined follow-up: range 3 months to 34 months	1043 (3 RCTs)	⊕◯◯◯ Very low[a,d,e]	RR 1.49 (0.68 to 3.25)	60 per 1,000	29 more per 1,000 (19 fewer to 134 more)
Falls (symptomatic hypotension as a surrogate) follow-up: median 27 months	8399 (1 RCT)	⊕⊕⊕◯ Moderate[f]	RR 1.52 (1.35 to 1.72)	92 per 1,000	48 more per 1,000 (32 more to 66 more)

ACEI: Angiotensin converting enzyme inhibitor; ARNI: Angiotensin receptor-neprilysin; BB: Beta-blocker; CI: Confidence interval; EQ-5D: EuroQoL 5-dimensions questionnaire; EQ-VAS: EuroQoL visual analogue scale; HF: Heart Failure; HR: Hazard ratio; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire – Clinical Summary Scores; KCCQ overall: Kansas City Cardiomyopathy Questionnaire – overall scores; MD: Mean difference; MRA: Mineralocorticoid receptor antagonist; RCT: Randomised controlled trial; RR: Relative risk; SF-12: Short Form-12 health survey; SF-36: Short Form-36 health survey

a) *Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x SMD where no baseline values given) for continuous outcomes. MID for KCCQ is 5; MID for EQ5D is 0.03; MID for EQ5D VAS is 7.39; MID for SF12 mental component score is 4.28; MID for SF12 physical component score is 3.37; MID for SF36 mental component score is 3; MID for SF36 physical component score is 2.*

b) *Downgraded by one increment for outcome indirectness (events data, not time-to-event data as specified in protocol)*

c) *Downgraded by 1 increment for inconsistency: McMurray 2014 and Tsutsui 2021 demonstrated opposite directions for the effect estimate so not appropriate to pool these trials.*
d) *Downgraded by 1 increment because evidence has some concerns for risk of bias (no information about allocation concealment).*
e) *Downgraded by two increments for inconsistency because of unexplained substantial heterogeneity (I2>60%).*
f) *Downgraded by one increment for outcome indirectness because symptomatic hypotension used as a surrogate for falls.*

Table 10: Clinical evidence summary: ARNI + BB versus ACEI + BB

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI + BB	Risk difference with ARNI + BB
All-cause mortality follow-up: 12 weeks	464 (1 RCT)	⊕⊕◯◯ Low[a]	RR 1.01 (0.06 to 16.03)	4 per 1,000	0 fewer per 1,000 (4 fewer to 65 more)
Health-related quality of life (KCCQ- overall summary score); change score Scale from: 0 to 100, higher scores better follow-up: 12 weeks	438 (1 RCT)	⊕⊕⊕◯ Moderate[b]	-	The mean KCCQ-overall summary score); change score was 4.2	mean 4.5 higher (1.69 higher to 7.31 higher)
Hyperkalaemia (K^+>5.3meq/L) follow-up: 12 weeks	464 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 1.24 (0.80 to 1.94)	129 per 1,000	31 more per 1,000 (26 fewer to 121 more)

ACEI: Angiotensin converting enzyme inhibitor; ARNI: Angiotensin receptor-neprilysin; BB: Beta-blocker; CI: Confidence interval; K^+: Potassium in blood serum; KCCQ overall: Kansas City Cardiomyopathy Questionnaire – overall scores; RCT: Randomised controlled trial: RR: Relative risk

a) *Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.*
b) *Downgraded by 1 increment for imprecision because the 95% confidence crosses one MID (KCCQ MID=5).*

1.1.6.4. Type 2 diabetes stratification

Table 11: Clinical evidence summary: SGLT2i + ACEI + BB + MRA *versus* ACEI + BB + MRA + placebo – stratified by presence or absence of type 2 diabetes

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Risk difference with SGLT2i + ACEI + BB + MRA
All-cause mortality (HR) - Diabetes present follow-up: 16 months	2139 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.78 (0.63 to 0.97)	Not estimable	
All-cause mortality (HR) - Diabetes absent follow-up: 16 months	2605 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.88 (0.70 to 1.11)	Not estimable	
All-cause mortality (dichotomous) - Diabetes present follow-up: 18.2 months	2139 (1 RCT)	⊕⊕◯◯ Low[a,b]	RR 0.80 (0.65 to 0.97)	167 per 1,000	33 fewer per 1,000 (59 fewer to 5 fewer)
All-cause mortality (dichotomous) - Diabetes absent follow-up: 18.2 months	2605 (1 RCT)	⊕⊕◯◯ Low[a,b]	RR 0.89 (0.71 to 1.11)	116 per 1,000	13 fewer per 1,000 (34 fewer to 13 more)
Cardiovascular mortality (HR) - Diabetes present follow-up: 16 months	1856 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.92 (0.71 to 1.20)	Not estimable	
Cardiovascular mortality (HR) - Diabetes absent follow-up: 16 months	606 (1 RCT)	⊕⊕⊕◯ Moderate[a]	HR 0.92 (0.68 to 1.24)	Not estimable	
Cardiovascular mortality (dichotomous) - Diabetes present follow-up: range 16 to 18.2 months	3995 (2 RCTs)	⊕⊕◯◯ Low[a,b]	RR 0.86 (0.73 to 1.01)	131 per 1,000	18 fewer per 1,000 (35 fewer to 1 more)
Cardiovascular mortality (dichotomous) - Diabetes absent follow-up: range 16 to 18.2 months	3211 (2 RCTs)	⊕⊕◯◯ Low[a,b]	RR 0.87 (0.70 to 1.09)	96 per 1,000	13 fewer per 1,000 (29 fewer to 9 more)
Health related quality of life (KCCQ clinical summary score); change score - Diabetes present Scale from: 0 to 100, higher	1856 (1 RCT)	⊕⊕⊕⊕ High	-	The mean health related quality of life	MD 2.41 higher (2.35 higher to

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Risk difference with SGLT2i + ACEI + BB + MRA
scores better follow-up: 8 months				(KCCQ clinical summary score); change score - Diabetes present was 0	2.47 higher)
Health related quality of life (KCCQ clinical summary score); change score - Diabetes absent Scale from: 0 to 100, higher scores better follow-up: 8 months	1874 (1 RCT)	⨁⨁⨁⨁ High	-	The mean health related quality of life (KCCQ clinical summary score); change score - Diabetes absent was 0	MD 1.1 higher (1.05 higher to 1.15 higher)
Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF, HR) - Diabetes present follow-up: range 16 to 18.2 months	3995 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	HR 0.72 (0.61 to 0.85)	Not estimable	
Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF, HR) - Diabetes absent follow-up: range 16 to 18.2 months	3211 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	HR 0.68 (0.56 to 0.82)	Not estimable	
Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF, dichotomous) - Diabetes present follow-up: range 16 to 18.2 months	3995 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	RR 0.71 (0.59 to 0.86)	257 per 1,000	75 fewer per 1,000 (106 fewer to 36 fewer)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Risk difference with SGLT2i + ACEI + BB + MRA
Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF, dichotomous) - Diabetes absent follow-up: range 16 to 18.2 months	3211 (2 RCTs)	⊕◯◯◯ Very low[a,b,c]	RR 0.72 (0.55 to 0.93)	135 per 1,000	38 fewer per 1,000 (61 fewer to 9 fewer)
Withdrawal due to drug-related adverse events - Diabetes present follow-up: range 16 to 18.2 months	3995 (2 RCTs)	⊕⊕◯◯ Low[a]	RR 0.94 (0.79 to 1.11)	117 per 1,000	7 fewer per 1,000 (25 fewer to 13 more)
Withdrawal due to drug-related adverse events - Diabetes absent follow-up: range 16 to 18.2 months	3211 (2 RCTs)	⊕⊕⊕⊕ High	RR 1.02 (0.87 to 1.18)	131 per 1,000	3 more per 1,000 (17 fewer to 24 more)
Hyperkalaemia - Diabetes present follow-up: 16 months	1856 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.83 (0.60 to 1.15)	80 per 1,000	14 fewer per 1,000 (32 fewer to 12 more)
Hyperkalaemia - Diabetes absent follow-up: 16 months	1866 (1 RCT)	⊕⊕◯◯ Low[a]	RR 0.90 (0.62 to 1.32)	57 per 1,000	6 fewer per 1,000 (22 fewer to 18 more)

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; CI: Confidence interval; HF: Heart failure; HR: Hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes; MID for KCCQ = 5.

bc. Downgraded by 1 increment for outcome indirectness because not time-to-event outcome as specified in the protocol.

c. Downgraded by 1 increment if I^2 40-60%.

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

1.1.7.1. Included studies

In total, after applicability and quality was assessed, there were 10 included studies for this review question, as follows:

- Mineralcorticoid receptor antagonists – 1 study
  - Lee et al. 2014 – eplerenone added to standard care (UK)
- Sacubitril valsartan – 4 studies
  - McMurray et al. 2018 – sacubitril valsartan vs enalapril (UK) – NICE TA388 manufacturer's model
  - Grant et al. 2020 – early vs later sacubitril valsartan (Canada)
  - Park et al. 2019 – sacubitril valsartan vs enalapril vs ARB (South Korea)
  - Van der Pol et al. 2019 – sacubitril valsartan vs enalapril vs candesartan (Germany)
- SGLT2 inhibitors – 4 studies
  - McEwan et al. 2020 – dapagliflozin adjunct to standard care (UK) – NICE TA679 manufacturer's model
  - Miller et al. 2023 – early vs later dapagliflozin (UK)
  - Reifsnider et al. 2020 – empagliflozin in a population with both CHF and T2DM (UK)
  - Tafazzoli et al. 2023 – empagliflozin adjunct to standard care (UK) – NICE TA773 manufacturer's model
- Quadruple therapy (Treatment sequencing) – 1 study
  - Van et al 2024 - Pharmacotherapy sequencing strategies for patients with heart failure with reduced ejection fraction (Canada)

These are summarised in the health economic evidence profile below (Table 12, Table 13, Table 14, Table 15) and the health economic evidence tables in Appendix H.

1.1.7.2. Excluded studies

A further 46 studies were ordered but not included. Some of these studies were selectively excluded because they had very similar methods to included studies but had a non-UK perspective:

- Mineralocorticoid receptor antagonists – 4 studies
- Sacubitril-valsartan – 5 studies
- SGLT2 inhibitors – 8 studies

These could have been included had there not been more applicable UK studies available.

One study conducted an economic evaluation of the STRONG-HF rapid titration but was excluded because it took a US perspective.

All studies that were ordered but not included are listed in Appendix J, with reasons for exclusion given.

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

1.1.8. Summary of included economic evidence

Table 12: Health economic evidence summary table: Eplerenone + ACEI + BB versus ACEI + BB for symptomatic heart failure with reduced ejection fraction

Study	Applicability and limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Lee et al. 2014 (UK)	Directly applicable[1] Potentially serious limitations[2]	• Decision analytic model (Discrete event simulation) • Effectiveness: RCT EMPHASIS-HF	£4,284	1.22 QALYs	£3,520 per QALY gained Added to ACEI+BB, eplerenone was cost-effective at a threshold of £20,000 per QALY.	Probability eplerenone cost-effective (£20K threshold): 100% Two scenario analyses using EMPHASIS-HF data with no extrapolation and another using only a 2-year time horizon generated ICERs of £20,730 and £20,101 per QALY gained, respectively. In all other scenario analyses eplerenone remained cost-effective.

ACEI: Angiotensin-converting enzyme inhibitor; BB: Beta-blockers; ICER: incremental cost-effectiveness ratio Classification; QALY: quality-adjusted life years; RCT: randomised controlled trial.
1. UK NHS perspective, however HRQoL is not reported directly from patients in the trial.
2 The analysis is based on estimates of relative treatment effect and resource use from a single study, so does not reflect all available evidence in this area. There is cross-over between the trial arms. Utility values are not reported directly from patients of the EMPHASIS-HF trial. Potential bias due to the sponsor of the study.

Table 13: Health economic evidence summary table: Sacubitril-valsartan vs ACE inhibitor or ARB for symptomatic heart failure with reduced ejection fraction

Study	Applicability and limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Grant et al. 2020 (Canada)	Partially applicable[1] Minor limitations[2]	• Decision analytic model (Cohort Markov) • Effectiveness: RCT PARADIGM HF	Late £2,360 Early: £2,677 De novo: £2,877	Late: 0.09 Early: 0.12 De novo: 0.14	Late: £23,234 per QALY gained Early: £20,714 per QALY gained	Probability sacubitril-valsartan cost-effective (£20K threshold): ~50% Results were sensitive to the mortality effect of sacubitril valsartan and the acquisition cost. Both could potentially push the ICERs above £30,000 per QALY gained.

Study	Applicability and limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
					De novo: £20,054 per QALY gained	
McMurray et al. 2018 (United Kingdom)	Directly applicable Potentially serious limitations[3]	• Decision analytic model (Cohort Markov) • Effectiveness: RCT PARADIGM-HF	vs enalapril £8,906	vs enalapril 0.52 QALYs	vs enalapril £17,100 per QALY gained	Probability sacubitril-valsartan cost-effective (£20/£30K threshold): 68%/94%
Park et al. 2019 (South Korea)	Partially applicable[1] Potentially serious limitations[3]	• Decision analytic model (Cohort Markov). • Effectiveness: RCT PARADIGM-HF (and NMA of ACEI vs placebo and ARB vs placebo RCTs)	vs enalapril £7,537 vs ARB £7,091	vs enalapril 0.59 vs ARB 0.59	vs enalapril £11,300 per QALY gained vs ARB £10,632 per QALY gained	Probability sacubitril-valsartan cost-effective (£18k threshold): vs ARB: 89.0% vs enalapril: 87.6% Results were robust to sensitivity analysis
Van der Pol et al. 2019 (Germany)	Partially applicable[1] Potentially serious limitations[2]	• Decision analytic model (Cohort Markov) • Effectiveness: RCTs PARADIGM-HF, SOLVD, CHARM	vs enalapril £14,760 vs Candesartan £14,684	vs enalapril 0.82 vs Candesartan 0.91	vs enalapril £18,047 per QALY gained Vs Candesartan £16,096 per QALY gained	Probability sacubitril-valsartan most cost-effective (£20/£30K threshold): ~50%/~80% Results were sensitive to the mortality effect of sacubitril valsartan, which could potentially push the ICERs above £30,000 per QALY gained.

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; NMA: network meta-analysis; QALY: quality-adjusted life years; RCT: randomised controlled trial.

1. Costs and utilities from a non-UK perspective; non-reference case discount rates applied.

2 Treatment effects from a single trial rather than a systematic review; baseline from a trial rather than real-world population.

3. Treatment effects from a single trial rather than a systematic review; baseline from a trial rather than real-world population; funded by manufacturer.

Table 14: Health economic evidence summary table: Sodium-Glucose co-transporter-2 inhibitors (SGLT2i) + Standard therapy versus Standard therapy for symptomatic heart failure with reduced ejection fraction

Study	Applicability and limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
McEwan et al. 2020 Dapagliflozin 10mg (UK)	Directly applicable Potentially serious limitations[1]	• Decision analytic model (Cohort Markov) • Effectiveness: RCT DAPA-HF	£2,780	0.48 QALYs	£5,822 per QALY gained	Probability dapagliflozin cost-effective (£20/£30K threshold): 96%/97% The results were similar across all subgroups analysed.
Miller et al. 2023 Dapagliflozin 10mg (UK)	Directly Applicable Potentially serious limitations[1]	• Decision analytic model (Cohort Markov) • Effectiveness: RCT DAPA-HF sub-population with a history of prior hospitalised heart failure	12-month delayed initiation: £3,436 Immediate initiation £3688	12-month delayed initiation: 0.591 QALYs Immediate initiation: 0.639 QALYs	12-month delayed: £5,821 per QALY gained, Immediate: £5,779 per QALY gained	Probability dapagliflozin cost-effective (£20/£30K threshold): >99%/>99% Deterministic sensitivity analyses: The ICER of immediate compared to 12-month delayed initiation of dapagliflozin was most sensitive to discounting parameters as well as intervention costs.
Reifsnider et al. 2020 Empagliflozin (UK)	Directly Applicable Potentially serious limitations[1]	• Decision analytic model (Discrete event simulation) • Effectiveness: RCT EMPA-REG OUTCOME trial (CHF subgroup of type 2 diabetes population)	£1,367	0.65 QALYs	£2,093 per QALY gained	The probability of empagliflozin being cost-effective in the CHF subpopulation at a £20 000 per QALY threshold was 91%. All scenarios produced ICERs well below the £20 000 per QALY.
Tafazzoli et al. 2023 Empagliflozin (UK)	Directly Applicable Potentially serious limitations[1]	• Decision analytic model (Cohort Markov) • Effectiveness: RCT EMPEROR-Reduced trial	£1,169	0.19 QALYs	£6,152 per QALY gained	Probability empagliflozin cost-effective (£20k threshold): 79.6% All scenarios produced ICERs well below the £20 000 per QALY.

CHF: chronic heart failure; QALY: quality-adjusted life years; RCT: randomised controlled trial

1 Effects were from a single trial rather than a systematic review. Baseline from trial population so might differ from real-world population. Funded by manufacturer.

Table 15: Health economic evidence summary table quadruple therapy for the treatment of heart failure with reduced ejection fraction

Study	Applicability and limitations	Other comments	Incremental cost[3]	Incremental effects	Cost-effectiveness[3]	Uncertainty
Van et al 2024	Partially applicable[1] Potentially serious limitations[2]	• Decision analytic model (micro-simulation model with a one week cycle length) • Treatment strategies: a: bi-weekly titration, b: weekly titration • Strategies 1 and 2 initiate one medication at a time prioritising titration over initiation of the next treatment. 1: Traditional sequencing, initiate ACEI/ARBs, followed by BB, MRA, ARNI and finally SGLT2i 2: SGLT2i followed by: MRA, ARNI, BB Strategies 3 and 4 initiate two treatments together, then prioritise initiation over titration 3: SGLT2i and BB, followed by ARNI, MRA (rapid titration) 4: ARNI and BB, followed by MRA then SGLT2i 5: Initiate ARNI, BB & SGLT2i, then initiate MRA and titrate other treatments 6: Initiate ARNI, BB, MRA & SGLT2i then titrate treatments	Compared with 1a: 1a: - 1b: £1,052 2a: £545 2b: £1,332 3a: £948 3b: £1,538 4a: £1,038 4b: £1,591 5a: £1,066 5b: £1,607 6a: £1,080 6b: £1,621	Compared with 1a: 1a: - 1b: 0.08 2a: 0.06 2b:0.12 3a:0.15 3b:0.16 4a: 0.16 4b:0.16 5a: 0.17 5b: 0.17 6a: 0.17 6b: 0.17	Compared with 1a: 1a: - 1b: £12,578 2a: £8,494 2b: £11,467 3a: £6,250 3b: £9,587 4a: £6,577 4b: £9727 5a: £6,488 5b: £9,590 6a: £6,387 6b: £9,485	One way sensitivity analysis found discount rate, incidence rate of death, and heart failure hospital admissions had the greatest impact on NMB. However all remaining under the cost per QALY threshold of £27,963 (CA$50,000) per QALY. Based on the cost-effectiveness acceptability curve strategy 6a was identified as the most optimal strategy based on a WTP threshold of £7,830 (CA$14,000) per QALY and had a 75% probability of being the optimal choice at a cost per QALY threshold of £27,963 (CA$50,000) per QALY.
NICE 2025	Directly applicable[1] Minor limitations[2]	• Probabilistic decision analytic model (Markov) based on RCTs • Cost-utility analysis (QALYs) • Population: ○ People with HFrEF who can tolerate ACEI	2 vs 1: £686 3 vs 2: £1,936 4 vs 3: £4,773 5 vs 3: £6,871	2 vs 1: 0.324 3 vs 2: 0.251 4 vs 3: 0.118 5 vs 3: 0.323	2 vs 1: £2,119 3 vs 2: £7,705 4 vs 3: Extendedly dominated 5 vs 3: £21,261	Strategy 4 was cost-effective in most scenarios, except when the improvements of quality of life of ARNI and SGLT2 inhibitors were

Study	Applicability and limitations	Other comments	Incremental cost[3]	Incremental effects	Cost-effectiveness[3]	Uncertainty
		• Comparators: 1. Current NICE pathway 2. Early MRA 3. Early MRA and early SGLT2i 4. Early MRA and early ARNI 5. Early MRA, early ARNI and early SGLT2i • Time horizon: Lifetime				summed together. In this scenario, strategy 5 became the most cost-effective. Strategy 2 became the most cost-effective when the trial results of the European subpopulation were used Early SGLT2i was the most cost-effective strategy in 58% of simulations
NICE 2025	Directly applicable[1] Minor limitations[2]	• Probabilistic decision analytic model (Markov) based on RCTs • Cost-utility analysis (QALYs) • Population: ○ People with HFrEF who can not tolerate ACEI • Comparators: 6. Current NICE pathway 7. Early MRA 8. Early MRA and early SGLT2i 9. Early MRA and early ARNI 10. Early MRA, early ARNI and early SGLT2i • Time horizon: Lifetime	2 vs 1: £675 3 vs 2: £1,902 4 vs 3: £5,028 5 vs 3: £7,128	2 vs 1: 0.323 3 vs 2: 0.252 4 vs 3: 0.249 5 vs 3: 0.454	2 vs 1: £2,088 3 vs 2: £7,537 4 vs 3: Extendedly dominated 5 vs 3: £15,700	Strategy 5 remained the most cost-effective strategy in almost all scenarios. Strategy 2 became the most cost-effective when the trial results of the European subpopulation were used. Early SGLT2i and early ARNI was found to be the most cost-effective strategy in around 72% of simulations

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; HFrEF: Chronic heart failure due to left ventricular dysfunction with reduced ejection fraction of ≤40%; MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

1. Costs and utilities from a non-UK perspective; non-reference case discount rates applied.

2. Not all relevant costs are included, costs of adverse events are not included, only disutility's associated with adverse events are included. The baseline data and assumptions are from a study 20 years old which may not be reflective

3.Canadian Dollars 2022 (presented here as 2022 UK pounds – converted using OECD Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx)

1.1.9. Economic model

A de novo Markov economic model was developed from the perspective of UK NHS and Personal Social Services (PSS) to address this review question. The model was a lifetime cost-utility analysis comparing the current NICE pathway with four alternative strategies with early use of further medications. Further details are available in the economic analysis report for chronic heart failure with reduced ejection fraction published alongside the guideline.

The analysis was run separately for people who can and cannot tolerate ACEI (ACE inhibitor) and assessed the following treatment regimens:

1. **Current NICE pathway**
    a. First-line: ACEI/ARB & BB
    b. Second-line: Add MRA
    c. Third-line: Replace ACEI/ARB with ARNI or add SGLT2 inhibitor
    d. Fourth-line: ARNI & BB & MRA & SGLT2 inhibitor
2. **Early MRA**
    a. First-line: ACEI/ARB & BB & MRA
    b. Second-line: Replace ACEI/ARB with ARNI
    c. Third-line: Add SGLT2 inhibitor
3. **Early MRA and early ARNI**
    a. First-line: ARNI & BB & MRA
    b. Second-line: Add SGLT2 inhibitor
4. **Early MRA and early SGLT2 inhibitor**
    a. First-line: ACEI/ARB & BB & MRA & SGLT2 inhibitor
    b. Second-line: Replace ACEI/ARB with ARNI
5. **Early MRA, early ARNI and early SGLT2 inhibitor**
    a. First-line: ARNI & BB & MRA & SGLT2 inhibitor

The model was a Markov cohort model in which people could transition across five mutually exclusive health states, defined by the number of treatments received plus a dead state. Transitions between states occurred with probabilities informed by survival analyses based on real-world data from the INTEGRATE project from the London School of Hygiene & Tropical Medicine. In addition, people were at risk of hospitalisation (either for CVD or HF) and death, with baseline probabilities also informed by INTEGRATE project data. Treatment effects on mortality, HF hospitalisation and adverse events were extracted from randomised controlled trials and applied to baseline risks based on the treatments received in each health state (see Table 16 and Table 17).

Table 16: Relative treatment effects - All-cause mortality

Comparison	Relative effect (95% CI)	Reference
ACEI/ARB + BB + **MRA** versus ACEI/ARB + BB	HR: 0.76 (0.62 to 0.93)	Zannad, et al., 2011
ACEI/ARB + BB + MRA + **SGLT2i** versus ACEI/ARB + BB + MRA	HR: 0.87 (0.77 to 0.98)	Clinical review (McMurray, et al., 2019, Packer, et al., 2020)
ARNI + MRA + BB versus **ACEI** + MRA + BB	HR: 0.84 (0.76 to 0.93)	Clinical review (McMurray, et al., 2014)
ARB + MRA + BB versus **ACEI** + MRA + BB	RR: 1.07 (0.98 to 1.16)	Park, et al., 2023

Note: All values are mean, 95% confidence intervals are shown in parentheses. 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 17: Relative treatment effects - Hospitalisation for heart failure

Comparison	Relative effect (95% CI)	Reference
ACEI/ARB + BB + **MRA** versus ACEI/ARB + BB	HR: 0.6 (0.5 to 0.72)	Clinical review (Asakura, et al., 2020, Tsutsui, et al., 2018, Zannad et al., 2011)
ACEI/ARB + BB + MRA + **SGLT2i** versus ACEI/ARB + BB + MRA	HR: 0.70 (0.63 to 0.78)	Clinical review (McMurray et al., 2019, Nassif, et al., 2019, Packer et al., 2020)
ARNI + MRA + BB versus **ACEI** + MRA + BB	HR: 0.80 (0.72 to 0.90)	Clinical review (McMurray et al., 2014)
ARB + MRA + BB versus **ACEI** + MRA + BB	RR: 1	Assumed based on clinical consensus

Note: All values are mean, 95% confidence intervals are shown in parentheses. 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

It was assumed that people who cannot tolerate ACEI are initiated to ARB which has the same effectiveness of ACEI in preventing hospitalisation, but inferior in reducing mortality risk.

Costs were estimated using standard UK sources such as NHS collection cost, PSSRU, drug tariff and the prescription cost analysis (PCA). Utility values across the treatment regimens were reported in the trials as KCCQ-OS and converted into EQ-5D using a published mapping algorithm (Thomas et al. 2021). Short-term disutilities were applied for each episode of hospitalisation or adverse event simulated in the model. For more details on the inputs, assumptions and model structure, please refer to the full economic report.

The results for people who can tolerate ACEI and those who cannot tolerate ACEI are reported in Table 18 and Table 19, respectively.

Table 18: Base-case probabilistic cost–utility results – people who can tolerate ACEI

Strategy*	Cost per person	QALYs per person	Incremental cost per QALY gained**	Mean NHB*** (95% CI)	Mean Rank*** (95% CI)	Probability 1st rank***
Current NICE Pathway	£9,504	5.144	-	4.67 (4.35 to 5.00)	5.0 (5,5)	0.0%
Early MRA	£10,188	5.468	£2,109	4.96 (4.46 to 5.48)	3.5 (2,4)	1.3%
Early MRA and early SGLT2i	£12,124	5.720	£7,699	5.11 (4.55 to 5.70)	1.6 (1,3)	55.8%
Early MRA and early ARNI	£16,860	5.839	Extendedly dominated	5.00 (4.45 to 5.55)	3.1 (1,4)	5.8%
Early MRA and early SGLT2i and early ARNI	£18,959	6.044	£21,070	5.10 (4.52 to 5.68)	1.8 (1,4)	37.1%

Note: All values are mean, 95% confidence intervals are shown in parentheses. ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; MRA: Mineralocorticoid receptor antagonist; NHB: Net health benefit, which is defined as: 'QALYs per person – (Cost per person /£20,000)'; QALYs=quality-adjusted life-years; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

** In ascending order of cost*

*** Compared with the next non-dominated row above*

**** At £20,000 per QALY*

Table 19: Base-case probabilistic cost–utility results – people who cannot tolerate ACEI

Strategy*	Cost per person	QALYs per person	Incremental cost per QALY gained**	Mean NHB*** (95% CI)	Mean Rank*** (95% CI)	Probability 1st rank***
Current NICE Pathway	£9,256	5.014	-	4.55 (4.19 to 4.92)	5.0 (5,5)	0.0%
Early MRA	£9,933	5.339	£2,083	4.84 (4.31 to 5.38)	3.8 (2, 4)	0.2%
Early MRA and early SGLT2i	£11,842	5.592	£7,532	5.00 (4.40 to 5.60)	2.3 (1, 4)	20.0%
Early MRA and early ARNI	£16,843	5.835	Extendedly dominated	4.99 (4.45 to 5.53)	2.5 (1, 4)	9.1%
Early MRA and early SGLT2i and early ARNI	£18,950	6.041	£15,821	5.09 (4.50 to 5.67)	1.3 (1, 3)	70.6%

Note: All values are mean, 95% confidence intervals are shown in parentheses. ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; MRA: Mineralocorticoid receptor antagonist; NHB: Net health benefit, which is defined as: 'QALYs per person – (Cost per person /£20,000)'; QALYs=quality-adjusted life-years; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

** In ascending order of cost*

*** Compared with the next non-dominated row above*

**** At £20,000 per QALY*

In people who can tolerate ACEI, the combination of early MRA and early SGLT2 inhibitor was the most cost-effective strategy, with a probability of 56%. This finding remained consistent across scenario analyses, except in the scenario that assumed the improvement in quality of life from SGLT2 inhibitor and ARNI was additive. In that case, the combination of early MRA, early SGLT2 inhibitor and early ARNI became the most cost-effective strategy.

In people who cannot tolerate ACEI, early MRA, early SGLT2 inhibitor and early ARNI was the most cost-effective strategy in 71% of the simulations. This conclusion remained robust across scenario analyses.

In both populations, early SGLT2 inhibitor and early ARNI ceased to be cost-effective when treatment effect data from the European subpopulations of the trials were used instead.

1.1.10. Unit costs

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

Table 20: 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	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 an ACE inhibitor (under expert supervision)	17.53%

Class	Drug	Tablets/pack	Price/ pack	Tablets per day	Cost per year at max dose	Dose	Indication	Proportion on each drug
ARB	Losartan	28	£1.66	1	£21.65	Initially 12.5mg once daily, increased if tolerated to up to 150 mg 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 5 mg 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 1.25mg once daily for 1-2 weeks, then increased if tolerated to 2.5mg once daily for 1-2 weeks, then increased if tolerated to 5 mg 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	Adjunct in stable patients with left ventricular ejection fraction ≤40% with evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event). Adjunct in chronic mild heart failure with left ventricular ejection fraction ≤30%	28.36%

Class	Drug	Tablets/pack	Price/ pack	Tablets per day	Cost per year at max dose	Dose	Indication	Proportion on each drug
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)	71.64%
ARNI	Sacubitril with Valsartan	56	£91.56	2	£1,194.37	Initially 24/26mg twice daily for 3-4 weeks, increased if tolerated to 49/51 mg twice daily for 3-4 weeks, then increased if tolerated to 97/103mg twice daily	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	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

1.1.11. Economic evidence statements

Ten published cost-utility analyses were identified:

- One cost-utility analysis (Lee et al., 2014) compared MRA added to standard care with standard care alone. This study found over a lifetime horizon eplerenone added to standard of care could be considered cost-effective with an ICER of £3,520 per QALY gained compared with standard of care alone. This analysis was from an NHS perspective and informed by EMPHASIS-HF clinical trial.
- Four cost-utility analyses based on PARADIGM-HF (McMurray et al., 2018, Park et al., 2019, Van der Pol et al., 2019 and Grant et al., 2020) compared ARNI with placebo or different timing of initiation. Three of these (McMurray et al., 2018, Park et al., 2019, Van der Pol et al., 2019) found ARNI cost-effective at a £20,000 per QALY threshold but they were assessed as having potentially serious limitation. One study comparing different timing of ARNI administration from a Canadian perspective (Grant et al., 2000), found that none of the administration was associated with a cost per QALY inferior than £20,000 compared with current care.
- Four cost-utility analyses (McEwan et al., 2020, Miller et al., 2023, Reifsnider et al., 2020, Tafazzoli et al., 2023) compared SGLT2 inhibitor with placebo and found the treatment cost-effective with a cost per QALY ranging between £2,000 per QALY (in people with diabetes) to £6,000. They were all rated as partially applicable except Tafazzoli et al., 2023 which was conducted from an NHS perspective.
- One cost-utility analysis (Van et al., 2024) compared six different initiation and titration sequences for quadruple therapy each with two different frequencies of titration, either weekly or bi-weekly giving a total of 12 strategies explored from a Canadian healthcare perspective. This study found over a lifetime horizon the strategy in which all four pillars were initiated together followed by bi-weekly titration visits had a the lowest ICER of £6,575.72 per QALY.

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

1.1.12.1. 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 for heart failure and specific adverse events: withdrawal due to drug-related adverse events, acute kidney injury, hyponatraemia, hyperkalaemia and falls. Composite outcomes such as combined measures of mortality and hospitalisation did not meet the protocol and have not been included. For the purposes of decision making, all outcomes were rated as critical. For this review there was no outcome data for one specific adverse event of interest: hyponatraemia. The committee agreed that symptomatic hypotension could be accepted as a surrogate outcome for falls.

All-cause mortality, cardiovascular mortality and unplanned hospitalisations or visits for heart failure were each preferred as time-to-event outcomes. However, the dichotomous 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 (not per treatment group). In such instances the committee used the relative effects (hazard ratios) to inform their decision-making.

The Committee placed a large emphasis on heart failure hospitalisations in their considerations of the evidence. Keeping chronic heart failure patients out of hospital is critical to improve health outcomes, especially among those who are older. During hospital stays, patients often lose weight, including lean muscle mass, and experience an increased risk of falls and infection.

1.1.12.2. The quality of the evidence

One trial, STRONG-HF, evaluated the efficacy and safety of rapid optimisation of heart failure therapy compared with usual heart failure therapy management. The confidence in the evidence provided by this trial was mostly low or very low and one outcome (health-related quality of life) was rated high.

The Committee discussed the trial population with 80% from Russia and Mozambique and a relatively small number of participants in the chronic heart failure with reduced ejection fraction (HFrEF) subgroup. It was thought that the clinical effects from these countries could be at least partially generalisable, although the standard care may be different to the UK (less well optimised). The intervention also included 5 additional nurse visits to titrate the medications, so rapid titration is not the only element being tested in this intervention. The intervention was a high-intensity care strategy with additional healthcare professional contact and monitoring, as well as rapid titration.

The remainder of the evidence addressed the following comparisons, where the randomised agents are presented in bold text and background treatment is not bolded.

Placebo comparisons (with background treatment):

- **SGLT2i** + ACEI/ARB + BB + MRA versus ACEI/ARB + BB + MRA + **placebo** (9 trials)
- **MRA** + ACEI/ARB + BB versus ACEI/ARB + BB + **placebo** (7 trials)
- MRA + ARB + BB versus ARB + BB + **placebo** (1 trial)
- **ARB** + ACEI + BB versus ACEI + BB + **placebo** (2 trials)

Head-to-head comparisons (with background treatment):

- **ARNI** + MRA + BB versus **ARB** + MRA + BB (3 trials)
- **ARNI** + MRA + BB versus **ACEI** + MRA + BB (4 trials)
- **ARNI** + BB versus **ACEI** + BB (1 trial)

It was noted that there was no evidence investigating comparisons that add ARNI to SGLT2i or vice versa.

Most of the available evidence addressed two comparisons: SGLT2i + ACEI/ARB + BB + MRA versus ACEI/ARB + BB + MRA + placebo; and MRA + ACEI/ARB + BB versus ACEI/ARB + BB + placebo. Using GRADE criteria, the certainty of the evidence for outcomes ranged from very low to high for both of these comparisons. Reasons for downgrading were for concerns about risk of bias, outcome indirectness, imprecision and inconsistency. The certainty of the stratified evidence for the SGLT2i + ACEI/ARB + BB + MRA versus ACEI/ARB + BB + MRA + placebo comparison, by T2DM status, was similar.

The single study investigating the comparison MRA + ARB + BB versus ARB + BB + placebo was very low certainty of evidence due to concerns about risk of bias and precision.

The limited evidence-base that considered the comparison ARB + ACEI + BB versus ACEI + BB + placebo, was of very low to high certainty according to GRADE criteria. The evidence was downgraded due to outcome indirectness and imprecision.

The limited evidence-base that considered the comparison ARNI + MRA + BB versus ARB + MRA + BB, was of very low to moderate certainty according to GRADE criteria. The evidence was downgraded due to concerns about risk of bias, intervention and outcome indirectness, imprecision and inconsistency.

The evidence for the comparison ARNI + MRA + BB versus ACEI + MRA + BB ranged from very low to high certainty. The evidence is downgraded for risk of bias, imprecision, inconsistency and outcome indirectness.

For both comparisons involving ARNI versus ARB or ACE inhibitor, the committee considered the evidence to be limited by the way in which study populations were selected for inclusion, specifically that the included patients still have reduced LVEF at enrolment despite prior ACEI/ARB treatment. Patients may have responded and improved in response to ACEI/ARB. However, to qualify for ARNI, any patient who is already on ACEI or ARB had to continue to have their LVEF lower than 35% and be symptomatic.

The single study investigating the comparison ARNI + BB versus ACE inhibitor + BB was low to moderate certainty of evidence due to concerns about imprecision.

The age of the study populations was noted as a general limitation for evidence in this clinical review. Many studies included patients that were younger than that expected in a CHF population. Furthermore, it is common for CHF patients to have multiple co-morbidities and polypharmacy. The trials also show variation in background treatments used; with the evidence available it is difficult to assess the impact of adding a single class of medicines, as the medicines are prescribed in combinations. The committee acknowledged these differences in CHF populations in the controlled environments of trials compared to real-world experiences but nonetheless considered it appropriate to use the evidence available to inform recommendations.

1.1.12.3. Benefits and harms

Rapid optimisation (STRONG-HF)

The mortality and hospitalisation outcomes in this trial that met the review protocol were not expressed as time-to-event (the primary composite outcome did not meet the protocol). However, the study did report dichotomous events and the committee agreed these were informative. When expressed as dichotomous events, the evidence showed clinically important benefits for cardiovascular mortality (3 fewer per 1,000) and clinically important harm for all-cause mortality (5 more per 1,000). There was a clinically important benefit for heart failure hospitalisation (46 fewer cases per 1,000). There were no clinically important

differences for health-related quality of life or the specific adverse events: acute kidney injury, hyperkalaemia and falls.

The committee discussed the effect size seen for rapid optimisation on cardiovascular mortality and heart failure hospitalisations in light of the limitations in quality of the evidence. Findings for people with reduced ejection fraction are based on a small subgroup, and the age of the study participants is much lower than expected in CHF population. They also noted that although the absolute reduction in heart failure hospitalisation was clinically important, the uncertainty in the estimate meant they did not have confidence that this reflected a generalisable effect. The committee agreed not to make a specific recommendation directly based on rapid optimisation as assessed in STRONG-HF. However, the committee's final recommendations (1.4.1 to 1.4.5 and 1.5.1 to 1.5.3) do not preclude a rapid optimisation approach in appropriate circumstances, if the resources to support this approach are available.

Placebo comparisons (with background treatment)

SGLT2i (+ ACEI/ARB + BB + MRA) versus (ACEI/ARB + BB + MRA +) placebo

When expressed as time-to-event data, the mortality and hospitalisation outcomes suggested some clinical benefit as HRs were <1 (0.87 for all-cause mortality, 0.86 for cardiovascular mortality, 0.70 for first unplanned HF hospitalisation or visit). The evidence also showed clinically important benefits for all-cause mortality (14 fewer per 1,000), cardiovascular mortality (14 fewer per 1,000) and hospitalisation for HF (41 fewer per 1,000) when expressed as dichotomous events.

The evidence showed no clinically important difference for health-related quality of life, withdrawal due to drug-related adverse events or any of the specific adverse events of interest (acute kidney injury, hyperkalaemia or falls).

Overall, the committee interpreted the mortality and hospitalisation benefits to support the addition of SGLT2i, because a further benefit is seen despite good background therapy already being in place.

SGLT2i (+ ACEI/ARB + BB + MRA) versus (ACEI/ARB + BB + MRA +) placebo: stratification by T2DM status

Outcomes for this comparison were stratified by patient T2DM status. Relative effect sizes for each outcome split by presence and absence of T2DM, were similar and any minor differences were not considered clinically meaningful. The committee considered patients both with and without T2DM would gain a meaningful benefit with this class of medicine.

MRA (+ ACEI/ARB + BB) versus (ACEI/ARB + BB +) placebo

The committee noted that the majority of the evidence for this comparison was in people with LVEF ≤30%, so meeting the protocol in terms of population (LVEF≤40%) but at the lower end of the spectrum for LVEF.

For some outcomes, the study results were not pooled due to heterogeneity between studies. When expressed as time-to-event data, the mortality outcomes for Zannad 2011 suggested some clinical benefit as HRs were <1 (0.76 for both all-cause mortality and cardiovascular mortality). However, HRs were >1 for the same outcomes for the Tsutsui 2017 study, suggesting a possible harm. The committee considered the evidence from Zannad 2011 (EMPHASIS-HF) to be from a large RCT including populations from the UK and other similar countries, and therefore more representative of the population of relevance.

Tsutsui 2017 is a similar trial (J-EMPHASIS-HF) with a much smaller sample size conducted in Japan, so patient characteristics are more specific to that country, and thus may harbour specific features that may not be representative of the UK population and thus less applicable to our patient cohort. When a larger number of studies were pooled for all-cause mortality as a dichotomous outcome, this indicated a clinically important benefit of 19 fewer per 1,000.

A larger number of studies were available for cardiovascular mortality when expressed as a dichotomous outcome. Again, substantial heterogeneity was present; the committee therefore considered the evidence in two subgroups based on location, using an assumption that geographical location is a proxy for ethnicity (which was a pre-specified subgroup in the protocol) and so appropriate to explore as a source of heterogeneity. In the Japanese subgroup, there was evidence of a clinically important harm for cardiovascular mortality (34 more per 1,000). In the European subgroup, which the committee considered closest to the patient population of most relevance to the guideline, there was evidence of a clinically important benefit (28 fewer per 1,000). When these Japanese and European studies were pooled, a clinically important benefit of 20 fewer cardiovascular deaths per 1,000 was seen.

For these two outcomes, the committee considered geographical location as a possible explanation for heterogeneity, but there was insufficient data to make a robust conclusion. No clear biological rationale was evident to explain the different mortality effects in the different populations.

When expressed as time-to-event data, the hospitalisation outcome showed a clinically important benefit as the HR was <1 (0.6). This was also supported by data expressed as dichotomous outcomes, showing a clinically important benefit of 60 fewer heart failure hospitalisations per 1,000 and a rate ratio of 0.53 for total hospitalisations for heart failure including repeat events.

The evidence showed no clinically important difference for health-related quality of life, withdrawal due to drug-related adverse events or acute kidney injury. There was some suggestion of an increase in hyperkalaemia with 42 more cases per 1,000. The committee considered this an expected consequence of the MRA class of medicine, and agreed it was best managed by careful monitoring. They used their expertise and experience to make recommendations about monitoring people on this class of medicine (recommendations 1.7.3 – 1.7.6).

MRA (+ ARB + BB) versus (ARB + BB +) placebo

The evidence for this comparison was limited to outcomes on adverse events. There were possible clinically important harms for withdrawal due to drug-related adverse events (47 more per 1,000) and hyperkalaemia (40 more per 1,000). The committee considered these expected consequences of the MRA class of medicine, and agreed it was best managed by careful monitoring. They used their expertise and experience to make recommendations about monitoring people on this class of medicine (recommendations 1.7.3 – 1.7.6).

Overall, the committee put more weight on the comparison MRA + ACEI/ARB + BB versus ACEI/ARB + BB + placebo, rather than the comparison MRA + ARB + BB versus ARB + BB + placebo, because the former is more reflective of current clinical practice. When the data for the former comparison was pooled, clinically important benefits on all-cause and cardiovascular mortality and heart failure hospitalisation were seen, which supports the use of MRA in addition to optimised treatment with ACE inhibitor/ARB and beta-blocker.

ARB (+ ACEI + BB) versus (ACEI + BB +) placebo

When expressed as time-to-event data, the mortality and HF hospitalisation outcomes showed clinically important benefits as the HRs were <1 (0.89 for all-cause mortality, 0.83 for cardiovascular mortality and 0.83 for hospitalisation for HF).

The evidence showed clinically important benefits for all-cause mortality (28 fewer per 1,000), cardiovascular mortality (35 fewer per 1,000) hospitalisation for HF (36 fewer per 1,000) when expressed as dichotomous events.

The evidence showed clinically important harms for withdrawal due to drug-related adverse events (58 more per 1,000) and falls (60 more per 1,000), though the latter was based on one very small study with few events. There was also some suggestion of an increase in hyperkalaemia with 27 more cases per 1,000.

However, the committee did not lend much weight to the findings from this comparison because in current clinical practice ACE inhibitor and ARB would not be used in combination, with the addition of an MRA being preferred because of the greater health benefits observed.

Head-to-head comparisons (with background treatment)

ARNI (+ MRA + BB) versus ARB (+ MRA + BB)

The evidence-base for this outcome comprises two trials that provide evidence in opposite directions for mortality and hospitalisation outcomes. When expressed as time-to-event data, the HRs from the Mann 2022 study all suggest an increase in all-cause mortality (HR=1.63), cardiovascular mortality (HR=1.58) and hospitalisation (HR=1.24). For the Ghafur 2020 study, HRs suggest a decrease in cardiovascular mortality (HR=0.37) and heart failure hospitalisation (HR= 0.80) for ARNI compared with ARB.

A similar pattern is evident with mortality and hospitalisation outcomes expressed as dichotomous outcomes. Mann 2022 shows a clinically important harm for ARNI of 24 more cardiovascular deaths per 1,000 patients and 49 more heart failure hospitalisations per 1,000 patients. All-cause mortality expressed a dichotomous outcome includes the Mann 2022 and a further study with zero events; this translates to a clinically important increase in all-cause mortality (20 more per 1,000) with ARNI. Ghafur 2020 shows a clinically important benefit of 141 fewer cardiovascular deaths per 1,000 patients, and a clinically important benefit of 160 fewer heart failure hospitalisations per 1,000 patients with ARNI.

There was no data available on health-related quality of life for this outcome. For adverse events, one small trial (not Mann 2022 or Ghafur 2020) suggested a decrease in withdrawal due to drug-related adverse events for ARNI, but this may not be clinically important (26 fewer cases per 1,000 patients). However, there was a clinically important harm of hyperkalaemia (60 more cases per 1,000).

The committee considered differences in the study characteristics of the two studies with heterogeneous results. Mann 2022 recruited ‘advanced CHF’ patients into this trial; their NYHA class was higher, LVEF was lower and inclusion criteria (including current or recent use of inotropic therapy) suggested that these patients were closer to palliative care. It is therefore likely that such differences explain the greater mortality and hospitalisation in this population group. The committee noted that ARNI would not usually be given to advanced CHF patients on inotropic therapy. Both trials were small with much shorter follow-ups compared to evidence for other comparisons, so there is some further uncertainty in this evidence-base.

ARNI (+ MRA + BB) versus ACEI (+ MRA + BB)

The committee noted that the majority of the evidence for this comparison was in people with LVEF ≤35%, so meeting the protocol in terms of population (LVEF≤40%) but at the lower end of the spectrum for LVEF. The committee acknowledged that patients who were already on ACE inhibitor or ARB had to continue to have their LVEF lower than 35% and be symptomatic, to qualify for ARNI in TA388 due to the evidence being in that population. However, they agreed that although the evidence was still in this population, it was suitable to inform recommendations for patients with reduced LVEF as defined in the review protocol (LVEF ≤40%). It was discussed that applying a different threshold for this medicine would be a barrier to implementation.

When expressed as time-to-event data, the mortality outcomes showed clinically important benefits for ARNI compared to ACE inhibitor as the HRs were <1 (0.84 for all-cause mortality and 0.81 for cardiovascular mortality); these translate to 29 fewer deaths per 1,000 patients. Similarly, the evidence showed clinically important benefits for all-cause mortality (25 fewer per 1,000) and cardiovascular mortality (29 fewer per 1,000) when expressed as dichotomous events.

The evidence base on hospitalisation outcomes for this comparison was heterogeneous, so reported separately for PARADIGM-HF (McMurray 2014a) and PARALLEL-HF (Tsutsui 2021); the latter study was conducted in Japan. Using time-to-event outcomes, the HR for first heart failure hospitalisation was <1 (HR=0.79) for the McMurray 2014a study and > 1 (HR=1.27) for the Tsutsui study 2021, suggesting a clinically important benefit in one study and a clinically important harm in another. The committee agreed that the large multi-centre trial (PARADIGM-HF) was more representative of the UK population and had more confidence in this finding being applicable in the NHS context. When expressed as dichotomous outcomes, there was an overall clinically important benefit of ARNI for first heart failure hospitalisation, with 25 fewer per 1,000 patients.

A range of health-related quality of life measures were available for this outcome, but none showed a clinically important difference for ARNI versus ACE inhibitor. Similarly, there was no clinically important difference between arms for the adverse events: withdrawal due to drug-related adverse events or acute kidney injury. There was a clinically important increase in falls (48 more cases per 1,000 patients for ARNI compared with ACE inhibitor). This was expected by the committee because ARNI causes more hypotension, which can be avoided by careful selection of patients with systolic BP > 100 mmHg before starting ARNI. The analyses on hyperkalaemia were split by those studies reporting a definition of hyperkalaemia that matched the protocol, and those that did not define hyperkalaemia. This suggested a benefit for ARNI of 25 fewer cases per 1000 in the study that did have definite hyperkalaemia according to the protocol, and suggested a harm of 29 more cases per 1000 in the studies that did not have definite hyperkalaemia according to the protocol. The committee noted that, despite ARNI being a stronger renin-angiotensin-aldosterone system inhibitor (RAASi) agent compared to ACE inhibitor, a lower risk of hyperkalaemia was reported than with ACE inhibitor. This is likely caused by the diuretic effect of the sacubitril part of the ARNI molecule. They considered this to be an important benefit.

ARNI (+ BB) versus ACEI (+ BB)

For this comparison, the evidence suggests no clinically important difference for all-cause mortality or health-related quality of life. There was evidence of an increase in cases of hyperkalaemia of 31 per 1,000 patients.

Monitoring for adverse events for all medicine classes

The committee discussed the importance of measuring renal function and electrolyte levels before prescribing an ACE inhibitor, ARNI, ARB and MRA. They should also be measured when the medicines are being titrated. The committee noted that if there is a change in renal

function it is important to assess fluid status to help decision making. The committee noted that local guidelines should be in place specifying what to do if the serum creatinine level rises by more than 50% or their potassium concentration increases to more than 5.5 mmol per litre. They highlighted that it is not uncommon for the medicines to be stopped, but that this might not be necessary. Some of the medicines can cause postural hypotension and this can increase the risk of falls. It is therefore important that blood pressure is measured when the person is standing and sitting or lying on their back whenever the dose is increased.

Beta-blockers can affect heart rate and rhythm. The committee agreed, based on their expertise and experience, that a 12-lead ECG should be undertaken in anyone with a heart rate of less than 60 beats per minute before prescribing them a beta-blocker.

Summary

Taken together, the clinical evidence on placebo and head-to-head comparisons supports the addition of SGLT2i (empagliflozin or dapagliflozin) and MRA to existing optimised treatment including beta-blocker and ACE inhibitor, and suggests a possible benefit of ARNI over ACE inhibitor. This supports the notion of 4 pillars of treatment for all HFrEF patients, in that all patients would benefit from 4 classes of medicines. This applies to people with either newly diagnosed or pre-existing chronic heart failure with reduced ejection fraction.

Taken together with the evidence from economic modelling discussed below, early combined use of an MRA, SGLT2 inhibitor, ACE inhibitor and beta-blocker is recommended. Since the most appropriate sequencing of these medicines will vary on in individual basis, the committee agreed to move away from a set of recommendations that include a sequence for introducing each drug medicine and instead listed treatment combinations for different scenarios. Specifically, an ARNI can replace an ACE inhibitor in people who remain symptomatic when receiving the combination of ACE inhibitor, beta-blocker, MRA and SGLT2 inhibitor. However, where this combination is providing symptomatic improvement, switching to an ARNI is not advised because it is less cost effective. People unable to tolerate an ACE inhibitor should be offered and ARNI instead of an ACE inhibitor. The committee acknowledged that the previous first choice in this situation was an ARB, but agreed this is no longer the preferred next option, although an ARB can still be used if an ARNI is not tolerated.

There are known risks related to renal function, electrolyte levels and falls, some of which were seen in the evidence reviewed. The committee therefore considered it important to provide guiding principles on monitoring patients for changes in renal function, electrolyte levels and postural hypotension, based on their expertise and experience (see recommendations 1.7.4 – 1.7.8).

1.1.12.4. Cost-effectiveness and resource use

The committee considered the ten cost-effectiveness studies identified in the literature on the use of MRA, SGLT2 inhibitor, ARNI or quadruple therapy (treatment sequencing of the four pillars) for the treatment of people with HFrEF. Although some studies were relevant and of good quality, the committee found that the evidence on the early use of key medicines was limited.

One study (Lee et al., 2014) was identified on the use of MRAs which was found to be cost-effective with an ICER of £4,284 with background therapies of ACEI plus BB. Four studies were identified comparing ARNI to ACE inhibitor or ARB in addition to background therapies. Although the committee considered McMurray et al. (2016) to be most applicable due to being the only UK-based study, non-UK studies were also included because they used ARB as the comparator therapy. Four studies were identified for the use of SGLT2 inhibitor in addition to background therapies and were considered directly applicable with an NHS perspective. The cost per QALY ranged from £2,093 for people with HF and type 2 diabetes to £6,152 for the broader population with HFrEF.

One study (Van et al., 2024) on quadruple therapy was identified; however, it was only partially applicable because it was conducted from a Canadian healthcare perspective. The strategies compared were all quadruple therapies with different titration approaches. This was deemed not directly relevant to the decision problem of this review, which focuses on sequential treatment strategies based on the worsening of the condition to be aligned with the current NICE guidance and clinical practice. Initiating ARNI, BB and SGLT2 inhibitor together followed by initiating MRA and then up-titrating the other treatments over time was found to be the preferred strategy based on net monetary benefit, with a cost per QALY of £6,576. However, the committee was concerned that the analysis underestimated costs associated with adverse events. Although short-term quality of life decrements and dose modifications due to adverse events were included in the analysis, the costs related to managing these events were not included.

To address these concerns, a de novo economic model was developed that included all relevant treatment strategies, using inputs and assumptions aligned with NHS clinical practice and informed by the literature, real-world data and committee expertise. Baseline characteristics, hospitalisation rates and mortality rates were informed by a bespoke analysis of real-world data by the INTEGRATE project team from the London School of Hygiene & Tropical Medicine. Hazard ratios, informed by the effectiveness review of RCTs, were applied to these baseline rates. The committee considered the results of the economic model alongside the clinical evidence for HFrEF. The analysis was stratified by individuals who can tolerate ACE inhibitor and those who cannot tolerate ACE inhibitor and are instead prescribed an ARB.

The probabilistic economic model results for people who can tolerate ACE inhibitor showed that the combination of early MRA and SGLT2 inhibitor yielded the highest net health benefit of 5.11. Early MRA and SGLT2 inhibitor was the most cost-effective strategy in 56% of simulations, with a mean cost per QALY of £7,669 compared to early MRA. The combination early MRA, SGLT2 inhibitor and ARNI was the most cost-effective strategy in only 37% of the simulations, with a cost per QALY of £21,070 compared to early MRA and SGLT2 inhibitor.

Early MRA and SGLT2 inhibitor remained the highest-ranked strategy for most of the deterministic scenario analyses, except in two cases: one scenario using treatment effect data from the European subpopulation and another assuming that quality of life benefits of ARNI and SGLT2 inhibitor were additive. In the first scenario, early MRA became the highest-ranked strategy, followed by early MRA and SGLT2 inhibitor, due to the modest treatment effect observed in this subpopulation. In the second scenario, early MRA, SGLT2 inhibitor and ARNI became the highest-ranked strategy, driven by the greater combined quality of life benefits of ARNI and SGLT2 inhibitor.

For the population intolerant to ACE inhibitor, the combination of early MRA, SGLT2 inhibitor and ARNI was the preferred strategy with the highest net health benefit of 5.09 and a cost per QALY of £15,821 compared to early MRA and SGLT2 inhibitor. The combination early MRA, SGLT2 inhibitor and ARNI was the most cost-effective strategy in 71% of simulations. The combination early MRA and early SGLT2 inhibitor was only cost-effective in 20% of simulations. The difference in the cost-effectiveness results between the two populations is attributed to the greater reductions in all-cause mortality observed when switching from ARB to ARNI compared to switching from ACE inhibitor to ARNI.

The committee discussed the scenario based on the European subpopulation and concluded that the results from the full trial population should be used. As the trials were not powered to detect differences in subpopulation or ethnicities, the committee agreed that the full population results were more reliable and better reflective of the ethnic diversity of the UK. Moreover, they acknowledged that entire populations results were more robust as based on a larger sample size. The committee also agreed that it was unlikely that the difference in relative treatment effects observed across regions in the clinical trials represented true differences as geographic location was not a statistically significant effect modifier. This

suggests that the observed differences may be due to sampling variability. However, as the TA388 committee had chosen to use the efficacy data from the European subpopulation, this introduced additional uncertainty in recommending early ARNI for the full population with reduced ejection fraction. Although early ARNI was the most cost-effective strategy in the scenario using additive benefits of ARNI and SGLT2 inhibitor, the committee judged this to be an overestimate of the combined treatment effect of the two medications and preferred the scenario in which only the greater of the two effects was applied.

The committee discussed the economic results for the population who can tolerate ACE inhibitor and decided not to recommend ARNI where an ACE inhibitor can be tolerated. However, given the additional survival benefits associated with ARNI compared with ARB, the committee agreed that the cost-effectiveness evidence was strong enough to support a recommendation for early MRA, SGLT2 inhibitor and ARNI in the population who cannot tolerate ACE inhibitor.

Where ARNI is recommended it is for all people with heart failure and reduced ejection fraction (that is <40%). However, the main trial evidence was in people with ejection fraction <35%. For this reason it is possible that the average treatment effect will be slightly smaller than that reported and cost per QALY gained slightly higher. However, it is difficult to discern between the two cut-offs in practice.

The committee noted that in current practice, ARNI is only prescribed by heart failure specialists. which can be a barrier for people to access this medication. The committee noted that SGLT2 inhibitors are already commonly prescribed in primary care for other conditions such that specialist advice is typically not necessary for heart failure. Although, the committee agreed that GPs are less familiar with ARNI, the committee thought that GPs should be able to prescribe ARNI too, if advice from a heart failure team is available. This should reduce barriers to their prescription.

The committee agreed that the recommendations represent a significant resource impact. However, the impact is mitigated by the alignment with European guidelines, which also recommend all four pillars of treatments as first-line therapy. Clinical practice has already been shifting in this direction, despite the absence of updated NICE guidance. The committee considered that whilst the recommendation to offer early MRA and SGLT2 inhibitor (and early ARNI for some) will lead to an increase in prescriptions, the increased rise in resource use will be more than offset by improvements in quality of life and reductions in hospitalisations and mortality.

Since the economic analysis was run, dapagliflozin recently‘s UK patent was ruled to no longer be valid (July 2025). Generic versions will soon enter the market, which would likely reduce the average price of SGLT2 in England, further increasing the cost-effectiveness of providing it first-line.

1.1.12.5 Other factors the committee took into account

The committee emphasised the importance of not treating people based on LVEF alone, but rather ensuring there are corroborating factors to indicate chronic heart failure. These include 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 peptides and/or objective evidence of pulmonary or systemic congestion on imaging (such as pleural effusions, pulmonary oedema, ascites, lung comets).

It was acknowledged that most of the trial evidence was in patients already optimised on ACE inhibitor/ARB and beta-blockers and that these relative treatment effects were applied to baseline rates from a real-world population to be to assess the cost-effectiveness of early treatment in de novo health economic modelling.

STRONG-HF study on rapid titration

The intervention also included 5 additional nurse visits to titrate the medications above usual care arm, so rapid titration is not the only aspect of the intervention that differed from the control arm, and the additional contact time required for safe up-titration may offset any cost benefit due to the requirement for heart failure nurse specialists. From a resource perspective this was not thought to be achievable in the current UK healthcare system. There was concern about rapid titration without careful monitoring. Although there was no signal of significant harm from rapid optimisation of the medications, adding medicines in quick succession could make it difficult to determine which agent has caused or contributed to a specific adverse event. Overall, the evidence was not thought to be robust enough to directly support a recommendation on rapid titration. Instead, clinical judgement would be required on titrations of medicines, taking into account individualised care required for each patient and shared decision-making.

Placebo and head-to-head comparisons

Many patients will already be on ACE inhibitor for other conditions, prior to being diagnosed with HFrEF. The committee agreed that these patients have already demonstrated tolerance to ACEI, so there is no need to switch to ARNI, as ARNI is not cost-effective for those tolerant to ACEI.

People are now living longer with CHF so expensive medicines will be used for a longer period of time. Therefore, there is no rationale to move away from the £20,000 cost per QALY threshold used by NICE. The committee considered that if a patient is intolerant to ACE inhibitor, ARNI should be considered as an alternative (over ARB) straight away; health economic modelling shows this option to be cost-effective.

The committee noted that their recommendations cannot address every clinical scenario. Chronic heart failure is a complex condition with multiple aetiologies, and comorbidities are common. It is recognised that trials in this area have some limitations in relation to their representativeness of the patient population and variations in background treatment. Some pragmatism is required; the committee’s recommendations aim to provide broad principles that are applicable to most situations and are suitable for use by non-specialists in chronic heart failure.

The committee also discussed the relative value of ensuring patients receive 4 pillars of medicine treatment (4 different classes of medicines), notwithstanding the doses of each medicine class. From their experience, the committee considered it preferable for a patient to receive any licensed dose of all 4 classes of medicine recommended, rather than maximise the dose of any one medicine at the expense of not receiving another (for example, receiving 3 out of the recommended 4 classes of medicine but on higher doses). This supports the notion of 4 pillars of treatment for all chronic heart failure patients. It was agreed that, in practice, the approach for initiating and optimising treatments will need to be individualised and the heart failure specialist should advise on this taking account of the individual's haemodynamic parameters, co-morbidities (particularly the presence or absence of hypertension), heart rate, the presence or absence of angina, the degree of renal impairment and the degree of the individual's frailty. This will influence the order of initiating the medicines, the intervals between the introduction of different pillars and whether more than one pillar can be commenced simultaneously. However, in those with lower systolic blood pressure or compromised renal function, no more than one agent should be commenced at any given time, although weekly intervals may still be appropriate. Those who are frail, who have lower blood pressure or more compromised renal function should have longer intervals between the initiations of the agents, for example 2-4 weeks.

The committee discussed the importance of a specialist team for diagnosing the type of heart failure (reduced, mildly reduced or preserved ejection fraction) not on LVEF and BNP alone but also taking into account other phenotypic characteristics (for example ruling out some

other conditions that can mimic HFmrEF and HFpEF). If LVEF improves in response to treatment, there is no need to de-escalate the treatment regimen from that recommended in HFrEF, and patients should continue to be treated based on the index diagnosis of reduced ejection fraction.

It was agreed that it is appropriate for primary care to be able to initiate all classes of medicine recommended, as sometimes the requirement for specialists to initiate medicines can be a barrier to patients accessing the most appropriate medicines for them. It was noted that non-specialists in chronic heart failure might need some support to initiate ARNI. However, the committee considered that ARNI could be initiated in primary care based on advice from a heart failure specialist team.

Lay members of the committee highlighted the importance of wording the recommendations to take account of patient preferences (for example around tolerating side effects) as well as clinical judgement. It was agreed that each patient should receive individualised care and that clinicians should engage in shared decision-making.

The committee discussed the increase of 'hospital at home' care, which may need to be taken account of in future health economic modelling but is not currently established as routine practice.

The Committee also noted that it is important to clarify that the recommendations in this guideline update are not intended for use with patients on palliative care.

The committee were aware of the NICE technology appraisals:

- Empagliflozin for treating chronic heart failure with reduced ejection fraction (2022) (TA773)
- Dapagliflozin for treating chronic heart failure with reduced ejection fraction (2021) (TA679)
- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (2016) (TA388)

1.1.13. Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1 to 1.4.4 and 1.7.3 to 1.7.8

1.1.14. References

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Appendices

Appendix A Review protocols

A.1 Review protocol for medicines for heart failure with reduced ejection fraction

Field	Content
Review title	First-line pharmacological treatment of chronic heart failure with reduced left ventricular ejection fraction (HFrEF).
Review question	Is it clinically- and cost-effective to use a combination of some of the following first-line pharmacological interventions in adults with chronic heart failure with reduced left ventricular ejection fraction: • ACE inhibitor • angiotensin-receptor blocker • angiotensin receptor neprilysin inhibitor • beta-blocker • mineralocorticoid receptor antagonist • sodium glucose co transporter 2 inhibitor
Objective	The current recommendations in NG106 do not reflect all treatment options now available to patients with HFrEF, and the recommendations on sequential introduction of therapeutic agents are no longer in line with ESC guidelines or UK clinical practice. Appropriate sequencing, or the appropriateness of introducing multiple pharmacological agents at treatment initiation, has not been assessed in an evidence review during the previous updates. Therefore, the aim of this review is to update the recommendations on first-line pharmacological management for people with chronic heart failure and reduced ejection fraction.
Searches	Key papers: - PARADIGM-HF (McMurray 2014) - STRONG HF (Mebazaa Alexander, Lancet 7 Nov 2022) The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL)

Field	Content
	• Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Date limitations – from date of searches in CG5, 2003 • English language studies • Human studies Other searches: • Inclusion lists of relevant systematic reviews The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details). 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 reduced ejection fraction
Population	**Inclusion**: Adults diagnosed with heart failure due to left ventricular dysfunction with reduced ejection fraction. Studies including an indirect population (for example mixed HFrEF and HFpEF) will only be included if ≥80% match the protocol criteria. 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)

Field	Content
	• High output heart failure • Adult congenital heart disease • Primary heart valve disease • Acute MI (within 3 months of the event) • Isolated pulmonary hypertension • Treatment with chemotherapy
Intervention	**Inclusion** Pharmacological agents as first-line treatment in combination with each other or with standard background therapy including diuretics when indicated: • 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) • SGLT2 inhibitor (dapagliflozin or empagliflozin) • Combinations of the above (e.g. ACE-I/ARB/ARNI + BB + MRA+ SGLT2i); including different initiation strategies At least 50% of the intervention group must be receiving more than one of the drugs listed above (either as the randomised intervention or as part of background treatment). First-line refers to the group of pharmacological agents that are considered when initially reviewing the patient. Studies that assess the listed interventions, but do not introduce them as first-line treatment (e.g., only after optimisation of other interventions) will be downgraded for intervention indirectness. **Mode of delivery:** oral. **Analysis groupings:** a class effect will be assumed.

Field	Content
	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** • Calcium channel blockers (because they are not used in current practice and have a do not use recommendation). • 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 o Ivabradine o Hydralazine-Nitrate o Omecamtiv mecarbil o Vericiguat • Medicines to manage comorbidities (except as part of background treatment): o Anticoagulants o Anti-arrhythmics
Comparator	• Different approaches to initiation (e.g., sequential introduction with up-titration of each agent in turn vs more rapid introduction of all initial treatments). • Other active treatments in combination with each other or with standard background therapy: o Angiotensin converting enzyme (ACE) inhibitor o Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan) o Angiotensin receptor antagonist / blocker (ARB) o Beta-adrenergic antagonist/blocker (BB) o Mineralocorticoid receptor antagonist (MRA) o SGLT2 inhibitor (dapagliflozin or empagliflozin)

Field	Content
	• Placebo + usual CHF care or usual CHF care alone At least 50% of the control group must be receiving more than one of the drugs listed above (either as the randomised comparator or as part of background treatment). This was because trials comparing any intervention with monotherapy or placebo alone are not relevant for this population for whom current practice includes a minimum of dual therapy (ACEI + BB). Therefore, such trials will be excluded from this update although they were considered in previous versions of the guideline.
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**: data from a parallel project using real world data may also inform committee discussions.
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) ○ 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)

Field	Content
	• 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	Where available, outcome data from new studies will be meta-analysed with corresponding data already included in NG106. • For analysis, interventions/comparisons will be grouped based on both the randomised and background treatment used by trial participants. To account for concomitant treatments, a protocol intervention will be included as part of the combination treatment if more than 50% of the participants were receiving it. • 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.

Field	Content	
	• 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 and useful given the data identified.	
Analysis of sub-groups	**Stratified analyses** will be carried out for the following subgroups if prespecified analyses are available from included studies investigating SGLT2 inhibitors as the randomised intervention (regardless of heterogeneity): • Presence or absence of type 2 diabetes. Analyses will be undertaken to determine if there are subgroup differences between those with and without type 2 diabetes for outcomes relevant to this review protocol. Indirectly relevant outcomes (e.g., composite endpoints combining two protocol outcomes) will be considered for inclusion if there is insufficient data from directly relevant outcomes. **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

Field	Content		
	☐	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	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact		

Field	Content
	Guideline Development Team NGC Named contact e-mail chfiatreatment@nice.org.uk 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	

Field	Content
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

	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

	All questions – health economic evidence
	If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. Setting: 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:

	All questions – health economic evidence
	The more recent the study, the more applicable it will be. Studies published in 2010 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2010 will be rated as 'Not applicable'. Studies published before 2010 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

Medicines for heart failure with reduced 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
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
#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

Searches
#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)):an494409
#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
#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

Searches	
#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
#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

Searches
#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)):an494409
#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
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

Searches
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
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

Searches		
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
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

Searches
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
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

Searches
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

Searches
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 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

Searches
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" 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

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
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
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

Searches		
38	36 not 37	11605
39	limit 38 to dc=20171201-20240229	4631

Database name: Medline economic evaluation

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

Searches		
39	37 not 38	5054
40	limit 39 to (letter or historical article or comment or editorial or news or case reports)	351
41	39 not 40	4703
42	limit 41 to ed=20171201-20240229	1516
43	limit 41 to dt=20171201-20240229	1616
44	42 or 43	1799

Database name: HTA economic evaluation

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

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

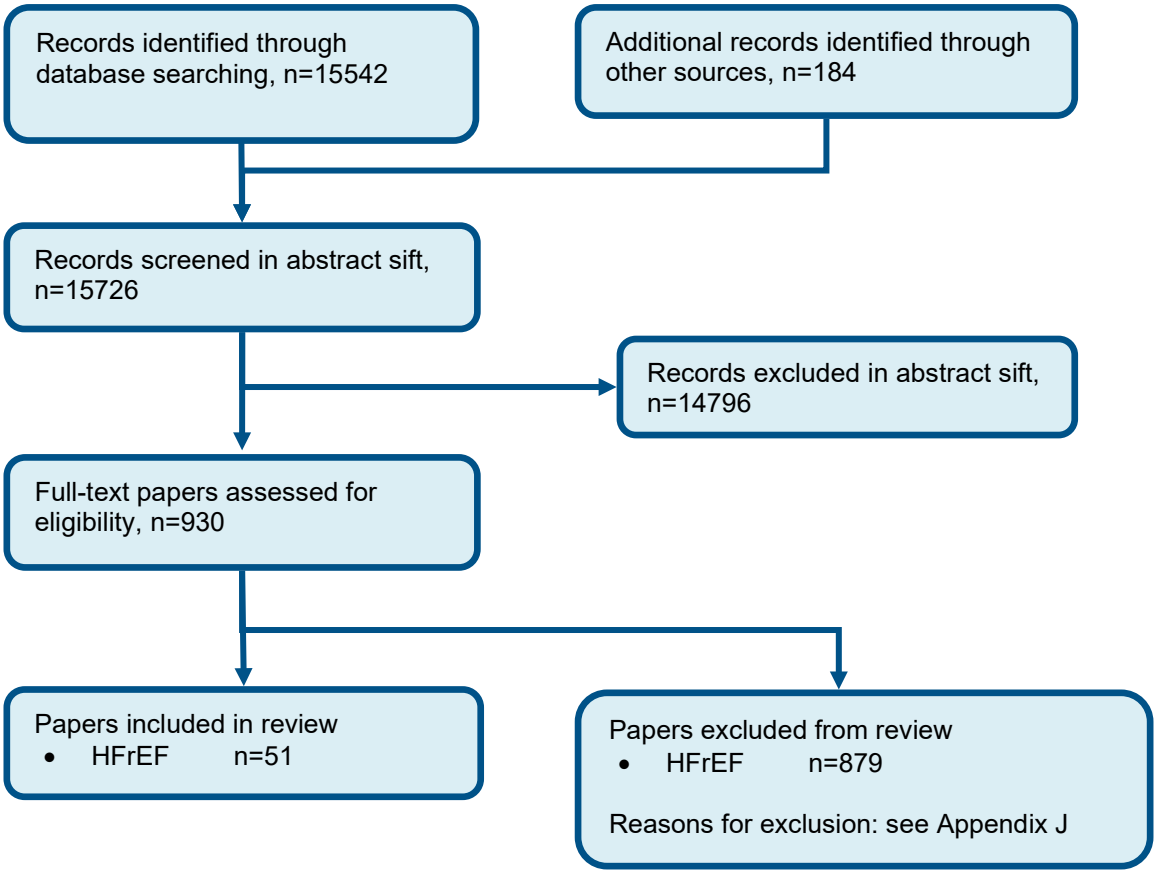
Database name: Medline Quality of Life

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
8	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 344
9	(cardiorenal adj2 syndrome*).tw.1393

Searches	
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 reviews of pharmacological management of heart failure with reduced or mildly reduced ejection fraction



Appendix D Effectiveness evidence

Abraham, 2021

Bibliographic Reference	Abraham, William T; Lindenfeld, JoAnn; Ponikowski, Piotr; Agostoni, Piergiuseppe; Butler, Javed; Desai, Akshay S; Filippatos, Gerasimos; Gniot, Jacek; Fu, Michael; Gullestad, Lars; Howlett, Jonathan G; Nicholls, Stephen J; Redon, Josep; Schenkenberger, Isabelle; Silva-Cardoso, Jose; Stork, Stefan; Krzysztof Wranicz, Jerzy; Savarese, Gianluigi; Brueckmann, Martina; Jamal, Waheed; Nordaby, Matias; Peil, Barbara; Ritter, Ivana; Ustyugova, Anastasia; Zeller, Cordula; Salsali, Afshin; Anker, Stefan D; Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes.; European heart journal; 2021; vol. 42 (no. 6); 700-710

Study details

Secondary publication of another included study – see primary study for details	N/A
Trial name / registration number	EMPERIAL-Reduced
Study type	Randomised controlled trial (RCT)
Study location	Multi-centre study
Study setting	No further information

Study dates	First patient recruited on 26 March 2018.
Sources of funding	Sponsored by Boehringer Ingelheim
Inclusion criteria	All of the following criteria needed to be met: · ≥18 years of age · Written informed consent prior to admission to the trial · Women of child-bearing potential must agree to use birth control measures with a failure rate of <1% per year during the treatment period of the study · Heart failure diagnosed ≥3 months before screening, and currently in NYHA class II–IV · Reduced ejection fraction, defined as LVEF ≤40% (echocardiography) at screening per local reading under stable conditions · 6MWTD of ≤350 m at screening and baseline · Elevated NT-proBNP; >450 pg/ml for patients without atrial fibrillation; >600 pg/ml for patients with atrial fibrillation at screening · On medical therapy for heart failure consistent with prevailing cardiovascular guidelines at a stable dose for ≥4 weeks prior to screening, except for diuretics which must have been stable for ≥2 weeks prior to screening · Clinically stable at randomization with no signs of heart failure decompensation (investigator's judgement) · Appropriate use of medical devices such as cardioverter defibrillator or a cardiac resynchronization therapy consistent with prevailing local or international cardiovascular guidelines, and if a device is required, it must have been implanted for at least 3 months prior to screening for cardiac resynchronization therapy and 1 month prior to screening for cardioverter defibrillator.
Exclusion criteria	· Myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischaemia or newly developed ischaemic echocardiogram changes), coronary artery bypass graft, or other major cardiovascular surgery, stroke, or transient ischaemic attack within 90 days prior to screening

	· Acute decompensated heart failure requiring intravenous diuretics, intravenous inotropes or intravenous vasodilators, or left ventricular assist device within 4 weeks prior to screening and up to baseline · Previous or current randomization in another empagliflozin heart failure trial · eGFR (CKD-EPIcr) <20 ml/min/1.73 m2 or requiring dialysis · Type 1 diabetes · Symptomatic hypotension or SBP <100 mmHg at screening or baseline · SBP ≥180 mmHg at screening or baseline, or SBP >160 mmHg at both screening and baseline · Unstable angina within 30 days prior to screening · 6MWTD of <100 m and baseline · Conditions that preclude exercise testing · Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm documented by echocardiogram at screening · Patients in a structured (investigator's judgement) exercise training program within 1 month prior to screening or planned to start one during the course of this trial · Heart transplant recipient or listed for heart transplant · Currently implanted left ventricular assist device · Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction · Untreated ventricular arrhythmia with syncope in patients without cardioverter defibrillator documented within the 3 months prior to screening · Planned implantation of cardioverter defibrillator or cardiac resynchronization therapy during the course of the trial · Diagnosis of cardiomyopathy induced by chemotherapy or peripartum within the 12 months prior to screening

	· Symptomatic bradycardia or second or third degree heart block without a pacemaker after adjusting beta-blocker therapy, if appropriate · Chronic pulmonary disease (i.e. with known forced expiratory volume in 1 second [FEV1] <50% requiring home oxygen, or oral steroid therapy or hospitalization for exacerbation within 12 months, or significant chronic pulmonary disease (investigator's opinion), or primary pulmonary arterial hypertension) · Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at screening · Haemoglobin <9 g/dL at screening · History of ketoacidosis · Major surgery (major according to investigator's opinion) performed within 90 days prior to screening, or scheduled major elective surgery (e.g. hip or knee replacement) during the course of the trial · Gastrointestinal surgery/disorder that could interfere with trial medication absorption in the investigator's opinion · Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix or low risk prostate cancer · Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial · Current use or prior use of a SGLT2 inhibitor or combined SGLT1 and -2 inhibitor within 12 weeks prior to screening or during screening period until randomization. Discontinuation of an SGLT2 inhibitor or combined SGLT1 and -2 inhibitor for the purposes of study enrolment is not permitted · Treatment with intravenous iron therapy or erythropoietin within 3 months prior to screening · Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded · Known allergy or hypersensitivity to empagliflozin or other SGLT2 inhibitors

	· Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial · Women who are pregnant, nursing, or who plan to become pregnant while in the trial o Any other clinical condition that would jeopardise patients' safety while participating in this trial, or may prevent the subject from adhering to the trial protocol
Recruitment / selection of participants	Screening period of 4 days to 3 weeks.
Intervention(s)	Empagliflozin 10mg once daily for 12 weeks Concomitant treatment: ACEI/ARB 51.9% ARNI 39.1% Beta-blockers 94.9% MRA 60.9%
Comparator	Placebo once daily for 12 weeks Concomitant treatment:

	ACEI/ARB 59.0% ARNI 34.0% Beta-blockers 94.2% MRA 55.8%
Number of participants	312
Duration of follow-up	12 weeks (assessments made within week of end of 12 week intervention)
Additional comments	Intention-to-treat

Study arms

SGLT2i (Empagliflozin) (N = 156)

ACEI/ARB 51.9% ARNI 39.1% Beta-blockers 94.9% MRA 60.9%

Placebo (N = 156)

ACEI/ARB 59.0% ARNI 34.0% Beta-blockers 94.2% MRA 55.8%

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (Empagliflozin) (N = 156)	Placebo (N = 156)
% Female Sample size	n = 35 ; % = 22.4	n = 45 ; % = 28.8
Age (years) Median (IQR)	69 (62.5 to 77)	70 (62.5 to 77)
White Sample size	n = 130 ; % = 83.3	n = 133 ; % = 85.3
Black/African American Sample size	n = 24 ; % = 15.4	n = 18 ; % = 11.5
Asian Sample size	n = 1 ; % = 0.6	n = 2 ; % = 1.3
Other including mixed race Sample size	n = 1 ; % = 0.6	n = 2 ; % = 1.3
II Sample size	n = 101 ; % = 64.7	n = 101 ; % = 64.7
III Sample size	n = 55 ; % = 35.3	n = 55 ; % = 35.3

Characteristic	SGLT2i (Empagliflozin) (N = 156)	Placebo (N = 156)
Ischaemic cause of HF Sample size	n = 71 ; % = 45.5	n = 87 ; % = 55.8
LVEF (%) Median (IQR)	30 (24.5 to 35)	30 (26 to 36)
Type 2 diabetes Patients with pre-treatment HbA1c >_6.5% Sample size	n = 87 ; % = 55.8	n = 100 ; % = 64.1
Atrial fibrillation Based on baseline ECG Sample size	n = 36 ; % = 23.1	n = 38 ; % = 24.4
Renal function (eGFR; mL/min/1.73m2) Median (IQR)	56.8 (44 to 73.3)	53 (42 to 74.3)
ACEI/ARB Sample size	n = 81 ; % = 51.9	n = 92 ; % = 59
ARNI Sample size	n = 61 ; % = 39.1	n = 53 ; % = 34
Beta-blockers Sample size	n = 148 ; % = 94.9	n = 147 ; % = 94.2

Characteristic	SGLT2i (Empagliflozin) (N = 156)	Placebo (N = 156)
MRA Sample size	n = 95 ; % = 60.9	n = 87 ; % = 55.8
Loop or high-celing diuretics Sample size	n = 135 ; % = 86.5	n = 139 ; % = 89.1
Thiazides or low celing diuretics Sample size	n = 9 ; % = 5.8	n = 24 ; % = 15.4
Lipid-lowering drugs Sample size	n = 130 ; % = 83.3	n = 117 ; % = 75

Outcomes

Study timepoints

Baseline

12 week

Continuous outcomes

Outcome	SGLT2i (Empagliflozin), Baseline, N = 156	SGLT2i (Empagliflozin), 12 week, N = 156	Placebo, Baseline, N = 156	Placebo, 12 week, N = 156
Health-related quality of life (KCCQ overall summary score) range 0-100, change score Mean (95% CI)	NR	9.65 (7.34 to 11.95)	NR	6.4 (4.1 to 8.7)
Health-related quality of life (KCCQ overall summary score) range 0-100, change score Median (IQR)	68.8 (50.5 to 83.3)	NR	68.8 (49.5 to 87.5)	NR
Health-related quality of life (KCCQ clinical summary score) range 0-100, change score Mean (95% CI)	NR	8.2 (5.98 to 10.47)	NR	4.82 (2.56 to 7.08)

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

Dichotomous outcomes

Outcome	SGLT2i (Empagliflozin), 12 week, N = 155	Placebo, 12 week, N = 156
Withdrawal due to drug-related adverse events (AEs leading to discontinuation of study medication) No of events	n = 9 ; % = 5.8	n = 10 ; % = 6.4

Withdrawal due to drug-related adverse events (AEs leading to discontinuation of study medication) - Polarity - Lower values are better

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

Health-related quality of life (KCCQ overall summary score, change score from baseline to 12 weeks)

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

Health-related quality of life (KCCQ clinical summary score, change score from baseline to 12 weeks)

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

Withdrawal due to drug-related adverse events (AEs leading to discontinuation)

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

Anker, 2021

Bibliographic Reference	Anker, Stefan D; Butler, Javed; Filippatos, Gerasimos; Khan, Muhammad Shahzeb; Marx, Nikolaus; Lam, Carolyn S P; Schnaidt, Sven; Ofstad, Anne Pernille; Brueckmann, Martina; Jamal, Waheed; Bocchi, Edimar A; Ponikowski, Piotr; Perrone, Sergio V; Januzzi, James L; Verma, Subodh; Bohm, Michael; Ferreira, Joao Pedro; Pocock, Stuart J; Zannad, Faiez; Packer, Milton; Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial.; Circulation; 2021; vol. 143 (no. 4); 337-349

Study details

Secondary publication of another included study – see primary study for details	Subgroup analysis of EMPEROR Reduced. See main trial paper for details: Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424. doi: 10.1056/NEJMoa2022190. Epub 2020 Aug 28. PMID: 32865377.
Trial name / registration number	
Study type	Randomised controlled trial (RCT)

Study arms

SGLT2i (empagliflozin) (N = 1863)

Patients received a daily dose of 10 mg empagliflozin in addition to recommended therapy Patients also received Beta-blocker (94.7%), ACEI / ARB without neprilysin inhibitor (70.5%), ACEI / ARB with neprilysin inhibitor (18.3%), MRA (70.1%)

Placebo (N = 1867)

Patients received daily placebo in addition to recommended therapy Patients also received Beta-blocker (94.7%), ACEI / ARB without neprilysin inhibitor (68.9%), ACEI / ARB with neprilysin inhibitor (20.7%), MRA (72.6%)

Outcomes

Study timepoints

Baseline

12 month

16 month

Dichotomous outcomes

Outcome	SGLT2i (empagliflozin), 16 month, N = 1863	Placebo, 16 month, N = 1867
CV mortality - with diabetes n= 927 SGLT2i, n= 929 Placebo No of events	n = 104 ; % = 11.2	n = 113 ; % = 12.2
CV mortality - no diabetes defined as HbA1c <5.7%. n = 304 SGLT2i, n=302 placebo No of events	n = 29 ; % = 9.5	n = 30 ; % = 9.9
Unplanned hospitalisation or visits (HF-related) first and recurrent hospital visit for HF) - with diabetes n= 927 SGLT2i, n= 929 Placebo	n = 221	n = 337

Outcome	SGLT2i (empagliflozin), 16 month, N = 1863	Placebo, 16 month, N = 1867
No of events		
Unplanned hospitalisation or visits (HF-related) (first and recurrent hospital visit for HF) - no diabetes defined as HbA1c <5.7%. n = 304 SGLT2i, n=302 placebo No of events	n = 57	n = 68
Withdrawal due to drug-related adverse events (adverse events) No of events	n = NA	n = NA
Withdrawal due to drug-related adverse events (adverse event) - with diabetes n= 927 SGLT2i, n= 929 placebo No of events	n = 175 ; % = 18.9	n = 176 ; % = 19
Withdrawal due to drug-related adverse events (adverse event) - no diabetes n= 936 SGLT2i, n = 937 placebo No of events	n = 147 ; % = 15.7	n = 152 ; % = 16.2
Hyperkalaemia (defined by MedDRA Preferred Terms "hyperkalaemia" and "blood potassium increased") - with diabetes n= 927 SGLT2i, n= 929 placebo No of events	n = 61 ; % = 6.6	n = 74 ; % = 8

Outcome	SGLT2i (empagliflozin), 16 month, N = 1863	Placebo, 16 month, N = 1867
Hyperkalaemia (defined by MedDRA Preferred Terms "hyperkalaemia" and "blood potassium increased") - no diabetes n= 936 SGLT2i, n = 937 placebo No of events	n = 48 ; % = 5.1	n = 53 ; % = 5.7

CV mortality - with diabetes n= 927 SGLT2i, n= 929 Placebo - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) first and recurrent hospital visit for HF) - with diabetes - Polarity - Lower values are better

Withdrawal due to drug-related adverse events (adverse events) - Polarity - Lower values are better

Hyperkalaemia (defined by MedDRA Preferred Terms "hyperkalaemia" and "blood potassium increased") - with diabetes - Polarity - Lower values are better

Hazard Ratios

Outcome	SGLT2i (empagliflozin) vs Placebo, 12 month, N2 = 927, N1 = 929	SGLT2i (empagliflozin) vs Placebo, 16 month, N2 = 927, N1 = 929
CV mortality - with diabetes Time to cardiovascular death n= 927 SGLT2i, n= 929 placebo Hazard ratio/95% CI	NA	0.92 (0.71 to 1.2)
CV mortality- no diabetes n= 936 SGLT2i, n = 937 placebo Hazard ratio/95% CI	NA	0.92 (0.68 to 1.24)

Outcome	SGLT2i (empagliflozin) vs Placebo, 12 month, N2 = 927, N1 = 929	SGLT2i (empagliflozin) vs Placebo, 16 month, N2 = 927, N1 = 929
Unplanned hospitalisation or visits (HF-related) first and recurrent hospital visit for HF) - with diabetes n= 927 SGLT2i, n= 929 placebo Hazard ratio/95% CI	NA	0.65 (0.5 to 0.85)
Unplanned hospitalisation or visits (HF-related) (first and recurrent hospital visit for HF) - no diabetes n= 936 SGLT2i, n = 937 placebo Hazard ratio/95% CI	NA	0.76 (0.57 to 1.01)
Health-related quality of life (KCCQ clinical summary score) - with diabetes n= 927 SGLT2i, n= 929 placebo Hazard ratio/95% CI	2.41 (0.64 to 4.17)	NA
Health-related quality of life (KCCQ clinical summary score) - no diabetes n= 936 SGLT2i, n = 937 placebo Hazard ratio/95% CI	1.1 (-0.64 to 2.85)	NA

CV mortality - with diabetes - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) first and recurrent hospital visit for HF) - with diabetes - Polarity - Lower values are better

Health-related quality of life (KCCQ clinical summary score) - with diabetes - Polarity - Higher values are better

Continuous outcomes

Outcome	SGLT2i (empagliflozin), Baseline, N = 1863	SGLT2i (empagliflozin), 12 month, N = 1863	Placebo, Baseline, N = 1867	Placebo, 12 month, N = 1867
Health-related quality of life (KCCQ clinical summary score) - no diabetes range 0-100, change score (adjusted mean). N= 936 SGLT2i, n = 938 placebo Mean (SD)	NR	5.43 (0.44)	NR	4.33 (0.63)
Health-related quality of life (KCCQ clinical summary score) - with diabetes range 0-100, change score (adjusted mean). N= 927 SGLT2i, n = 929 placebo Mean (SD)	NR	6.58 (0.63)	NR	4.17 (0.64)

Health-related quality of life (KCCQ clinical summary score) - no diabetes - Polarity - Higher values are better

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

Hyperkalaemia (defined by MedDRA Preferred Terms “hyperkalaemia” and “blood potassium increased”); subgroup with diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

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

Withdrawal due to drug-related adverse events (adverse event); subgroup with diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

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

CV mortality, subgroup with diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality subgroup no diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (first and recurrent hospital visit for HF); subgroup with diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (first and recurrent hospital visit for HF); subgroup no diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Withdrawal due to drug-related adverse events (adverse event); subgroup no diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

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

Hyperkalaemia (defined by MedDRA Preferred Terms “hyperkalaemia” and “blood potassium increased”); subgroup no diabetes. No of events. SGLT2i (empagliflozin) v Placebo following 16 months

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

Health-related quality of life (KCCQ clinical summary score); subgroup no diabetes. change from baseline and HR. SGLT2i (empagliflozin) v Placebo following 12 months

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

Health-related quality of life (KCCQ clinical summary score); subgroup with diabetes. Change from baseline and HR. SGLT2i (empagliflozin) v Placebo following 12 months

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

CV mortality; subgroup with diabetes. TTE. SGLT2i (empagliflozin) v Placebo at 16 months

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

CV mortality; subgroup no diabetes. TTE. SGLT2i (empagliflozin) v Placebo at 16 months

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

Unplanned hospitalisation or visits (HF-related) (first and recurrent hospital visit for HF); subgroup with diabetes. TTE. SGLT2i (empagliflozin) v Placebo at 16 months

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

Unplanned hospitalisation or visits (HF-related) (first and recurrent hospital visit for HF); subgroup no diabetes. TTE. SGLT2i (empagliflozin) v Placebo at 16 months

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

Asakura, 2022

Bibliographic Reference	Asakura, Masanori; Ito, Shin; Yamada, Takahisa; Saito, Yoshihiko; Kimura, Kazuo; Yamashina, Akira; Hirayama, Atsushi; Kobayashi, Youichi; Hanatani, Akihisa; Tsujimoto, Mitsuru; Yasuda, Satoshi; Abe, Yukio; Higashino, Yorihiko; Tamaki, Yodo; Sugino, Hiroshi; Niinuma, Hiroyuki; Okuhara, Yoshitaka; Koitabashi, Toshimi; Momomura, Shin-Ichi; Asai, Kuniya; Nomura, Akihiro; Kawai, Hiroya; Satoh, Yasuhiro; Yoshikawa, Tsutomu; Hirata, Ken-Ichi; Yokoi, Yoshiaki; Tanaka, Jun; Shibata, Yoshisato; Maejima, Yasuhiro; Tamaki, Shunsuke; Kawata, Hiroyuki; Iwahashi, Noriaki; Kobayashi, Masatake; Higuchi, Yoshiharu; Kada, Akiko; Yamamoto, Haruko; Kitakaze, Masafumi; 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; 2022; vol. 8 (no. 2); 108-117

Study details

Secondary publication of another included study – see primary study for details	N/A
Other publications associated with this study included in review	Asakura 2015 - trial rationale and design

Trial name / registration number	EARLIER trial JMACCT clinical trials registry identifier: JMA-IIA00127
Study type	Randomised controlled trial (RCT)
Study location	Japan - 27 centres
Study setting	Recruited in hospital and followed up after discharge
Study dates	Recruitment June 2013 to April 2018
Sources of funding	Japan Medical Association (academic/government) The drugs were provided by Pfizer USA based on the policy of the Japanese local Good Clinical Practice
Inclusion criteria	Japanese men and women who aged 20 years or older. Clinical evidence of acute decompensated HF, at no earlier than the date of the visit and within 72 h of enrollment, demonstrated by at least one of the following events: 1) de novo AHF, 2) acute exacerbation of chronic heart failure, and 3) post-AMI heart failure applicable to 1). signs of pulmonary congestion LVEF 40 % or less, at no earlier than the date of visit and within 3 days of enrollment.
Exclusion criteria	1. Patients with aldosterone antagonist therapy for 7 consecutive days, patients who developed a clinically significant hyperkalemia or renal dysfunction at an early stage of such aldosterone antagonist therapy, or patients who discontinued such aldosterone antagonist therapy no later than 3 months prior to randomisation. 2. Patients who in the past have received aldosterone antagonist therapy for less than 7 days. 3. Patients who have had an anamnesis of hyperpotacemia by ACE or ARB administration before this clinical trial. 4. Refractory hypertension defined by SBP >180mmHg or DBP >110 mmHg.

	5. Symptomatic hypotension or SBP immediately prior to enrollment <90 mmHg. 6. Cardiogenic shock. 7. Heart failure caused by pericardial disease, obstructive cardiomyopathy or restrictive cardiomyopathy, or a surgically-operable valvular disease; patients with heart failure due to a surgically-inoperable valvular disease may be enrolled in this study. 8. Patients using an intra-aortic balloon pump or other mechanically assisted circulatory support 9. Patients waiting for cardiac transplantation. 10. Patients whose PCI or CABG is planned during the first hospitalization. 11. Serum potassium level within 24 h prior to randomization >5.0 mmol/L. 12. Estimated glomerular filtration rate (eGFR) within 24 h prior to randomization <30 mL/min/1.73 m2. 13. Hemoglobin level within 24 h prior to enrollment <10 g/dL. 14. Clinically relevant liver disease. 15. Patients who have undergone gastric bypass, subtotal gastrectomy, or any other gastrointestinal tract surgery that may affect the absorption of eplerenone. 16. Patients in serious conditions (e.g., cancer, acquired immunodeficiency syndrome, etc.) or progressive lethal disease (except for congestive heart failure). 17. Patients with a diagnosed life expectancy <3 years. 18. Patients receiving immunosuppressive therapy or anticancer therapy. 19. Patients intolerant to eplerenone or spironolactone. 20. Patients requiring spironolactone, potassium canrenoate, potassium sparing diuretics, strong CYP3A4 inhibitor, or strong CYP3A4 inducer. 22. Women who are pregnant or breast-feeding.

	23. Patients who have participated in a clinical study of other investigational drug or post-marketing product (including medical devices) simultaneously to or within 30 days prior to the enrollment in this study. 24. Patients who are in other severe acute/chronic medical or psychological state or have abnormal clinical laboratory results, for which study participation or study drug treatment could increase the risk, or which could affect the interpretation of the study results, or patients who are inappropriate to participate in the study for any other reason as determined by the investigator or sub-investigator.
Recruitment / selection of participants	Study subjects will be stratified into three subgroups including [1] patients with post-AMI heart failure, [2] patients with AHF but not post-AMI patients and with SBP exceeding 140 mmHg, and [3] patients with AHF but not post-AMI patients and with SBP not greater than 140 mmHg
Intervention(s)	Eplerenone 25mg/day, increased to 50mg/day
Comparator	Matched placebo
Population subgroups	Age (<65 vs ≥65) eGFR (<60 vs ≥60 mL/min/1.73m2)
Number of participants	297 Adherence: 143 (95.9%) and 148 (98.0%) in the eplerenone and placebo groups, respectively.
Duration of follow-up	6 months The mean duration of treatment with the study drug was 142.5 and 147.9 days in the eplerenone and placebo groups, respectively.
Indirectness	
Method of analysis	ITT analysis

Study arms

Mineralocorticoid receptor antagonist (eplerenone) (N = 149)

Eplerenone 25mg/day, increased to 50mg/day Background treatment: ACEI/ARB = 89.9%; BB = 62.4%

Placebo (N = 151)

Background treatment: ACEI/ARB = 89.4%; BB = 65.6%

Characteristics

Arm-level characteristics

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 149)	Placebo (N = 151)
% Female Sample size	% = 32.9	% = 21.9
Age Median (IQR)	69 (63 to 76)	66 (56 to 76)
NYHA I Sample size	% = 4.7	% = 7.9
NYHA II Sample size	% = 37.6	% = 33.8

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 149)	Placebo (N = 151)
NYHA III Sample size	% = 43.6	% = 38.4
NYHA IV Sample size	% = 13.4	% = 18.5
Ischaemic Sample size	% = 37.6	% = 34.4
Non-ischaemic Sample size	% = 62.4	% = 65.6
LVEF Median (IQR)	31 (25 to 35.9)	30 (25 to 36)
Atrial fibrillation Sample size	% = 36.9	% = 33.1
Previous heart failure hospitalisation Sample size	% = 12.1	% = 12.6
Renal function (eGFR; mL/min/1.73m2) Median (IQR)	61 (48.5 to 73)	63 (53 to 75)
ACEI or ARB	% = 89.9	% = 89.4

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 149)	Placebo (N = 151)
Sample size		
b-Blockers Sample size	% = 62.4	% = 65.6
Diuretics Sample size	% = 91.9	% = 89.4
Pacemaker Sample size	% = 3.4	% = 3.3
Defibrillator Sample size	% = 1.3	% = 1.3
Cardiac resynchronisation therapy Sample size	% = 0.7	% = 0

Outcomes

Study timepoints

6 month

Dichotomous outcomes - ITT analysis

Outcome	Mineralocorticoid receptor antagonist (eplerenone), 6 month, N = 149	Placebo, 6 month, N = 151
All-cause mortality No of events	n = 2 ; % = 1.3	n = 0 ; % = 0
CV mortality No of events	n = 2 ; % = 1.3	n = 0 ; % = 0
• **Unplanned hospitalisation or visits (HF-related) (first re-hospitalisation due to HF)** No of events	n = 7 ; % = 4.7	n = 11 ; % = 7.3

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

• Unplanned hospitalisation or visits (HF-related) (first re-hospitalisation due to HF) - Polarity - Lower values are better

Hazard ratio

Outcome	Mineralocorticoid receptor antagonist (eplerenone) vs Placebo, 6 month, N2 = 149, N1 = 151
• **Unplanned hospitalisation or visits (HF-related) (first re-hospitalisation due to HF)** Cox proportional hazard model adjusted for the onset/relapse, stratified via the patient classification Hazard ratio/95% CI	0.55 (0.21 to 1.43)

• Unplanned hospitalisation or visits (HF-related) (first re-hospitalisation due to HF) - Polarity - Lower values are better

Dichotomous outcomes - safety analysis

Outcome	Mineralocorticoid receptor antagonist (eplerenone), 6 month, N = 148	Placebo, 6 month, N = 149
Withdrawal due to drug-related adverse events No of events	n = 10 ; % = 6.8	n = 6 ; % = 4
Hyperkalaemia (undefined) No of events	n = 6 ; % = 4.1	n = 4 ; % = 2.7

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

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

All-cause mortality - 6 months -dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

CV mortality - 6 months - dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits (HF-related) (first re-hospitalisation due to HF) - 6 months - dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits (HF-related) (first re-hospitalisation due to HF) - 6 months - HR

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

Withdrawal due to drug-related adverse events - 6 months

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

Hyperkalaemia (undefined)- 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome not defined)*

Asakura, 2015

Bibliographic Reference	Asakura, Masanori; Yamamoto, Haruko; Asai, Kuniya; Hanatani, Akihisa; Hirata, Ken-ichi; Hirayakma, Atsushi; Kimura, Kazuo; Kobayashi, Youichi; Momomura, Shin-ichi; Nakagawa, Yoshihisa; Nishi, Yutaro; Saito, Yoshihiko; Satoh, Yasuhiro; Yamada, Takahisa; Yamashina, Akira; Yasuda, Satoshi; Yoshikawa, Tsutomu; Kada, Akiko; Uesaka, Hiroyuki; Kitakaze, Masafumi; 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; 2015; vol. 29 (no. 2); 179-85

Study details

Secondary publication of	Rationale and design paper. See Asakura 2020 for **Study details**

another included study – see primary study for details	

Berry, 2007

Bibliographic Reference	Berry, Colin; Murphy, Niamh F; De Vito, Giuseppe; Galloway, Stuart; Seed, Alison; Fisher, Carol; Sattar, Naveed; Vallance, Patrick; Hillis, W Sewart; McMurray, John; Effects of aldosterone receptor blockade in patients with mild-moderate heart failure taking a beta-blocker.; European journal of heart failure; 2007; vol. 9 (no. 4); 429-34

Study details

Secondary publication of another included study – see primary study for details	N/A
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	NR

Study setting	NR
Study dates	NR
Sources of funding	British Heart Foundation
Inclusion criteria	Ambulant patients with mild–moderate heart failure(NYHA class I–III) and a left ventricular ejection fraction of <40% An optimal maintenance dose of both a beta-blocker and either an ACE inhibitor or anangiotensin receptor blocker for at least 30 days
Exclusion criteria	Use of potassium-sparing diuretics Serum creatinine concentration of >220µmol/L and a serum potassium concentration of >5 mmol/L before randomisation.
Recruitment / selection of participants	NR
Intervention(s)	MRA (sprionolactone) Patients received 25 mg MRA (spironolactone) for 12 weeks. Patients also received ACEI or ARB (100%), ACEI (85%) ARB (15%), Beta-blocker (100%) Digoxin (5%), Diuretic (85%), HMG CoA reductase inhibitor (60%)
Comparator	Patients received Placebo for 12 weeks. Patients also received ACEI or ARB (100%), ACEI (90%) ARB (10%), Beta-blocker (100%) Digoxin (20%), Diuretic (70%), HMG CoA reductase inhibitor (60%)

Population subgroups	NA
Number of participants	40
Duration of follow-up	12 weeks
Indirectness	NA
Method of analysis	Other
Additional comments	Little information on analysis so unable to determine

Study arms

MRA (spironolactone) (N = 20)

Patients received 25 mg MRA (spironolactone) for 3 months. Patients also received ACEI or ARB (100%), ACEI (85%) ARB (15%), Beta-blocker (100%) Digoxin (5%)

Placebo (N = 20)

Patients received placebo for 3 months. Patients also received ACEI or ARB (100%), ACEI (90%) ARB (10%), Beta-blocker (100%) Digoxin (20%)

Characteristics

Arm-level characteristics

Characteristic	MRA (spironolactone) (N = 20)	Placebo (N = 20)
% Female Sample size	n = 5 ; % = 25	n = 4 ; % = 20
Age (Years (mean, SD)) Mean (SD)	65 (7.4)	59 (9.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
NYHA class Sample size	n = NA	n = NA
Class I Sample size	n = 2 ; % = 10	n = 6 ; % = 30
Class II Sample size	n = 15 ; % = 75	n = 13 ; % = 65
Class III Sample size	n = 3 ; % = 15	n = 1 ; % = 5
Heart failure aetiology Sample size	n = NA	n = NA
Ischaemic heart disease	n = 18 ; % = 90	n = 10 ; % = 50

Characteristic	MRA (spironolactone) (N = 20)	Placebo (N = 20)
Sample size		
Idiopathic Sample size	n = 2 ; % = 10	n = 8 ; % = 40
Hypertension classed as aetiology Sample size	n = 0 ; % = 0	n = 1 ; % = 5
Alcohol classed as aetiology Sample size	n = 0 ; % = 0	n = 1 ; % = 5
LVEF (%) Mean (SD)	29 (8)	28 (9)
Type 2 diabetes Sample size	n = 2 ; % = 10	n = 2 ; % = 10
Atrial fibrillation Sample size	n = NR ; % = NR	n = NR ; % = NR
Previous heart failure hospitalisation Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (eGFR; mL/min/1.73m2)	NR	NR

Characteristic	MRA (spironolactone) (N = 20)	Placebo (N = 20)
Mean (SD)		
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACE inhibitor Sample size	n = 17 ; % = 85	n = 18 ; % = 90
Angiostensin receptor blocker Sample size	n = 3 ; % = 15	n = 2 ; % = 10
ACE-inhibitor or ARB Sample size	n = 20 ; % = 100	n = 20 ; % = 100
Beta-blocker Sample size	n = 20 ; % = 100	n = 20 ; % = 100
Digoxin Sample size	n = 1 ; % = 5	n = 4 ; % = 20
Aspirin Sample size	n = 17 ; % = 85	n = 8 ; % = 40
Warfarin Sample size	n = 2 ; % = 10	n = 3 ; % = 15

Characteristic	MRA (spironolactone) (N = 20)	Placebo (N = 20)
HMG-CoA reductase inhibitors Sample size	n = 12 ; % = 60	n = 12 ; % = 60
Diuretic Sample size	n = 17 ; % = 85	n = 14 ; % = 70
Device therapy Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

Baseline

12 week

Dichotomous

Outcome	MRA (spironolactone), 12 week, N = 20	Placebo, 12 week, N = 20
Acute kidney injury (defined as adverse event related to renal dysfunction) No of events	n = 0 ; % = 0	n = 0 ; % = 0

Acute kidney injury (defined as adverse event related to renal dysfunction) - Polarity - Lower values are better

Continuous outcomes

Outcome	MRA (spironolactone), Baseline, N = 20	MRA (spironolactone), 12 week, N = 20	Placebo, Baseline, N = 20	Placebo, 12 week, N = 20
Health-related quality of life (EQ-VAS) range 0-100, change score. No baseline data reported Mean (SE)	*NA*	-6 (3)	*NA*	6 (4)

Health-related quality of life (EQ-VAS) - Polarity - Higher values are better

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

Acute kidney injury (defined as adverse event related to renal dysfunction) (No. of events) MRA (spironolactone) v placebo at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Lack of detail regarding randomisation, concealment, the differences in attrition and unclear how the difference was accounted for. Additionally no details on pre-specified plan)*
Overall bias and Directness	Overall Directness	Directly applicable

Health-related quality of life (EQ-VAS)-MeanSE-MRA (spironolactone)-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Lack of detail regarding randomisation, concealment, the differences in attrition and unclear how the difference was accounted for. Additionally no details on pre-specified plan)*
Overall bias and Directness	Overall Directness	Directly applicable

Butler, 2021

Bibliographic Reference	Butler, Javed; Anker, Stefan D; Filippatos, Gerasimos; Khan, Muhammad Shahzeb; Ferreira, Joao Pedro; Pocock, Stuart J; Giannetti, Nadia; Januzzi, James L; Pina, Ileana L; Lam, Carolyn S P; Ponikowski, Piotr; Sattar, Naveed; Verma, Subodh; Brueckmann, Martina; Jamal, Waheed; Vedin, Ola; Peil, Barbara; Zeller, Cordula; Zannad, Faiez; Packer, Milton; Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial.; European heart journal; 2021; vol. 42 (no. 13); 1203-1212

Study details

Secondary publication of another included study – see primary study for details	Packer, 2020
Other publications associated with this study included in review	Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J, Filippatos G, Hauske SJ, Brueckmann M, Pfarr E, Schnee J, Wanner C, Packer M. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. Circulation. 2021 Jan 26;143(4):310-321. doi:

	Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, Schnaidt S, Ofstad AP, Brueckmann M, Jamal W, Bocchi EA, Ponikowski P, Perrone SV, Januzzi JL, Verma S, Böhm M, Ferreira JP, Pocock SJ, Zannad F, Packer M. Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. Circulation. 2021 Jan 26;143(4):337-349. doi: 10.1161/CIRCULATIONAHA.120.051824. Epub 2020 Nov 11. PMID: 33175585; PMCID: PMC7834911. Lam CSP, Ferreira JP, Pfarr E, Sim D, Tsutsui H, Anker SD, Butler J, Filippatos G, Pocock SJ, Sattar N, Verma S, Brueckmann M, Schnee J, Cotton D, Zannad F, Packer M. Regional and ethnic influences on the response to empagliflozin in patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. Eur Heart J. 2021 Nov 14;42(43):4442-4451. doi: 10.1093/eurheartj/ehab360. PMID: 34184057; PMCID: PMC8599078.
Trial name / registration number	EMPEROR-Reduced/ NCT03057977
Study location	See primary study
Study dates	See primary study
Sources of funding	See primary study
Inclusion criteria	Adult patients who had chronic heart failure NYHA functional class II-IV symptoms with a left ventricular ejection fraction of ≤40%
Exclusion criteria	Symptomatic hypotension or a systolic blood pressure of <100mmHg and an estimated glomerular filtration rate (eGFR) of <20mL/min/1.73m2 body surface area or requiring dialysis.
Recruitment / selection of participants	See primary study

Intervention(s)	See primary study
Comparator	See primary study
Population subgroups	Patients are stratified by baseline tertiles of Kansas City Cardiomyopathy (Tertile 1= <62.5, Tertile 2= 62.6-85.4 and Tertile 3= ≥85.4)
Number of participants	3705 participants
Duration of follow-up	12 months
Indirectness	NA
Additional comments	Intention to treat

Study arms

Empagliflozin (SGLT2i) (N = 1853)

Placebo (N = 1852)

Characteristics

Study-level characteristics

Characteristic	Study (N = 3705)
% Female Sample size	n = NA ; % = NA
% Female - Tertile <62.5 Sample size	n = 393 ; % = 32.2
% Female - Tertile 62.6- 85.4 Sample size	n = 292 ; % = 23.3
% Female - Tertile ≥85.4 Sample size	n = 200 ; % = 16.2
Age Mean (SD)	NA (NA)
Age - Tertile <62.5 Mean (SD)	66.6 (11.4)
Age - Tertile 62.6- 85.4 Mean (SD)	67.3 (10.5)
Age - Tertile ≥85.4 Mean (SD)	66.7 (11.1)
Ethnicity	n = NA ; % = NA

Characteristic	Study (N = 3705)
Sample size	
Ethnicity - Asian (Tertile, <62.5) Sample size	n = 104 ; % = 8.5
Ethnicity - Asian (Tertile 62.6- 85.4) Sample size	n = 209 ; % = 16.7
Ethnicity - Asian (Tertile ≥85.4) Sample size	n = 348 ; % = 28.2
Ethnicity - Black (Tertile <62.5) Sample size	n = 112 ; % = 9.2
Ethnicity - Black (Tertile 62.6- 85.4) Sample size	n = 79 ; % = 6.3
Ethnicity - Black (Tertile ≥85.4) Sample size	n = 66 ; % = 5.4
Ethnicity - White (Tertile <62.5) Sample size	n = 952 ; % = 78
Ethnicity - White (Tertile 62.6- 85.4) Sample size	n = 909 ; % = 72.5

Characteristic	Study (N = 3705)
Ethnicity - White (Tertile ≥85.4) Sample size	n = 754 ; % = 61.2
Ethnicity - Other or missing (Tertile <62.5) Sample size	n = 52 ; % = 4.3
Ethnicity - Other or missing (Tertile 62.6- 85.4) Sample size	n = 56 ; % = 4.5
Ethnicity - Other or missing (Tertile ≥85.4) Sample size	n = 64 ; % = 5.2
NYHA class Sample size	n = NA ; % = NA
NYHA class - Class II (Tertile <62.5) Sample size	n = 670 ; % = 54.9
NYHA class - Class II (Tertile 62.6- 85.4) Sample size	n = 990 ; % = 79
NYHA class - Class II (Tertile ≥85.4) Sample size	n = 1121 ; % = 91
NYHA class - Class III (Tertile <62.5)	n = 532 ; % = 43.6

Characteristic	Study (N = 3705)
Sample size	
NYHA class - Class III (62.6- 85.4) Sample size	n = 263 ; % = 21
NYHA class - Class III (≥85.4) Sample size	n = 109 ; % = 8.8
NYHA class - Class IV (Tertile <62.5) Sample size	n = 18 ; % = 1.5
NYHA class - Class IV (Tertile 62.6- 85.4) Sample size	n = 0 ; % = 0
NYHA class - Class IV (Tertile ≥85.4) Sample size	n = 2 ; % = 0.2
LVEF Custom value	NA
LVEF - Tertile (<62.5) Custom value	27.3 (6.1%)
LVEF - Tertile (62.6- 85.4) Custom value	27.4 (5.9%)

Characteristic	Study (N = 3705)
LVEF - Tertile (≥85.4) Custom value	27.7 (6.0%)
Type 2 diabetes No of events	n = NA ; % = NA
Type 2 diabetes - Tertile <62.5 No of events	n = 656 ; % = 53.8
Type 2 diabetes - Tertile 62.6- 85.4 No of events	n = 595 ; % = 47.5
Type 2 diabetes - Tertile ≥85.4 No of events	n = 593 ; % = 48.1
Atrial fibrillation No of events	n = NA ; % = NA
Atrial fibrillation - Tertile < 62.5 No of events	n = 490 ; % = 40.2
Atrial fibrillation - Tertile 62.6- 85.4 No of events	n = 457 ; % = 36.5
Atrial fibrillation - Tertile ≥85.4	n = 414 ; % = 33.6

Characteristic	Study (N = 3705)
No of events	
Previous heart failure hospitalisation No of events	n = NA ; % = NA
Previous heart failure hospitalisation - Tertile <62.5 No of events	n = 384 ; % = 31.5
Previous heart failure hospitalisation - Tertile 62.6- 85.4 No of events	n = 382 ; % = 30.5
Previous heart failure hospitalisation - Tertile ≥85.4 No of events	n = 378 ; % = 30.7
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	NA (NA)
Renal function (eGFR; mL/min/1.73m2) - Tertile <62.5 Mean (SD)	60.8 (21.8)
Renal function (eGFR; mL/min/1.73m2) - Tertile 62.6- 85.4 Mean (SD)	61.8 (21.4)
Renal function (eGFR; mL/min/1.73m2) - Tertile ≥85.4 Mean (SD)	63.3 (21.3)

Characteristic	Study (N = 3705)
Background (non-randomised) heart failure medications No of events	n = NA ; % = NA
Background (non-randomised) heart failure medications - ACEI- Tertile <62.5 No of events	n = 545 ; % = 44.7
Background (non-randomised) heart failure medications - ACEI- Tertile 62.6- 85.4 No of events	n = 572 ; % = 45.7
Background (non-randomised) heart failure medications - ACEI- Tertile ≥85.4 No of events	n = 570 ; % = 46.3
Background (non-randomised) heart failure medications - ARB- Tertile <62.5 No of events	n = 306 ; % = 25.1
Background (non-randomised) heart failure medications - ARB Tertile 62.6- 85.4 No of events	n = 303 ; % = 24.2
Background (non-randomised) heart failure medications - ARB Tertile ≥85.4 No of events	n = 293 ; % = 23.8
Background (non-randomised) heart failure medications - ARNI- Tertile <62.5 No of events	n = 226 ; % = 18.5
Background (non-randomised) heart failure medications - ARNI Tertile 62.6- 85.4	n = 241 ; % = 19.2

Characteristic	Study (N = 3705)
No of events	
Background (non-randomised) heart failure medications - ARNI- Tertile ≥85.4	n = 258 ; % = 20.9
No of events	
Background (non-randomised) heart failure medications - Diuretic- Tertile <62.5	n = 1107 ; % = 90.7
No of events	
Background (non-randomised) heart failure medications - Diuretic- Tertile 62.6- 85.4	n = 1099 ; % = 87.7
No of events	
Background (non-randomised) heart failure medications - Diuretic- Tertile ≥85.4	n = 1020 ; % = 82.8
No of events	
Background (non-randomised) heart failure medications - Cardiac gylcosides - Tertile <62.5	n = 237 ; % = 19.4
No of events	
Background (non-randomised) heart failure medications - Cardiac glycosides- Tertile 62.6- 85.4	n = 183 ; % = 14.6
No of events	
Background (non-randomised) heart failure medications - Cardiac gylocsides- Tertile ≥85.4	n = 170 ; % = 13.8
No of events	
Background (non-randomised) heart failure medications - Beta-blocker- Tertile <62.5	n = 1156 ; % = 94.8
No of events	

Characteristic	Study (N = 3705)
Background (non-randomised) heart failure medications - Beta-blocker- Tertile 62.6- 85.4 No of events	n = 1186 ; % = 94.7
Background (non-randomised) heart failure medications - Beta-blocker- Tertile≥85.4 No of events	n = 1168 ; % = 94.8
Background (non-randomised) heart failure medications - MRA- Tertile <62.5 No of events	n = 896 ; % = 73.4
Background (non-randomised) heart failure medications - MRA- Tertile 62.6- 85.4 No of events	n = 889 ; % = 70.9
Background (non-randomised) heart failure medications - MRA- Tertile ≥85.4 No of events	n = 855 ; % = 69.4
Background (non-randomised) heart failure medications - Anti-platelet- Tertile <62.5 No of events	n = 658 ; % = 53.9
Background (non-randomised) heart failure medications - Anti-platelet- Tertile 62.6- 85.4 No of events	n = 666 ; % = 53.2
Background (non-randomised) heart failure medications - Anti-platelet- Tertile ≥85.4 No of events	n = 651 ; % = 52.8
Background (non-randomised) heart failure medications - Anti-coagulant- Tertile <62.5	n = 490 ; % = 40.2

Characteristic	Study (N = 3705)
No of events	
Background (non-randomised) heart failure medications - Anti-coagulant- Tertile 62.6- 85.4	n = 493 ; % = 39.3
No of events	
Background (non-randomised) heart failure medications - Anti-coagulant- Tertile ≥85.4	n = 465 ; % = 37.7
No of events	
Background (non-randomised) heart failure medications - Statin- Tertile <62.5	n = 826 ; % = 67.7
No of events	
Background (non-randomised) heart failure medications - Statin- Tertile 62.6-85.4	n = 872 ; % = 69.6
No of events	
Background (non-randomised) heart failure medications - Statin- Tertile ≥85.4	n = 836 ; % = 67.9
No of events	
Device therapy	n = NA ; % = NA
No of events	
Device therapy - Implantable cardiac defibrillator - Tertile <62.5	n = 379 ; % = 31.1
No of events	
Device therapy - Implantable cardiac defibrillator- Tertile 62.6- 85.4	n = 431 ; % = 34.4
No of events	

Characteristic	Study (N = 3705)
Device therapy - Implantable cardiac defibrillator- Tertile ≥85.4 No of events	n = 357 ; % = 29
Device therapy - Cardiac-resynchronization therapy- Tertile <62.5 No of events	n = 139 ; % = 11.4
Device therapy - Cardiac- resynchronization therapy - Tertile 62.6- 85.4 No of events	n = 169 ; % = 13.5
Device therapy - Cardiac-resynchronization therapy- Tertile ≥85.4 No of events	n = 131 ; % = 10.6

Outcomes

Study timepoints

Baseline

12 month

Continuous outcomes

Outcome	Empagliflozin (SGLT2i), Baseline, N = 1853	Empagliflozin (SGLT2i), 12 month, N = 1853	Placebo, Baseline, N = 1852	Placebo, 12 month, N = 1852

Contrast outcomes (mean difference)

Outcome	Empagliflozin (SGLT2i) vs Placebo, Baseline, N2 = 1853, N1 = 1852	Empagliflozin (SGLT2i) vs Placebo, 12 month, N2 = 1853, N1 = 1852
Health-related quality of life (KCCQ overall summary score) range 0-100, change score Mean (95% CI)	NR	1.52 (0.29 to 2.74)

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

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

Health-related quality of life (KCCQ overall summary score)-MD 95%CI-FUP 12 mo

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

Chan, 2007

Bibliographic Reference	Chan, Anna K Y; Sanderson, John E; Wang, Tian; Lam, Wynnie; Yip, Gabriel; Wang, Mei; Lam, Yat-Yin; Zhang, Yan; Yeung, Leata; Wu, Eugene B; Chan, Wilson W M; Wong, John T H; So, Nina; Yu, Cheuk-Man; Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure.; Journal of the American College of Cardiology; 2007; vol. 50 (no. 7); 591-6

Study details

Secondary publication of another included study – see primary study for details	N/A
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	NR
Study setting	NR
Study dates	NR
Sources of funding	NR
Inclusion criteria	Eligible patients with left ventricular ejection fraction (LVEF) <40% and receiving ACE inhibitors more than 6 months
Exclusion criteria	Significant valvular heart disease; congenital heart disease; any life-threatening disease with limited life expectancy; or standard contraindications for CMR examination, creatinine concentration >200 umol/l, potassium level >5 mmol/l, and a history of allergy or side-effect with spironolactone
Recruitment / selection of participants	No additional information
Intervention(s)	ARB (candesartan) + MRA (spironolactone)

	Patients received 8mg ARB (candesartan) + 25 mg MRA (spironolactone) once daily for 52 weeks. Patients also received beta-blockers (69.6%) and nitrates (60.9%) diuretics (47.%), aspirin (65.2%) and statins (39.1%). Dosages for the background medications except diuretics were not allowed to change after randomisation
Comparator	ARB (candesartan) + Placebo Patients received 8mg ARB (candesartan) and a matching identical placebo once daily for 52 weeks. Patients also received beta-blockers (72%) and nitrates (10%) diuretics (68%), aspirin (80%) and statins (60%). Dosages for the background medications except diuretics were not allowed to change after randomisation
Population subgroups	
Number of participants	48
Duration of follow-up	52 weeks
Indirectness	
Method of analysis	ITT analysis
Additional comments	Not implicitly stated however explanations appears in line with ITT analysis

Study arms

ARB (candesartan) + MRA (spironolactone) (N = 23)

Patients received 8mg ARB (candesartan) + 25 mg MRA (spironolactone) once daily for 52 weeks. Patients also received Beta-blockers (69.6%) and nitrates (60.9%)

ARB (candesartan) + placebo (N = 25)

Patients received 8mg ARB (candesartan) + placebo once daily for 52 weeks. Patients also received Beta-blockers (72%) and nitrates (10%)

Characteristics

Arm-level characteristics

Characteristic	ARB (candesartan) + MRA (spironolactone) (N = 23)	ARB (candesartan) + placebo (N = 25)
% Female Sample size	n = 3 ; % = 13	n = 5 ; % = 20
Age (Years (mean, SD)) Mean (SD)	61.4 (12.3)	65 (0.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
NYHA class Sample size	n = NA	n = NA
Class I Sample size	n = 4 ; % = 17.4	n = 3 ; % = 12

Characteristic	ARB (candesartan) + MRA (spironolactone) (N = 23)	ARB (candesartan) + placebo (N = 25)
Class II Sample size	n = 16 ; % = 69.6	n = 18 ; % = 72
Class III Sample size	n = 3 ; % = 13	n = 4 ; % = 16
Heart failure aetiology Sample size	n = NA	n = NA
Ischaemic heart disease Sample size	n = 11 ; % = 47.8	n = 17 ; % = 68
Dilated cardiomyopathy Sample size	n = 11 ; % = 47.8	n = 7 ; % = 28
Hypertension Listed as primary aetiology of HF Sample size	n = 1 ; % = 4.3	n = 2 ; % = 8
LVEF Mean (SD)	26 (2)	28 (2)
Type 2 diabetes Sample size	n = NA	n = NA

Characteristic	ARB (candesartan) + MRA (spironolactone) (N = 23)	ARB (candesartan) + placebo (N = 25)
Atrial fibrillation Sample size	n = NA	n = NA
Previous heart failure hospitalisation Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (eGFR; mL/min/1.73m2) Sample size	n = NR ; % = NR	n = NR ; % = NR
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
Diuretics Sample size	n = 11 ; % = 47.8	n = 17 ; % = 68
Beta-blocker Sample size	n = 16 ; % = 69.6	n = 18 ; % = 72
Nitrates Sample size	n = 14 ; % = 60.9	n = 10 ; % = 40
Aspirin Sample size	n = 15 ; % = 65.2	n = 20 ; % = 80

Characteristic	ARB (candesartan) + MRA (spironolactone) (N = 23)	ARB (candesartan) + placebo (N = 25)
Statins Sample size	n = 9 ; % = 39.1	n = 15 ; % = 60
Device therapy Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

52 week

Dichotomous Outcomes

Outcome	ARB (candesartan) + MRA (spironolactone), 52 week, N = 23	ARB (candesartan) + placebo, 52 week, N = 25
Withdrawal due to drug-related adverse events No of events	n = 2 ; % = 8.7	n = 1 ; % = 4
Hyperkalaemia (undefined) No of events	n = 1 ; % = 4.3	n = 0 ; % = 0

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

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

Withdrawal due to drug-related adverse events (No. of events) ARB (candesartan) +MRA (spironolactone) v Placebo at 52 week follow-up

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No details given on randomisation, concealment, attrition, adherence or prespecified plan)*
Overall bias and Directness	Overall Directness	Directly applicable

Hyperkalaemia (undefined) (No. of events). ARB (candesartan) + MRA (spironolactone) v Placebo at 52 week follow up

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No details given on randomisation, concealment, attrition, adherence or prespecified plan)*
Overall bias and Directness	Overall Directness	Directly applicable

Cicoira, 2002

Bibliographic Reference	Cicoira, M; Zanolla, L; Rossi, A; Golia, G; Franceschini, L; Brighetti, G; Marino, P; Zardini, P; 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; 2002; vol. 40 (no. 2); 304-310

Study details

Secondary publication of another included study – see primary study for details	N/A
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	NR
Study dates	NR
Sources of funding	Supported by a grant from the European Section of the Aldosterone Council (ESAC)
Inclusion criteria	Patients were eligible for enrollment if they had a diagnosis of CHF and were in stable clinical condition for at least six months, if they were on an ACE inhibitor at the maximal tolerated dose and had a left ventricular ejection fraction (LVEF) of no more than 45%. Only patients in sinus rhythm were included.
Exclusion criteria	Patients were excluded from the study if they had valvular heart disease, unstable angina, recent myocardial infarction (<6 months), active cancer, renal failure (serum creatinine >150 umol/l), hyperkaliemia (serum potassium .5.0 mEq/l) or hepatic failure. Treatment with potassium sparing diuretics was also not permitted

Recruitment / selection of participants	NR
Intervention(s)	MRA (spironolactone) Spironolactone was given at a dose of 25 mg/day in 22 patients and was uptitrated to 50 mg/day in 16 patients. In the remaining nine patients a dose of 12.5 mg/day was given for 12 months. All patients were receiving ACE inhibitors and 72% receiving beta-blockers
Comparator	Standard of care All patients were receiving ACE inhibitors and 65% receiving beta-blockers
Population subgroups	NA
Number of participants	106
Duration of follow-up	12 months
Indirectness	
Method of analysis	Other
Additional comments	Mode of analysis unclear

Study arms

MRA (spironolactone) (N = 54)

Patients received either 12.5 mg, 25 mg or 50 mg per day for 12 months. Patients also received ACEI (100%), and Beta-blockers (72%)

Standard of care (N = 52)

All patients received ACE inhibitors (100%) and 65% were also receiving beta-blockers

Characteristics

Arm-level characteristics

Characteristic	MRA (spironolactone) (N = 54)	Standard of care (N = 52)
% Female Sample size	n = 8 ; % = 14.8	n = 6 ; % = 11.5
Age Mean (SD)	62.5 (7.9)	61.7 (9.8)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
NYHA class Sample size	n = NR ; % = NR	n = NR ; % = NR
Heart failure aetiology Sample size	n = NA	n = NA

Characteristic	MRA (spironolactone) (N = 54)	Standard of care (N = 52)
Idiopathic Sample size	n = 19 ; % = 35	n = 19 ; % = 37
Ischaemic Sample size	n = 35 ; % = 65	n = 33 ; % = 63
LVEF (%) Mean (SD)	33 (7)	34 (7)
Type 2 diabetes Sample size	n = NR ; % = NR	n = NR ; % = NR
Atrial fibrillation Sample size	n = NR ; % = NR	n = NR ; % = NR
Previous heart failure hospitalisation Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	NR	NR
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACE inhibitor	n = 54 ; % = 100	n = 52 ; % = 100

Characteristic	MRA (spironolactone) (N = 54)	Standard of care (N = 52)
Sample size		
Beta-blocker Sample size	n = 39 ; % = 72	n = 34 ; % = 65
Device therapy Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

12 month

Dichotomous outcomes

Outcome	MRA (spironolactone), 12 month, N = 54	Standard of care, 12 month, N = 52
All-cause mortality No of events	n = 3 ; % = 5.6	n = 4 ; % = 7.7
Withdrawal due to drug-related adverse events No of events	n = 7 ; % = 12.9	n = 6 ; % = 11.5
Hyperkalaemia (undefined)	n = 3 ; % = 5.6	n = 0 ; % = 0

Outcome	MRA (spironolactone), 12 month, N = 54	Standard of care, 12 month, N = 52
No of events		

All-cause mortality - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

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

All-cause mortality (number of events); MRA (spironolactone) v Standard of care following 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No details regarding randomisation, concealment, adherence, pre-specified plan)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Hyperkalaemia (undefined) (No. of Events); MRA (spironolactone)v Standard of care following 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No details regarding randomisation, concealment, adherence, pre-specified plan)*
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to drug-related adverse events (No. of events); MRA (spironolactone) v Standard of care following 12 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No details regarding randomisation, concealment, adherence, pre-specified plan)*
Overall bias and Directness	Overall Directness	Directly applicable

Cotter, 2021

Bibliographic Reference	Cotter G; Davison B; Metra M; Sliwa K; Voors AA; Addad F; Celutkiene J; Chioncel O; Cohen Solal A; Diaz R; Damasceno A; Duengen HD; Filippatos G; Goncalvesova E; Merai I; Ponikowski P; Privalov D; Sani MU; Takagi K; Shogenov Z; Saidu H; Mebazaa A; Amended STRONG-HF study design.; European journal of heart failure; 2021; vol. 23 (no. 11)

Study details

Secondary publication of another included study – see primary study for details	Amended STRONG-HF study design. See main trial report for details: Mebazza 2022

Desai, 2019

Bibliographic Reference	Desai, Akshay S; Solomon, Scott D; Shah, Amil M; Claggett, Brian L; Fang, James C; Izzo, Joseph; McCague, Kevin; Abbas, Cheryl A; Rocha, Ricardo; Mitchell, Gary F; Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial.; JAMA; 2019; vol. 322 (no. 11); 1077-1084

Study details

Secondary publication of another included study – see primary study for details	N/A
Trial name / registration number	EVALUATE-HF/ NCT02874794
Study location	United States
Study setting	85 hospital and clinic-based study sites
Study dates	August 17, 2016 to June 28, 2018
Sources of funding	Novartis Pharmaceuticals
Inclusion criteria	age 50 years or older; history of hypertension at both screening and pre-randomization; chronic heart failure with left ventricular ejection fraction of 40% or less; New York Heart Association class I, II, or III symptoms; treatment with stable doses of guideline-directed medical therapy other than ACE inhibitors or ARBs with systolic blood pressure greater than 105 mm Hg at both screening and randomization; and on an optimal medical regimen of diuretics and background medications to effectively treat co-morbidities such as HTN, DM, and coronary artery disease

Exclusion criteria	History of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs; Previous history of intolerance to sacubitril/valsartan, ACEI or ARB standard of care doses despite appropriate and gradual up-titration; History of angioedema, drug-related or otherwise; Requirement of treatment with both ACE inhibitor and ARB; Current or prior treatment with sacubitril/valsartan
Recruitment / selection of participants	NA
Intervention(s)	ARNI (sacubitril-valsartan) + Placebo (ACE inhibitor - Enalapril placebo) initial dosage, 24/26 mg twice daily titrated to a target dosage of 97/103 mg twice daily
Comparator	ACE inhibitor - Enalapril initial dosage, 2.5 mg twice daily, titrated to a target dosage of 10 mg twice daily. Patients taking an ACE inhibitor prior to study enrollment underwent 36-hour washout prior to randomization
Population subgroups	NA
Number of participants	464
Duration of follow-up	12 weeks
Indirectness	NA
Method of analysis	Available case analysis analysis-of-covariance model adjusted for baseline values and treatment assignment without imputation for missing values

Additional comments	NA

Study arms

ARNI (sacubitril-valsartan) (N = 231)

initial dosage, 24/26 mg twice daily titrated to a target dosage of 97/103 mg twice daily

ACE inhibitor (Enalapril) (N = 233)

initial dosage, 2.5 mg twice daily, titrated to a target dosage of 10 mg twice daily

Characteristics

Arm-level characteristics

Characteristic	ARNI (sacubitril-valsartan) (N = 231)	ACE inhibitor (Enalapril) (N = 233)
% Female Sample size	n = 61 ; % = 26	n = 48 ; % = 21
Age (years) Mean (SD)	67.8 (9.8)	66.7 (8.5)
White	n = 166 ; % = 72	n = 175 ; % = 75

Characteristic	ARNI (sacubitril-valsartan) (N = 231)	ACE inhibitor (Enalapril) (N = 233)
Sample size		
Black Sample size	n = 62 ; % = 27	n = 53 ; % = 23
Asian, Native American, Pacific Islander, specified other, and unknown Sample size	n = 3 ; % = 1	n = 5 ; % = 2
Hispanic/Latino Sample size	n = 70 ; % = 30	n = 82 ; % = 35
I NYHA Sample size	n = 33 ; % = 14	n = 28 ; % = 12
II NYHA Sample size	n = 152 ; % = 66	n = 161 ; % = 69
III NYHA Sample size	n = 56 ; % = 20	n = 44 ; % = 19
Ischemic heart disease Sample size	n = 137 ; % = 59	n = 146 ; % = 63
LVEF	34 (10)	33 (10)

Characteristic	ARNI (sacubitril-valsartan) (N = 231)	ACE inhibitor (Enalapril) (N = 233)
Mean (SD)		
Previous heart failure hospitalisation (%) Sample size	n = 128 ; % = 55	n = 115 ; % = 49
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	70 (22)	69 (20)
ACE/ARB Sample size	n = 187 ; % = 81	n = 204 ; % = 88
Beta-blockers Sample size	n = 196 ; % = 85	n = 204 ; % = 88
Loop diuretics Sample size	n = 130 ; % = 56	n = 128 ; % = 55
MRAs Sample size	n = 57 ; % = 25	n = 58 ; % = 25

Outcomes

Study timepoints

12 week

Dichotomous outcomes

Outcome	ARNI (sacubitril-valsartan), 12 week, N = 231	ACE inhibitor (Enalapril), 12 week, N = 233
All-cause mortality No of events	n = 1	n = 1
Hyperkalaemia (K>5.3 meq/L) No of events	n = 37 ; % = 16	n = 30 ; % = 12.9

All-cause mortality - Polarity - Lower values are better

Hyperkalaemia (K>5.3 meq/L) - Polarity - Lower values are better

Continuous outcomes

Outcome	ARNI (sacubitril-valsartan), 12 week, N = 216	ACE inhibitor (Enalapril), 12 week, N = 222
Health-related quality of life (KCCQ overall summary score) range 0-100, change score Mean (95% CI)	8.7 (6.7 to 10.7)	4.2 (2.2 to 6.2)

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

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

All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Hyperkalaemia (K>5.3 meq/L)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: events recorded as potassium levels >5.3 mEq/L. Threshold is less than the protocol's)*

Health-related quality of life (KCCQ overall summary scores)

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

Edelmann, 2020

Bibliographic Reference	Edelmann, Frank; Jaarsma, Tiny; Comin-Colet, Josep; Schorr, Jessica; Ecochard, Laurent; Hussain, Rizwan I; Piepoli, Massimo F; 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; 2020; vol. 22 (no. 9); 1724-1733

Study details

Secondary publication of another included study – see primary study for details	This paper reports the rationale and study design for the OUTSTEP-HF trial. See Piepoli 2021 for **Study details**.
Other publications associated with this study included in review	See primary publication - Piepoli 2020 (EPPI ID = 15339028)
Trial name / registration number	NCT02900378

Eschalier, 2013

Bibliographic Reference	Eschalier R; McMurray JJ; Swedberg K; van Veldhuisen DJ; Krum H; Pocock SJ; Shi H; Vincent J; Rossignol P; Zannad F; Pitt B; ; 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; 2013; vol. 62 (no. 17)

Study details

Secondary publication of another included study – see primary study for details	See primary study
Other publications associated with this study included in review	Zannad, 2011; Tsutsui, 2018; Rogers, 2012
Trial name / registration number	EMPHASIS-HF/ NCT00232180
Study location	308 study locations including USA, Argentina, Australia, Belgium, Canada, Czechia, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Italy, Korea, Mexico, the Netherlands, Poland, Portugal, Russian Federation, Singapore, Slovakia, South Africa, Spain, Sweden, Ukraine, United Arab Emirates, United Kingdom, and Venezuela (information retrieved from NCT registration page)
Study setting	Specified study centres
Study dates	See primary study
Sources of funding	Not specified

Inclusion criteria	Aged 55 years or older NYHA functional class II Had a left ventricular ejection fraction <30% (or if between 30% and 35%, the QRS duration had to be >130 ms) Treated with the recommended or maximally tolerated dose of ACE-i or an ARB and BB (unless contraindicated) Had been hospitalised for a cardiovascular reason within the past 6 months (or had a B-type natriuretic peptide level >250 pg/ml or N-terminal pro–B-type natriuretic peptide >500 pg/ml in males and 750 pg/ml for females)
Exclusion criteria	Patients with an eGFR <30 ml/min/1.73 m2 Need for a potassium sparring diuretic Any other significant comorbid condition
Recruitment / selection of participants	See primary study
Intervention(s)	See primary study
Comparator	See primary study
Population subgroups	Patients aged 75 years or older, with diabetes mellitus, with chronic kidney disease, an estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m2), and systolic blood pressure (SBP) < median (123 mm Hg), and patients at high risk of hyperkalemia
Number of participants	2737 participants
Duration of follow-up	See primary study

Indirectness	None
Method of analysis	Per protocol analysis
Additional comments	The paper contains a primary outcome that presents the data as hospitalisation for HF or death from cardiovascular causes (this value is combined). Number of events reported.

Study arms

Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)

Started at a dose of 25 mg once daily (or if the eGFR was 30 to 49 ml/min/1.73 m2, at a dose of 25 mg every other day) and increased to 50 mg once daily at 4 weeks, provided the serum potassium was no more than 5.0 mmol/l (or if the eGFR was 30 to 49 ml/min/1.73 m2 at baseline to 25 mg daily). Serum potassium was measured every 4 months and the dose was reduced (if serum potassium was 5.5 to 5.9 mmol/l) and the dose was withheld if the serum potassium was >6.0 mmol/l.

Placebo (N = 1373)

Placebo

Characteristics

Arm-level characteristics

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)	Placebo (N = 1373)
% Female	n = 309 ; % = 22.7	n = 301 ; % = 21.9
Sample size		

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)	Placebo (N = 1373)
Age Mean (SD)	68.7 (7.7)	68.6 (7.6)
LVEF Mean (SD)	26.2 (4.6)	26.1 (4.7)
Type 2 diabetes Sample size	n = 459 ; % = 33.7	n = 400 ; % = 29.1
Previous heart failure hospitalisation No of events	n = 714 ; % = 52.3	n = 726 ; % = 52.9
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	71.2 (21.9)	70.4 (21.7)
ACE-inhibitor Sample size	n = 1068 ; % = 78.3	n = 1055 ; % = 76.8
ARB Sample size	n = 261 ; % = 19.1	n = 266 ; % = 19.4
Diuretic Sample size	n = 1150 ; % = 84.3	n = 1176 ; % = 85.7
ACE-inhibitor, ARB, or both	n = 1282 ; % = 94	n = 1275 ; % = 92.9

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)	Placebo (N = 1373)
Sample size		
Beta-blocker Sample size	n = 1181 ; % = 86.6	n = 1193 ; % = 86.9

Outcomes

Hyperkalemia

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1336	Placebo, , N = 1340
Hyperkalaemia (serum potassium concentration >5.5 mmol/l) No of events	n = 158 ; % = 11.8	n = 96 ; % = 7.2
Participants 75 years or older N = 322vs 318 No of events	n = 40 ; % = 12.4	n = 21 ; % = 6.6
Participants with diabetes mellitus N = 447 vs 387 No of events	n = 63 ; % = 14.1	n = 33 ; % = 8.5
Participants with CKD N = 422 vs 461	n = 70 ; % = 16.6	n = 43 ; % = 9.3

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1336	Placebo, , N = 1340
No of events		
Participants with low systolic blood pressure (<123 mm Hg) N = 658 vs 660 No of events	n = 72 ; % = 10.9	n = 48 ; % = 7.3

Hyperkalaemia (serum potassium concentration >5.5 mmol/l) - Polarity - Lower values are better

potassium levels > 5.5 mmol/l

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

Hyperkalaemia (serum potassium concentration >5mmol/l) - Participants with low systolic blood pressure

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

Hyperkalaemia (serum potassium concentration >5mmol/l) - Participants with CKD

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(Directly applicable)*

Hyperkalaemia (serum potassium concentration >5mmol/l) - Participants with diabetes mellitus

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

Hyperkalaemia (serum potassium concentration >5mmol/l) - Participants 75 years or older

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

Hyperkalaemia (serum potassium concentration >5mmol/l)

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(Directly applicable)*

Ghafur, 2020

Bibliographic Reference	Ghafur, Shakil; Zahid, Md; Sarkar, Haripada; Barman, Rabindra; Al-Mahmud, Abdullah; Rahman, Mahbubur; Islam, Hasanul; 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; 2020; vol. 10; 21-34

Study details

Secondary publication of another included study – see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	N/A

Study type	Randomised controlled trial (RCT)
Study location	Bangladesh
Study setting	Department of Cardiology, Rangpur Medical College Hospital, Rangpur
Study dates	Patients screening took place between 10 May 2018 and 3 December 2018.
Sources of funding	Study sponsored by General Pharmaceuticals Limited, Bangladesh
Inclusion criteria	Patients with chronic heart failure aged 40 years and over, NYHA class II - IV and and reduced ejection fraction (LVEF ≤40%) NT-proBNP ≥400 pg/Ml
Exclusion criteria	Any prior measurement of LVEF < 40% Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery within 3 months, or urgent percutaneous coronary intervention within 3 months or elective PCI within 30 days prior to entry. Any clinical event within 6 months prior to entry which could have reduced the LVEF (e.g., MI, CABG), unless an echo measurement performed after the event confirms LVEF ≥45%. Current acute decompensated HF requiring therapy. Patients requiring treatment with 2 or more of the following: ACEI, ARB or a renin inhibitor.
Recruitment / selection of participants	No further information
Intervention(s)	Sacubitril/valsartan initiated at 50 mg twice daily and titrated to 100 mg twice daily. Background treatments (ACEI or ARBs) were discontinued 24 hours before enrolment.

Comparator	Valsartan initiated at 40 mg twice daily and titrated to 80 mg twice daily. Background treatments (ACEI or ARBs) were discontinued 24 hours before enrolment.
Number of participants	100 patients randomised
Duration of follow-up	88 days median follow-up
Method of analysis	ITT analysis

Study arms

ARNI (Sacubitril/valsartan) (N = 50)

Sacubitril/valsartan 100 mg twice daily. Background treatments (ACEI or ARB) were discontinued.

ARB (Valsartan) (N = 50)

Valsartan 80 mg twice daily. Background treatments (ACEI or ARB) were discontinued.

Characteristics

Arm-level characteristics

Characteristic	ARNI (Sacubitril/valsartan) (N = 50)	ARB (Valsartan) (N = 50)
% Female	n = 17 ; % = 34	n = 16 ; % = 32
Sample size		

Characteristic	ARNI (Sacubitril/valsartan) (N = 50)	ARB (Valsartan) (N = 50)
Age (years) Mean (SD)	60.8 (11.4)	61.9 (12.5)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
NYHA class Sample size	n = NA	n = NA
Class II Sample size	n = 1 ; % = 2	n = 4 ; % = 8
Class III Sample size	n = 48 ; % = 96	n = 46 ; % = 92
Class IV Sample size	n = 1 ; % = 2	n = 0 ; % = 0
Heart failure aetiology Sample size	n = NR ; % = NR	n = NR ; % = NR
LVEF (%) Mean (SD)	30.44 (6.71)	30.57 (6.05)

Characteristic	ARNI (Sacubitril/valsartan) (N = 50)	ARB (Valsartan) (N = 50)
Type 2 diabetes Diabetes (type not specified) Sample size	n = 14 ; % = 28	n = 11 ; % = 22
Atrial fibrillation Sample size	n = NR ; % = NR	n = NR ; % = NR
Previous heart failure hospitalisation Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (eGFR; mL/min/1.73m2) (ml/min/1.73 m2) Mean (SD)	53.42 (18.15)	46.62 (18.85)
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACEI Sample size	n = 11 ; % = 22	n = 5 ; % = 10
ARB Sample size	n = 11 ; % = 22	n = 5 ; % = 10
Beta-blocker Sample size	n = 44 ; % = 88	n = 41 ; % = 82

Characteristic	ARNI (Sacubitril/valsartan) (N = 50)	ARB (Valsartan) (N = 50)
Diuretics Sample size	n = 38 ; % = 76	n = 41 ; % = 82
MRA (Spironolactone) Sample size	n = 37 ; % = 74	n = 38 ; % = 76
Device therapy Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

88 day (88 days median)

Dichotomous outcomes

Outcome	ARNI (Sacubitril/valsartan), 88 day, N = 50	ARB (Valsartan), 88 day, N = 50
CV mortality No of events	n = 4 ; % = 8	n = 11 ; % = 22
Unplanned hospitalisation or visits (HF-related) (hospitalisation followed by receiving treatment)	n = 2 ; % = 4	n = 10 ; % = 20

Outcome	ARNI (Sacubitril/valsartan), 88 day, N = 50	ARB (Valsartan), 88 day, N = 50
No of events		
Hyperkalaemia (elevated potassium ≥5.5 mEq/L) No of events	n = 1 ; % = 2.22	n = 1 ; % = 2.56

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (hospitalisation followed by receiving treatment) - Polarity - Lower values are better

Hyperkalaemia (elevated potassium ≥5.5 mEq/L) - Polarity - Lower values are better

Time to event outcomes

Outcome	ARNI (Sacubitril/valsartan) vs ARB (Valsartan), 88 day, N2 = 50, N1 = 50
CV mortality Hazard ratio/95% CI	0.37 (0.34 to 0.64)
Unplanned hospitalisations or visits (HF related) (hospitalisation followed by receiving treatment) Hazard ratio/95% CI	0.8 (0.57 to 0.92)

CV mortality - Polarity - Lower values are better

Unplanned hospitalisations or visits (HF related) (hospitalisation followed by receiving treatment) - Polarity - Lower values are better

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

CV mortality-ARNI (Sacubitril/valsartan) vs ARB (Valsartan) at 88 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality (time to event) - ARNI (Sacubitril/valsartan) vs ARB (Valsartan) at 88 days

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

Unplanned hospitalisation or visits (HF related) (hospitalisation followed by receiving treatment) - ARNI (Sacubitril/valsartan) vs ARB (Valsartan) at 88 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits (HF related) (hospitalisation followed by receiving treatment) -time to event outcome -ARNI (Sacubitril/valsartan)-ARB (Valsartan)- at 88 days

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

Hyperkalaemia (elevated potassium ≥5.5 mEq/L) - ARNI (Sacubitril/valsartan) vs ARB (Valsartan) at 88 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome reported as elevated serum potassium ≥5.5 mEq/L)*

Halle, 2021

Bibliographic Reference	Halle, Martin; Schobel, Christoph; Winzer, Ephraim B; Bernhardt, Peter; Mueller, Stephan; Sieder, Christian; Lecker, Laura S M; 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; 2021; vol. 23 (no. 12); 2073-2082

Study details

Secondary publication of another included study – see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial name / registration number	NCT02768298
Study type	Randomised controlled trial (RCT)
Study location	Germany (34 centres)
Study setting	No further information
Study dates	Not reported
Sources of funding	Novartis Pharma AG
Inclusion criteria	Ambulatory patients ≥ 18 years with a diagnosis of chronic heart failure (New York Heart Association class III and a reduced ejection fraction of ≤40%) Objectively reduced exercise capacity (peak VO2 ≤ 18 mL/min/kg) Patients taking an ACEI or ARB at a stable dose of at least enalapril 10mg/day or equivalent for at least 4 weeks before screening and until randomisation visit

Exclusion criteria	History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBs, or neprilysin inhibitors as well as known or suspected contraindications to the study drugs Previous history of intolerance to recommended target doses of ACEIs or ARBs Known history of angioedema Requirement for treatment with ACEIs and ARBs Current acute decompensated heart failure Symptomatic hypotension and/or a SBP <100 mmHg at screening or at randomisation eGFR <30 mL/min/1,73m2, as measured by MDRD at screening or randomisation Serum potassium >5.2 mmol/L at screening or randomisation Acute coronary syndrome, stroke, transient ischaemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention, or carotid angioplasty within 3 months prior to screening Coronary or carotid artery disease likely to require surgical or percutaneous intervention within 6 months prior to screening Implantation of a cardiac resynchronisation therapy pacemaker (CRT-P) or a cardiac resynchronisation therapy defibrillator (CRT-D), or upgrading of existing conventional pacemaker or implantable cardioverter defibrillator (ICD) to CRT device within 3 months prior to screening or intent to implant. Patients who had implantation of a conventional pacemaker or an ICD or had a revision of a pacemaker or other device leads within 1 month before screening are excluded Heart transplant or ventricular assistance device or intent to transplant or implant during the study timeframe pregnancy or lactation Patients with severe obesity (Adipositas permagna - BMI ≥40 mg/m2)
Recruitment / selection of participants	No further information

Intervention(s)	ARNI (sacubitril/valsartan) initiated at 49/51 mg twice daily for weeks 1 and 2, up-titrated to 97/103 mg twice daily for 10 weeks. Patients continued background medication for heart failure, except for ARBs and ACEIs (ACEIs discontinued 36 hours prior to initiation of study drug).
Comparator	ACEI (enalapril) 5 mg twice daily for weeks 1 and 2, up-titrated to 10 mg twice daily for 10 weeks. Patients continued background medication for heart failure, except for ARBs and ACEIs (ACEIs discontinued 36 hours prior to initiation of study drug).
Population subgroups	
Number of participants	201 patients randomised
Duration of follow-up	12 weeks
Indirectness	
Method of analysis	Other Type of analysis is unclear

Study arms

ARNI (sacubitril/valsartan) (N = 103)

Sacubitril/valsartan initiated at 49/51 mg twice daily for weeks 1 and 2, up-titrated to 97/103 mg twice daily for 10 weeks. Patients continued background medication for heart failure, except for ARBs and ACEIs (ACEIs discontinued 36 hours prior to initiation of study drug).

ACEI (enalapril) (N = 98)

Enalapril 5 mg twice daily for weeks 1 and 2, up-titrated to 10 mg twice daily for 10 weeks. Patients continued background medication for heart failure, except for ARBs and ACEIs (ACEIs discontinued 36 hours prior to initiation of study drug).

Characteristics

Arm-level characteristics

Characteristic	ARNI (sacubitril/valsartan) (N = 103)	ACEI (enalapril) (N = 98)
% Female Sample size	n = 17 ; % = 16.5	n = 21 ; % = 21.4
Age (years) Mean (SD)	66.1 (10.8)	67.6 (10)
Ethnicity Race (ethnicity not reported) Sample size	n = NA	n = NA
Caucasian Sample size	n = 101 ; % = 98.1	n = 96 ; % = 98
Black Sample size	n = 0 ; % = 0	n = 1 ; % = 1
Other Sample size	n = 2 ; % = 1.9	n = 1 ; % = 1

Characteristic	ARNI (sacubitril/valsartan) (N = 103)	ACEI (enalapril) (N = 98)
NYHA class Sample size	n = NA	n = NA
NYHA Class II Sample size	n = 0 ; % = 0	n = 1 ; % = 1
NYHA Class III Sample size	n = 103 ; % = 100	n = 97 ; % = 99
Heart failure aetiology Primary aetiology ischaemic Sample size	n = 61 ; % = 59.2	n = 64 ; % = 65.3
LVEF (%) Mean (SD)	31.9 (6.1)	32 (5.7)
Type 2 diabetes Sample size	n = NR ; % = NR	n = NR ; % = NR
Atrial fibrillation Sample size	n = NR ; % = NR	n = NR ; % = NR
Previous heart failure hospitalisation Sample size	n = 57 ; % = 55.3	n = 51 ; % = 52

Characteristic	ARNI (sacubitril/valsartan) (N = 103)	ACEI (enalapril) (N = 98)
Renal function (eGFR; mL/min/1.73m2) (ml/min/1.73 m²) Sample size	n = NR ; % = NR	n = NR ; % = NR
less than 30 Sample size	n = 0 ; % = 0	n = 0 ; % = 0
30-60 Sample size	n = 42 ; % = 40.8	n = 42 ; % = 42.9
60 and over Sample size	n = 61 ; % = 59.2	n = 56 ; % = 57.1
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACEI Sample size	n = 75 ; % = 72.8	n = 62 ; % = 63.3
ARB Sample size	n = 28 ; % = 27.2	n = 36 ; % = 36.7
MRA Sample size	n = 81 ; % = 78.6	n = 74 ; % = 75.5

Characteristic	ARNI (sacubitril/valsartan) (N = 103)	ACEI (enalapril) (N = 98)
Beta-blocker Sample size	n = 95 ; % = 92.2	n = 95 ; % = 96.9
Ivabradine Sample size	n = 8 ; % = 7.8	n = 6 ; % = 6.1
Diuretics (total) Sample size	n = 79 ; % = 76.7	n = 75 ; % = 76.53
Loop diuretics - torasemide Sample size	n = 67 ; % = 65	n = 60 ; % = 61.2
Loop diuretics - Furosemide Sample size	n = 7 ; % = 6.8	n = 6 ; % = 6.1
Loop diuretics - Piretanide Sample size	n = 1 ; % = 1	n = 1 ; % = 1
Digoxin Sample size	n = 4 ; % = 3.9	n = 7 ; % = 7.1
Statins Sample size	n = 82 ; % = 79.6	n = 79 ; % = 80.6

Characteristic	ARNI (sacubitril/valsartan) (N = 103)	ACEI (enalapril) (N = 98)
Device therapy Sample size	n = NA	n = NA
Pacemaker implanted Pacemaker category does not include cardiac resynchronisation therapy systems Sample size	n = 23 ; % = 22.3	n = 18 ; % = 18.4
ICD implanted - total Sample size	n = 58 ; % = 56.3	n = 57 ; % = 58.2
ICD implanted - single chamber Sample size	n = 23 ; % = 22.3	n = 28 ; % = 28.6
ICD implanted - dual chamber Sample size	n = 19 ; % = 18.4	n = 17 ; % = 17.3
ICD implanted - biventricular Sample size	n = 16 ; % = 15.5	n = 12 ; % = 12.2

Outcomes

Study timepoints

12 week

Dichotomous outcomes

Outcome	ARNI (sacubitril/valsartan), 12 week, N = 103	ACEI (enalapril), 12 week, N = 98
All-cause mortality No of events	n = 2 ; % = 1.9	n = 1 ; % = 1
CV mortality (comprises MI and worsening HF (ARNI) and cardiogenic shock + hypotension (ACEI)) No of events	n = 2 ; % = 1.9	n = 1 ; % = 1
Withdrawal due to drug-related adverse events No of events	n = 1 ; % = 1	n = 4 ; % = 4.1
Hyperkalaemia (undefined) No of events	n = 9 ; % = 8.7	n = 3 ; % = 3.1

All-cause mortality - Polarity - Lower values are better

CV mortality (comprises MI and worsening HF (ARNI) and cardiogenic shock + hypotension (ACEI)) - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

Continuous outcomes

Outcome	ARNI (sacubitril/valsartan), 12 week, N = 103	ACEI (enalapril), 12 week, N = 98
Health-related quality of life (KCCQ overall summary score) range 0-100, change score Mean (SD)	8.11 (16.7)	5.84 (14.51)
Health-related quality of life (KCCQ clinical summary score) range 0-100, change score Mean (SD)	7.33 (15.33)	4.92 (14.42)
Health-related quality of life (SF-36 physical component score) range 0-100, change score Mean (SD)	2.32 (5.78)	1.87 (5.77)
Health-related quality of life (SF-36 mental component score) range 0-100, change score Mean (SD)	0.78 (7.42)	1.75 (7.22)

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

Health-related quality of life (SF-36 physical component score) - Polarity - Higher values are better

Health-related quality of life (SF-36 mental component score) - Polarity - Higher values are better

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

All-cause mortality - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality (comprises MI and worsening HF (ARNI) and cardiogenic shock + hypotension (ACEI)) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Withdrawal due to drug-related adverse events - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

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

Hyperkalaemia (undefined)- ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: definition for hyperkalaemia not provided)*

Health-related quality of life (KCCQ overall summary score)- ARNI (sacubitril/valsartan) vs ACEI (enalapril) mean change from baseline at 12 weeks

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

Health-related quality of life (KCCQ clinical summary score) -ARNI (sacubitril/valsartan)-ACEI (enalapril) mean change from baseline at 12 weeks

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

Health-related quality of life (SF-36 physical component score) -ARNI (sacubitril/valsartan) vs ACEI (enalapril) mean change from baseline at 12 weeks

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

Health-related quality of life (SF-36 mental component score)-ARNI (sacubitril/valsartan) vs ACEI (enalapril) change from baseline at 12 weeks

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

Jensen, 2020

Bibliographic Reference	Jensen, Jesper; Omar, Massar; Kistorp, Caroline; Poulsen, Mikael Kjaer; Tuxen, Christian; Gustafsson, Ida; Kober, Lars; Gustafsson, Finn; Faber, Jens; Fosbol, Emil L; Bruun, Niels Eske; Brond, Jan Christian; Forman, Julie Lyng; Videbaek, Lars; Moller, Jacob Eifer; Schou, Morten; 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; 2020; vol. 228; 47-56

Study details

Secondary publication of another included study – see	N/A

primary study for details	
Other publications associated with this study included in review	Jensen J, Omar M, Kistorp C, Poulsen MK, Tuxen C, Gustafsson I, Køber L, Gustafsson F, Fosbøl E, Bruun NE, Videbæk L, Frederiksen PH, Møller JE, Schou M. Empagliflozin in heart failure patients with reduced ejection fraction: a randomized clinical trial (Empire HF). Trials. 2019 Jun 21;20(1):374. doi: 10.1186/s13063-019-3474-5. PMID: 31227014; PMCID: PMC6588901.
Trial name / registration number	EMPIRE HF / NCT03198585.
Study type	Randomised controlled trial (RCT)
Study location	Denmark
Study setting	Patients recruited from specialised HF clinics, assessments performed at at two hospital sites
Study dates	From June 29 2017 to January 17 2020
Sources of funding	Supported by the Research Council at Herlev and Gentofte University Hospital, Denmark; the Research and Innovation Foundation of the Department of Cardiology, Herlev and Gentofte University Hospital, Denmark ; the Capital Region of Denmark; the Danish Heart Foundation; the A.P. Møller Foundation for the Advancement of Medical Science and the Steno Diabetes Center Odense, Denmark Multiple authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	Optimal HF therapy in accordance with European and national guidelines LVEF ≤ 0.40 eGFR > 30 ml/min/1.73 m2 BMI < 45 kg/m2

	NYHA functional class I-III Age > 18 years If T2D – optimal treatment in accordance with European and national guidelines If T2D – stable doses of antidiabetic treatment for 30 days If T2D – HbA1c 48-83 mmol/mol (6.5-10.0 %
Exclusion criteria	CRT-D/-P implanted < 90 days Uncorrected severe valvular heart disease Non-compliance Use of metalozone NYHA IV Age > 85 years Dementia Hospitalization for HF < 30 days Known sustained ventricular tachycardia Symptomatic hypotension and systolic blood pressure < 95 mmHg Unable to perform an exercise test Immobilization Pregnancy Participation in other medical trials Previous intolerance of empagliflozin or excipients

Recruitment / selection of participants	NR
Intervention(s)	SGLT2i (empagliflozin) Patients received 10 mg daily empagliflozin for 12 weeks
Comparator	Placebo Patients received daily placebo for 12 weeks
Population subgroups	
Number of participants	n=190
Duration of follow-up	12 weeks
Indirectness	NA
Method of analysis	ITT analysis
Additional comments	Intention-to-treat

Study arms

SGLT2i (empagliflozin) (N = 95)

Patients received 10 mg empagliflozin once daily for 12 weeks in addition to background therapy Patients receiving Beta-blocker (96%), ACEI, ARB or sacubitril valsartan (95%), Sacubitril-valsartan (33%)

Placebo (N = 95)

Patients received once daily placebo for 12 weeks in addition to background therapy Patients receiving Beta-blocker (94%), ACEI, ARB or sacubitril valsartan (97%), Sacubitril-valsartan (28%)

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (empagliflozin) (N = 95)	Placebo (N = 95)
% Female Sample size	n = 16 ; % = 17	n = 12 ; % = 13
Age (Years (mean, SD)) Median (IQR)	64 (57 to 73)	63 (55 to 72)
Ethnicity Sample size	n = NA	n = NA
Caucasian Sample size	n = 92 ; % = 97	n = 94 ; % = 99
NYHA class	n = NA	n = NA

Characteristic	SGLT2i (empagliflozin) (N = 95)	Placebo (N = 95)
Sample size		
Class I Sample size	n = 5 ; % = 5.3	n = 7 ; % = 7.4
Class II Sample size	n = 72 ; % = 76	n = 77 ; % = 81
Class III Sample size	n = 18 ; % = 19	n = 11 ; % = 12
Heart failure aetiology Sample size	n = NA	n = NA
Ischaemic Sample size	n = 48 ; % = 51	n = 49 ; % = 52
Non-ischaemic Sample size	n = 47 ; % = 49	n = 46 ; % = 48
LVEF Median (IQR)	30 (25 to 35)	30 (25 to 35)
Type 2 diabetes history or newly diagnosed T2DM	n = 19 ; % = 20	n = 14 ; % = 15

Characteristic	SGLT2i (empagliflozin) (N = 95)	Placebo (N = 95)
Sample size		
Atrial fibrillation Sample size	n = 12 ; % = 12.6	n = 10 ; % = 10.5
Previous heart failure hospitalisation Sample size	n = 49 ; % = 52	n = 50 ; % = 53
Renal function (eGFR; mL/min/1.73m2) Median (IQR)	73 (57 to 89)	74 (60 to 89)
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACE-inhibitor, ARB or sacubitril-valsartan Sample size	n = 90 ; % = 95	n = 92 ; % = 97
Sacubitril-valsartan Sample size	n = 31 ; % = 33	n = 27 ; % = 28
Beta-blocker Sample size	n = 91 ; % = 96	n = 89 ; % = 94
MRA	n = 62 ; % = 65	n = 63 ; % = 66

Characteristic	SGLT2i (empagliflozin) (N = 95)	Placebo (N = 95)
Sample size		
Digitalis Sample size	n = 2 ; % = 2.1	n = 2 ; % = 2.1
Loop diuretic Sample size	n = 62 ; % = 65	n = 59 ; % = 62
Long-acting nitrates Sample size	n = 4 ; % = 4.2	n = 5 ; % = 5.3
Lipid lowering medication Including statins, fibrates, ezetemibe, anion exchange resins and/or proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitor. Sample size	n = 60 ; % = 63	n = 65 ; % = 68
Device therapy Sample size	n = NA	n = NA
CRT Including CRT with or without ICD Sample size	n = 18 ; % = 19	n = 18 ; % = 19
Including ICD or CRT with ICD Sample size	n = 45 ; % = 47	n = 46 ; % = 48

Outcomes

Study timepoints

Baseline

12 week

Dichotomous Outcomes

Outcome	SGLT2i (empagliflozin), Baseline, N = 95	SGLT2i (empagliflozin), 12 week, N = 95	Placebo, Baseline, N = 95	Placebo, 12 week, N = 95
All-cause mortality No of events	n = NA	n = 0 ; % = 0	n = NA	n = 0 ; % = 0
Health-related quality of life (KCCQ overall summary score) range 0-100, baseline and final score Mean (SD)	75.6 (18.3)	77.6 (17.6)	74.9 (17.8)	76.8 (19.8)
Health-related quality of life (KCCQ clinical summary score) range 0-100, baseline and final score Mean (SD)	78.1 (18.9)	81.4 (16.3)	78 (16.1)	78.5 (18.8)
CV mortality No of events	n = NA	n = 0 ; % = 0	n = NA	n = 0 ; % = 0

Outcome	SGLT2i (empagliflozin), Baseline, N = 95	SGLT2i (empagliflozin), 12 week, N = 95	Placebo, Baseline, N = 95	Placebo, 12 week, N = 95
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) No of events	n = NA	n = 1 ; % = 1.1	n = NA	n = 0 ; % = 0
Falls (hospitalisation for orthostatic hypotension as a surrogate)) No of events	n = NA	n = 0 ; % = 0	n = NA	n = 1 ; % = 1.1

All-cause mortality - Polarity - Lower values are better

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

CV mortality - Polarity - Lower values are better

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

Falls (hospitalisation for orthostatic hypotension as a surrogate)) - Polarity - Lower values are better

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

Health-related quality of life (KCCQ overall summary score); Final score. SGLT2i (empagliflozin) v Placebo following 12 weeks

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

Health-related quality of life (KCCQ clinical summary score); Final score. SGLT2i (empagliflozin) v Placebo following 12 weeks

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

All-cause mortality; No of events. SGLT2i (empagliflozin) v Placebo at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality; No of events. SGLT2i (empagliflozin) v Placebo at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF); No of events. SGLT2i (empagliflozin) v Placebo at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Falls (hospitalisation for orthostatic hypotension as a surrogate)-Events-12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: symptomatic hypotension used as a surrogate for falls)*

Jensen, 2019

Bibliographic Reference	Jensen, Jesper; Omar, Massar; Kistorp, Caroline; Poulsen, Mikael Kjaer; Tuxen, Christian; Gustafsson, Ida; Kober, Lars; Gustafsson, Finn; Fosbol, Emil; Bruun, Niels Eske; Videbaek, Lars; Frederiksen, Peter Hartmund; Moller, Jacob Eifer; Schou, Morten; Empagliflozin in heart failure patients with reduced ejection fraction: a randomized clinical trial (Empire HF).; Trials; 2019; vol. 20 (no. 1); 374

Study details

Secondary publication of another included	EMPIRE-HF trial design See Jensen 2020 for **Study details**

study – see primary study for details	

Kimmoun, 2019

Bibliographic Reference	Kimmoun, Antoine; Cotter, Gad; Davison, Beth; Takagi, Koji; Addad, Faouzi; Celutkiene, Jelena; Chioncel, Ovidiu; Solal, Alain Cohen; Diaz, Rafael; Damasceno, Albertino; Duengen, Hans-Dirk; Filippatos, Gerasimos; Goncalvesova, Eva; Merai, Imad; Metra, Marco; Ponikowski, Piotr; Privalov, Dmitry; Sliwa, Karen; Sani, Mahmoud Umar; Voors, Adriaan A; Shogenov, Zaur; Mebazaa, Alexandre; 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; 2019; vol. 21 (no. 11); 1459-1467

Study details

Secondary publication of another included study – see primary study for details	Rationale for and design of the STRONG-HF trial See main trial report for details: Mebazza 2022
Other publications associated with this study included in review	Pagnesi 2023: LVEF subgroup data

Lee, 2021

Bibliographic Reference	Lee, Matthew M Y; Brooksbank, Katriona J M; Wetherall, Kirsty; Mangion, Kenneth; Roditi, Giles; Campbell, Ross T; Berry, Colin; Chong, Victor; Coyle, Liz; Docherty, Kieran F; Dreisbach, John G; Labinjoh, Catherine; Lang, Ninian N; Lennie, Vera; McConnachie, Alex; Murphy, Clare L; Petrie, Colin J; Petrie, John R; Speirits, Iain A; Sourbron, Steven; Welsh, Paul; Woodward, Rosemary; Radjenovic, Aleksandra; Mark, Patrick B; McMurray, John J V; Jhund, Pardeep S; Petrie, Mark C; Sattar, Naveed; 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; 2021; vol. 143 (no. 6); 516-525

Study details

Other publications associated with this study included in review	NA
Trial name / registration number	SUGAR-DM-HF
Study location	Scotland
Study setting	Fifteen hospitals in Scotland took part in the trial.
Study dates	Recruitment took place between April 2018 and August 2019; follow-up visits were completed in May 2020.
Sources of funding	Supported by investigator-initiated study grant from Boehringer Ingelheim
Inclusion criteria	1. age ≥18 years

	2. heart failure (HF) with left ventricular ejection fraction (LVEF) ≤40% on screening visit echocardiogram, New York Heart Association (NYHA) II-IV symptoms, stable doses of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, angiotensinreceptor neprilysin inhibitor or β-blocker for 4 weeks prior 3. type 2 diabetes (glycohemoglobin ≤97 mmol/mol [≤11%], diet-controlled or on stable treatment for 6 weeks prior) or prediabetes (glycohemoglobin 39-47 mmol/mol [5.7%- 6.4%])
Exclusion criteria	1. type 1 diabetes 2. diabetic ketoacidosis 3. insulin use within 1 year of diagnosis of diabetes 4. history of acute or chronic pancreatitis and on insulin treatment for diabetes or low residual c-peptide (random non-fasting level of <0.2 nmol/L) 5. eGFR <30 mL/min/1.73m2 (based on latest available result) 6. persistent/permanent atrial fibrillation/flutter 7. acute coronary syndrome, stroke or surgery within 1 month 8. body mass index >52 kg/m2 9. liver disease (defined by serum alanine transferase, aspartate aminotransferase, alkaline phosphatase >3x upper limit of normal) 10. bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption 11. any condition with life expectancy <2 years 12. active malignancy requiring treatment (except successfully treated basal cell or squamous cell carcinoma, adjuvant hormonal therapy for breast or prostate cancer 13. blood dyscrasias or any disorders causing hemolysis or unstable red blood cells 14. systemic steroids within 6 weeks prior

	15. any uncontrolled endocrine disorder except type 2 diabetes or prediabetes 16. alcohol/drug abuse within 3 months that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake 17. known hypersensitivity to empagliflozin or excipients 18. known hypersensitivity to gadolinium 19. inability to give informed consent 20. sodium-glucose cotransporter 2 (SGLT2) inhibitor use (current or previous) 21. devices or any other contraindication to magnetic resonance imaging (MRI) 22. currently pregnant, planning pregnancy, or currently breastfeeding 23. history of previous lower limb amputation (non-traumatic) 24. current participation in another interventional medical study or within the last 90 days 25. anyone who, in the investigator's opinion, is not suitable to participate in the trial for other reasons (e.g. claustrophobia)
Recruitment / selection of participants	The clinical research team on each site screened patients in primary and secondary care. Patients aged ≥18 years, of either sex, with a history of HF and type 2 diabetes or prediabetes were prospectively identified, supported by review of (electronic) health records. Potential participants 2 were approached (and given patient information sheet) either in person by the clinical care team at a routine outpatient appointment, or by letter drop. Interested patients were then followed up by telephone to ascertain interest and confirm initial eligibility, and then invited to attend for an initial screening visit. If device therapy was indicated or further up titration of heart failure and/or diabetes therapy was required, screening was put on hold.
Intervention(s)	SGLT2i (Empagliflozin) 10mg once daily Concomitant treatment:

	ACEI/ARB/ARNI =94.2% ACEI =48.1% ARB=5.8% ARNI= 40.4% Beta-blocker- 88.5% MRA=61.5% Loop diuretic 59.6% Digoxin 7.7% Ivabradine 15.4%
Comparator	Matched placebo Concomitant treatment: ACEI/ARB/ARNI =96.2% ACEI =45.3% ARB=22.6% ARNI= 28.3% B eta-blocker= 94.3% MRA=58.5% Loop diuretic 54.7% Digoxin 1.9%

	Ivabradine 5.7%
Population subgroups	All participants had T2DM or pre-diabetes: documented history of diabetes or previously undiagnosed diabetes with glycohemoglobin ≥48 mmol/mol [≥6.5%]), or prediabetes (glycohemoglobin 39–47 mmol/mol [5.7%– 6.4%])
Number of participants	105 randomised.
Duration of follow-up	36 weeks
Additional comments	Intention-to-treat

Study arms

SGLT2i (Empagliflozin) (N = 52)

10mg once daily Concomitant treatment: ACEI/ARB/ARNI =94.2% ACEI =48.1% ARB=5.8% ARNI= 40.4% Beta-blocker- 88.5% MRA=61.5%

Placebo (N = 53)

Concomitant treatment: ACEI/ARB/ARNI =96.2% ACEI =45.3% ARB=22.6% ARNI= 28.3% Beta-blocker= 94.3% MRA=58.5%

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (Empagliflozin) (N = 52)	Placebo (N = 53)
% Female Calculated as non-male Sample size	n = 18 ; % = 34.6	n = 10 ; % = 18.9
Age Mean (SD)	68.2 (11.7)	69.2 (10.6)
NYHA Class II Sample size	n = 37 ; % = 71.2	n = 44 ; % = 83
NYHA Class III Sample size	n = 15 ; % = 28.8	n = 9 ; % = 17
NYHA Class III Sample size	n = 0 ; % = 0	n = 0 ; % = 0
LVEF (%) Cadiovascular magnetic resonance left ventricular ejection fraction Mean (SD)	32.1 (10.3)	32.9 (9.3)
T2DM One patient newly diagnosed at screening No of events	n = 40 ; % = 76.9	n = 42 ; % = 79.2
Prediabetes	n = 12 ; % = 23.1	n = 11 ; % = 20.8

Characteristic	SGLT2i (Empagliflozin) (N = 52)	Placebo (N = 53)
No of events		
Previous heart failure hospitalisation Sample size	n = 21 ; % = 40.4	n = 31 ; % = 58.5
Renal function (eGFR; mL/min/1.73m2) (ml/min/1.73 m2) Estimated GFR - chronic kidney disease epidemiology collaboration Mean (SD)	69.5 (22.3)	65.1 (21.8)
ACEI/ARB/ARNI Sample size	n = 49 ; % = 94.2	n = 51 ; % = 96.2
ACEI Sample size	n = 25 ; % = 48.1	n = 24 ; % = 45.3
ARB Sample size	n = 3 ; % = 5.8	n = 12 ; % = 22.6
ARNI Sample size	n = 21 ; % = 40.4	n = 15 ; % = 28.3
Beta-blocker Sample size	n = 46 ; % = 88.5	n = 50 ; % = 94.3
MRA	n = 32 ; % = 61.5	n = 31 ; % = 58.5

Characteristic	SGLT2i (Empagliflozin) (N = 52)	Placebo (N = 53)
Sample size		
Loop diuretic Sample size	n = 31 ; % = 59.6	n = 29 ; % = 54.7
Digoxin Sample size	n = 4 ; % = 7.7	n = 1 ; % = 1.9
Ivabradine Sample size	n = 8 ; % = 15.4	n = 3 ; % = 5.7

Outcomes

Study timepoints

Baseline

36 week

40 week

Dichotomous outcomes

Outcome	SGLT2i (Empagliflozin), 40 week, N = 52	Placebo, 40 week, N = 53
All-cause mortality	n = 2 ; % = 3.8	n = 0 ; % = 0

Outcome	SGLT2i (Empagliflozin), 40 week, N = 52	Placebo, 40 week, N = 53
No of events		
Acute kidney injury (undefined) No of patients who experienced at least one event No of events	n = 1 ; % = 1.9	n = 0 ; % = 0
Hyperkalaemia (undefined) No of patients who experienced at least one event No of events	n = 4 ; % = 7.7	n = 5 ; % = 9.4
Falls (hypotension as a surrogate) No of events	n = 29 ; % = 55.8	n = 31 ; % = 58.5

All-cause mortality - Polarity - Lower values are better

Acute kidney injury (undefined) - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

Falls (hypotension as a surrogate) - Polarity - Lower values are better

Continuous outcomes

Outcome	SGLT2i (Empagliflozin), Baseline, N = 44	SGLT2i (Empagliflozin), 36 week, N = 44	Placebo, Baseline, N = 51	Placebo, 36 week, N = 51
Health-related quality of life (KCCQ overall summary score) range 0-100, change score Mean (SD)	73.4 (22)	0.7 (17.5)	74.7 (19.5)	4.2 (13.8)

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

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

Health-related quality of life (KCCQ overall summary score, change score at 36 weeks)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data higher in intervention compared to control group and missingness likely to be related to outcome (side effects of drug); no information about pre-specified analyses in published protocol/design paper)*
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality -Events-FUP 40 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data higher in intervention compared to control group and missingness likely to be related to outcome (side effects of drug); no information about pre-specified analyses in published protocol/design paper)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Acute kidney injury (undefined) -Events-FUP 40 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data higher in intervention compared to control group and missingness likely to be related to outcome (side effects of drug); no information about pre-specified analyses in published protocol/design paper)*
Overall bias and Directness	Overall Directness	Directly applicable

Hyperkalaemia (undefined)-Events-FUP 40 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data higher in intervention compared to control group and missingness likely to be related to outcome (side effects of drug); no information about pre-specified analyses in published protocol/design paper)*
Overall bias and Directness	Overall Directness	Directly applicable

Falls (hypotension as a surrogate)-Events-FUP 40 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data higher in intervention compared to control group and missingness likely to be related to outcome (side effects of drug); no information about pre-specified analyses in published protocol/design paper)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: symptomatic hypotension used as a surrogate for falls)*

Lewis, 2017

Bibliographic Reference	Lewis, Eldrin F; Claggett, Brian L; McMurray, John J V; Packer, Milton; Lefkowitz, Martin P; Rouleau, Jean L; Liu, Jiankang; Shi, Victor C; Zile, Michael R; Desai, Akshay S; Solomon, Scott D; Swedberg, Karl; Health-Related Quality of Life Outcomes in PARADIGM-HF.; Circulation. Heart failure; 2017; vol. 10 (no. 8)

Study details

Secondary publication of another included study – see primary study for details	Quality of life outcomes for PARADIGM-HF See main report for details: McMurray 2014

Study arms

ARNI (Sacubitril/valsartan) (N = 4187)

Also known as LCZ696, 200mg twice daily. Concomitant treatment: Beta-blocker 93.1% MRA 54.2%

ACEI (Enalapril) (N = 4212)

10mg twice daily Concomitant treatment: Beta-blocker 92.9% MRA 57.0%

Outcomes

Study timepoints

Baseline

8 month

Continuous outcomes

Outcome	ARNI (Sacubitril/valsartan), Baseline, N = 3797	ARNI (Sacubitril/valsartan), 8 month, N = 3460	ACEI (Enalapril), Baseline, N = 3826	ACEI (Enalapril), 8 month, N = 3421
Health-related quality of life (KCCQ overall summary score) range 0-100 Mean (SD)	73.48 (19.51)	-	72.27 (19.43)	-
Health-related quality of life (KCCQ overall summary score) range 0-100, change score (adjusted for baseline score and treatment Mean (SE)	-	1.13 (0.25)	-	-0.14 (0.25)

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

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

Change in KCCQ OSS at 8 months

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

Lin, 2024

Bibliographic Reference	Lin, Meng-Jiao; Zou, Shu-Bin; Zhu, Bai-Xiang; Effect of dapagliflozin on uric acid in patients with chronic heart failure and hyperuricemia.; World journal of clinical cases; 2024; vol. 12 (no. 18); 3468-3475

Study details

Trial name / registration number	This study is registered at the Clinical Registry. https://www.researchregistry.com (Reviewreg1890).
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Tertiary hospitals
Study dates	Between January 2022 and January 2024

Sources of funding	Supported by General Medical Research Fund Project, No. TYYLKYJJ-2022-025.
Inclusion criteria	Patients with HFrEF and hyperuricemia who met the following inclusion criteria: Age 18 years or older, left ventricular ejection fraction (LVEF) ≤ 40%, New York Heart Association (NYHA) functional class II-IV, serum uric acid level ≥ 7 mg/dL (≥ 416 μmol/L), and stable medical therapy for CHF for at least 4 wk.
Exclusion criteria	type 1 diabetes mellitus, severe renal impairment [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2], active gout or history of gouty arthritis, use of urate-lowering agents, hypersensitivity to dapagliflozin or placebo, pregnancy or lactation, and any condition that could interfere with the study protocol or compromise the safety of the participants
Recruitment / selection of participants	Recruited from 10 teritary hospitals in China (no further detail).
Intervention(s)	SGLT2i (dapagliflozin) N=100 10mg daily dose Background therapy: ACEI/ARB: 92%; β blocker: 88%; MRA: 72%
Comparator	Placebo N=100 Background therapy: ACEI/ARB: 90%; β blocker: 86%; MRA: 70%
Number of participants	200
Duration of follow-up	24 months
Method of analysis	ITT analysis

Additional comments	The intention-to-treat principle was applied to all analyses.

Study arms

SGLT2i (dapagliflozin) (N = 100)

10mg daily dose Background therapy: ACEI/ARB: 92%; β blocker: 88%; MRA: 72%

Placebo (N = 100)

Background therapy: ACEI/ARB: 90%; β blocker: 86%; MRA: 70%

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (dapagliflozin) (N = 100)	Placebo (N = 100)
% Female Sample size	n = 32 ; % = 32	n = 34 ; % = 34
Age Mean (SD)	62.3 (9.8)	63.1 (10.2)
NYHA class - II NYHA Sample size	n = 36 ; % = 36	n = 38 ; % = 38

Characteristic	SGLT2i (dapagliflozin) (N = 100)	Placebo (N = 100)
NYHA class - III NYHA Sample size	n = 52 ; % = 52	n = 50 ; % = 50
NYHA class - IV NYHA Sample size	n = 12 ; % = 12	n = 12 ; % = 12
LVEF Mean (SD)	32.5 (6.7)	33.2 (7.1)
Type 2 diabetes (diabetes) Sample size	n = 42 ; % = 42	n = 40 ; % = 40
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	60.4 (15.8)	59.8 (16.2)
Background (non-randomised) heart failure medications - ACEI/ARB Sample size	n = 92 ; % = 92	n = 90 ; % = 90
Background (non-randomised) heart failure medications - Beta-blocker Sample size	n = 88 ; % = 88	n = 86 ; % = 86
Background (non-randomised) heart failure medications - MRA Sample size	n = 72 ; % = 72	n = 70 ; % = 70

Outcomes

Study timepoints

24 month

Dichotomous outcomes

Outcome	SGLT2i (dapagliflozin), 24 month, N = 100	Placebo, 24 month, N = 100
All-cause mortality No of events	n = 8 ; % = 8	n = 10 ; % = 10

All-cause mortality - Polarity - Lower values are better

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

All-cause mortality - No of events-FUP 24 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about pre-specified outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Mann, 2022

Bibliographic Reference	Mann, Douglas L; Givertz, Michael M; Vader, Justin M; Starling, Randall C; Shah, Palak; McNulty, Steven E; Anstrom, Kevin J; Margulies, Kenneth B; Kiernan, Michael S; Mahr, Claudius; Gupta, Divya; Redfield, Margaret M; Lala, Anuradha; Lewis, Gregory D; DeVore, Adam D; Desvigne-Nickens, Patrice; Hernandez, Adrian F; Braunwald, Eugene; Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial.; JAMA cardiology; 2022; vol. 7 (no. 1); 17-25

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with this study included in review	Mann 2020 - rationale and design paper
Trial name / registration number	Entresto [LCZ696] in Advanced Heart Failure [LIFE trial]; NCT02816736)
Study type	Randomised controlled trial (RCT)
Study location	USA - 38 centres
Study dates	Ennrollment began on March 2, 2017; because of the high risk for adverse outcomes associated with COVID-19 infection, trial enrollment was suspended on March 23, 2020.

Sources of funding	Novartis Pharmaceuticals Corporation provided the study drug and partial funding through the Investigator Initiated Trial (IIT) program (CLCZ696BUS04T).
Inclusion criteria	1. Advanced HFrEF defined as LVEF ≤35% documented during the preceding 12 months AND NYHA class IV symptomatology, defined as chronic dyspnea or fatigue at rest or on minimal exertion in the previous 3 months, or patients who require chronic inotropic therapy AND Minimum of 3 months GDMT for HF and/or intolerant to therapy 2. Systolic blood pressure ≥90 mm Hg 3. Serum NT-proBNP ≥800 pg/mL OR BNP ≥250 pg/mL (most recent—less than 3 months old) 4. Any one or more of the following objective findings of advanced HF including: a. Current inotropic therapy or use of inotropes in the past 6 months b. ≥1 hospitalization for heart failure in the past 6 months (not including the index hospitalization for inpatient participants) c. LVEF ≤25% (within the past 12 months) d. Peak VO2 <55% predicted or peak VO2 ≤16 mL/kg/min for men or ≤14 mL/kg/min for women (Respiratory Exchange Ratio [RER] ≥1.05) (within the past 12 months) e. 6 min walk test distance <300 m (within the past 3 months) 5. Age ≥18 years and ≤85 years 6. Signed Informed Consent form
Exclusion criteria	1. Currently taking sacubitril/valsartan 2. History of hypersensitivity or intolerance (unmodifiable) to Entresto, an ACEI or ARB as well as known or suspected contraindications (including hereditary angioedema) to the study drugs 3. Estimated glomerular filtration rate (eGFR) <20 mL/min/1.73m2 at baseline 4. Co-morbid conditions that may interfere with completing the study protocol (e.g., recent history of drug or alcohol abuse) or cause death within 1 year 5. Symptomatic hypotension at randomization or systolic blood pressure <90 mm Hg

	6. Serum potassium >5.5 mmol/L 7. Severe liver dysfunction (Childs-Pugh Class C) 8. Acute coronary syndrome within 4 weeks as defined by electrocardiographic (ECG) changes and biomarkers of myocardial necrosis (e.g., troponin) in an appropriate clinical setting (chest discomfort or anginal equivalent) 9. Planned or recent (≤4 weeks) PCI, coronary artery bypass grafting, or biventricular pacing 10. Currently hospitalised and listed status 1A, 1B or 1-4 for heart transplant 11. Current or scheduled for LVAD implantation within 30 days of study enrollment 12. Active infection (current use of oral or IV antimicrobial agents) 13. Primary hypertrophic or infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis or tamponade 14. Complex congenital heart disease 15. Concomitant use of aliskiren in patients with diabetes or renal impairment (eGFR <60 mL/min/1.73m²) 16. Known pregnancy or anticipated pregnancy within the next 6 months or breastfeeding mothers 17. Enrollment in any other investigational clinical trial within 30 days prior to screening 18. Inability to comply with study procedures
Recruitment / selection of participants	The study was composed of 3 phases: 1) a screening visit; 2) an open-label run-in period; and 3) a double-blind treatment phase (for patients who tolerated the run-in)
Intervention(s)	First dose of study drug as follows: For subjects not previously taking ACEI or ARB, previously taking ACEI or ARB at a low dose, or subjects who have an eGFR < 30 mL/min/1.73m², the starting dose of LCZ696 will be 50 mg po BID. For subjects taking an ARB at greater than low dose, the starting dose of LCZ696 will be 100 mg po BID.

	For subjects taking an ACEI at greater than low dose, the ACEI will be withheld for ≥ 36 hours prior to randomization. The starting dose of LCZ696 will be 100 mg po BID Dose adjustments performed every 2 weeks by doubling the dose up to the target maximum dose. The doses of LCZ696 are 50 mg (one 50 mg active and 1 placebo tablet), 100 mg (one 100 mg active and 1 placebo tablet) and 200 mg (two 100 mg active and 2 placebo tablets). These doses are equivalent to 24/26 mg, 49/51 mg, and 97/103 mg commercial Entresto™, respectively. The doses of valsartan are 40mg (one 40 mg active and 1 placebo tablet), 80 mg (one 80 mg active and 1 placebo tablet), and 160 mg (two 80 mg active and 2 placebo tablets). The criteria for doubling the dose will be based on systolic blood pressure (a SBP > 90 mmHg is required for up titration), changes in renal function (maximum serum creatinine of 2.0 mg/dL), and the absence of symptoms of hypotension. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose. Median total daily dose was 178.4 mg (IQR, 100.0-331.3 mg); 48% of the target dose
Comparator	First dose of study drug as follows: For subjects not previously taking ACEI or ARB, previously taking ACEI or ARB at a low dose, or subjects who have an eGFR < 30 mL/min/1.73m², the starting dose of valsartan will be 40 mg po BID and the starting dose of LCZ696 will be 50 mg po BID. For subjects taking an ARB at greater than low dose, the starting dose of valsartan will be 80 mg po BID and the starting dose of LCZ696 will be 100 mg po BID. For subjects taking an ACEI at greater than low dose, the ACEI will be withheld for ≥ 36 hours prior to randomization. The starting dose of valsartan will be 80 mg po BID and the starting dose of LCZ696 will be 100 mg po BID Dose adjustments performed every 2 weeks by doubling the dose up to the target maximum dose. The doses of valsartan are 40mg (one 40 mg active and 1 placebo tablet), 80 mg (one 80 mg active and 1 placebo tablet), and 160 mg (two 80 mg active and 2 placebo tablets). The criteria for doubling the dose will be based on systolic blood pressure (a SBP > 90 mmHg is required for up titration), changes in renal function (maximum serum creatinine of 2.0 mg/dL), and the absence of symptoms of hypotension. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose.

	Median total daily dose was 138.6 mg (IQR, 80.9-263.7); 48% of the target dose
Population subgroups	None for protocol outcomes
Number of participants	335 Due to the COVID-19 pandemic the data analysis plan for the LIFE trial was changed so that the primary analyses includes only those patients who were randomized on December 7, 2019, or earlier (n = 335). Additionally, any study visits performed after March 1, 2020, were excluded from the primary analyses if the patients and were randomized on or prior to December 7, 2019.
Duration of follow-up	24 weeks The study drug was discontinued in 49 patients (29%) receiving sacubitril/valsartan and 36 patients (21%) receiving valsartan (*P* = .10).
Method of analysis	ITT analysis

Study arms

ARNI (sacubitril valsartan) + placebo (N = 167)

Orally twice per day titrated to target dose of 97 mg/103 mg twice per day Background treatment: BB (73%); MRA (62%)

ARB (valsartan) + placebo (N = 168)

Orally twice per day titrated to target dose of 160 mg twice per day Background treatment: BB (83%); MRA (52%)

Characteristics

Arm-level characteristics

Characteristic	ARNI (sacubitril valsartan) + placebo (N = 167)	ARB (valsartan) + placebo (N = 168)
% Female Sample size	n = 47 ; % = 28	n = 43 ; % = 26
Age Mean (SD)	60.2 (13.4)	58.3 (13.1)
Black Sample size	n = 64 ; % = 38	n = 63 ; % = 38
White Sample size	n = 98 ; % = 59	n = 103 ; % = 61
Other Sample size	n = 5 ; % = 3	n = 2 ; % = 1
NYHA Class I Sample size	n = 3 ; % = 2	n = 5 ; % = 3
NYHA Class II Sample size	n = 38 ; % = 23	n = 37 ; % = 22
NYHA Class III Sample size	n = 67 ; % = 40	n = 70 ; % = 42

Characteristic	ARNI (sacubitril valsartan) + placebo (N = 167)	ARB (valsartan) + placebo (N = 168)
NYHA class IV Sample size	n = 59 ; % = 35	n = 55 ; % = 33
Ischaemic Sample size	n = 140 ; % = 84	n = 121 ; % = 72
LVEF (%) Mean (SD)	19.9 (6.2)	20.9 (6.8)
Type 2 diabetes 'Diabetes' Sample size	n = 74 ; % = 44	n = 83 ; % = 49
Atrial fibrillation Sample size	n = 72 ; % = 43	n = 80 ; % = 48
1+ Sample size	n = 65 ; % = 39	n = 67 ; % = 40
≤2 Sample size	n = 39 ; % = 23	n = 35 ; % = 21
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	63.2 (24.3)	65.7 (25.9)

Characteristic	ARNI (sacubitril valsartan) + placebo (N = 167)	ARB (valsartan) + placebo (N = 168)
Loop diuretics Sample size	n = 157 ; % = 94	n = 155 ; % = 92
Beta-blocker Sample size	n = 122 ; % = 73	n = 140 ; % = 83
Aldosterone antagonist Sample size	n = 103 ; % = 62	n = 87 ; % = 52
Digoxin Sample size	n = 37 ; % = 22	n = 30 ; % = 18
Hydralazine and nitrates Sample size	n = 17 ; % = 10	n = 14 ; % = 8
Device therapy ICD or CRT-D Sample size	n = 110 ; % = 66	n = 107 ; % = 64

Outcomes

Study timepoints

24 week

Dichotomous outcomes

Outcome	ARNI (sacubitril valsartan) + placebo, 24 week, N = 167	ARB (valsartan) + placebo, 24 week, N = 168
All-cause mortality No of events	n = 13 ; % = 8	n = 8 ; % = 5
CV mortality No of events	n = 11 ; % = 7	n = 7 ; % = 4
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) No of events	n = 44 ; % = 26	n = 36 ; % = 21
Hyperkalaemia (potassium level >=5.5 mEq/L) No of events	n = 28 ; % = 17	n = 15 ; % = 9

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

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

Hyperkalaemia (potassium level >=5.5 mEq/L) - Polarity - Lower values are better

Hazard ratios

Outcome	ARNI (sacubitril valsartan) + placebo vs ARB (valsartan) + placebo, 24 week, N2 = 168, N1 = 168
All-cause mortality	1.63 (0.68 to 3.94)

Outcome	ARNI (sacubitril valsartan) + placebo vs ARB (valsartan) + placebo, 24 week, N2 = 168, N1 = 168
Hazard ratio/95% CI	
CV mortality Hazard ratio/95% CI	1.58 (0.61 to 4.07)
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) Hazard ratio/95% CI	1.24 (0.8 to 1.93)

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

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

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

All-cause mortality - dichotomous - 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: not TTE outcome as specified in the protocol; intervention indirectness: only 78% had combination therapy)*

CV mortality - dichotomous - 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: not TTE outcome as specified in the protocol; intervention indirectness: only 78% had combination therapy)*

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF) - dichotomous - 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: not TTE outcome as specified in the protocol; intervention indirectness: only 78% had combination therapy)*

All-cause mortality - HR- 24 weeks

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

CV mortality - HR- 24 weeks

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

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF) - HR - 24 weeks

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

Hyperkalaemia (potassium level >=5.5 mEq/L) - 24 weeks

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

Mann, 2020

Bibliographic Reference	Mann, Douglas L; Greene, Stephen J; Givertz, Michael M; Vader, Justin M; Starling, Randall C; Ambrosy, Andrew P; Shah, Palak; McNulty, Steven E; Mahr, Claudius; Gupta, Divya; Redfield, Margaret M; Lala, Anuradha; Lewis, Gregory D; Mohammed, Selma F; Gilotra, Nisha A; DeVore, Adam D; Gorodeski, Eiran Z; Desvigne-Nickens, Patrice; Hernandez, Adrian F; Braunwald, Eugene; Sacubitril/Valsartan in Advanced Heart Failure With Reduced Ejection Fraction: Rationale and Design of the LIFE Trial.; JACC. Heart failure; 2020; vol. 8 (no. 10); 789-799

Study details

Secondary publication of another included study – see primary study for details	Rationale and design paper for LIFE trial See Mann 2022 for **Study details**

McMurray, 2019

Bibliographic Reference	McMurray, John J V; DeMets, David L; Inzucchi, Silvio E; Kober, Lars; Kosiborod, Mikhail N; Langkilde, Anna M; Martinez, Felipe A; Bengtsson, Olof; Ponikowski, Piotr; Sabatine, Marc S; Sjostrand, Mikaela; Solomon, Scott D; 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; 2019; vol. 21 (no. 5); 665-675

Study details

Secondary publication of another included	DAPA-HF trial design See McMurray 2019 for **Study details**.

study – see primary study for details	

McMurray, 2019

Bibliographic Reference	McMurray, John J V; DeMets, David L; Inzucchi, Silvio E; Kober, Lars; Kosiborod, Mikhail N; Langkilde, Anna Maria; Martinez, Felipe A; Bengtsson, Olof; Ponikowski, Piotr; Sabatine, Marc S; Sjostrand, Mikaela; Solomon, Scott D; The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics.; European journal of heart failure; 2019; vol. 21 (no. 11); 1402-1411

Study details

Secondary publication of another included study – see primary study for details	McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.

McMurray, 2023

Bibliographic Reference	McMurray, John J V; Docherty, Kieran F; de Boer, Rudolf A; Hammarstedt, Ann; Kitzman, Dalane W; Kosiborod, Mikhail N; Maria Langkilde, Anna; Reicher, Barry; Senni, Michele; Shah, Sanjiv J; Wilderang, Ulrica; Verma, Subodh; Solomon, Scott D;

Effect of Dapagliflozin Versus Placebo on Symptoms and 6-Minute Walk Distance in Patients With Heart Failure: The DETERMINE Randomized Clinical Trials.; Circulation; 2023

Study details

Secondary publication of another included study – see primary study for details	N/A
Trial name / registration number	DETERMINE-reduced NCT03877237
Study type	Randomised controlled trial (RCT)
Study location	Multi-centre study (international)
Study setting	Clinical setting
Study dates	First patient enrolled April 9, 2019; the last patient completed the last visit on March 7, 2020.
Sources of funding	Sponsored by AstraZeneca
Inclusion criteria	Men and women aged ≥18 years. Patients were also required to have a left ventricular ejection fraction (LVEF) ≤40%, an NT-proBNP (N-terminal prohormone of B-type natriuretic peptide) level ≥400 pg/mL (or ≥300 pg/mL if hospitalized for HF within the previous 12 months or ≥800 pg/mL if atrial fibrillation was present, irrespective of history of HF hospitalization
Exclusion criteria	Any condition that precludes exercise testing.

	Participation in a structured exercise training programme in the 1 month prior to screening or planned to start during the trial. Receiving therapy with an SGLT2 inhibitor within 4 weeks prior to randomisation or previous intolerance to an SGLT2 inhibitor. T1DM eGFR <25 mL/min/1.73 m2 (chronic kidney disease-epidemiology collaboration [CKD-EPI] formula) Systolic blood pressure (BP) <95 mmHg on 2 consecutive measurements at 5-minute intervals Systolic BP ≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments Current acute decompensated HF or hospitalisation due to decompensated HF <4 weeks prior to enrolment. Myocardial infarction, unstable angina, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial flutter/fibrillation, valve repair/replacement, implantation of a cardiac resynchronisation therapy device within 12 weeks prior to enrolment. Planned coronary revascularization, ablation of atrial flutter/fibrillation and/or valve repair/replacement. Stroke or transient ischemic attack within 12 weeks prior to enrolment. Probable alternative or concomitant diagnoses which in the opinion of the Investigator could account for the patient's HF symptoms and signs (eg, anaemia, hypothyroidism). Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronisation therapy. Prior implantation of a ventricular assistance device or similar device, or implantation expected after randomisation. HF due to any of the following: known infiltrative cardiomyopathy (eg, amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, or uncorrected primary valvular disease.

	A life expectancy of <2 years due to any non-cardiovascular condition, based on Investigator's clinical judgement. Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin). Acute or chronic liver disease with severe impairment of liver function Women of child-bearing potential (ie, those who are not chemically or surgically sterilised or post-menopausal): (a) Who are not willing to use a medically accepted method of contraception considered reliable in the judgment of the Investigator, OR (b) Who have a positive urine pregnancy test OR (c) Who are breast-feeding.
Recruitment / selection of participants	Patients recruited from sites involved in routine cardiology clinical practice.
Intervention(s)	SGLT2i (dapaglifloxin) N=156 10mg once daily Background therapy: ACEI 35.9%, ARB 23.7%, ARNI 35.3%, BB 92.9%, MRA 57.1%
Comparator	Placebo N=157 Background therapy: ACEI 29.9%, ARB 26.8%, ARNI 36.9%, BB 98.1%, MRA 59.9%
Number of participants	313 randomised
Duration of follow-up	16 weeks

Additional comments	Assumed intention to treat (based on n that were randomised)

Study arms

SGLT2i (dapaglifloxin) (N = 156)

10mg once daily Background therapy: ACEI 35.9%, ARB 23.7%, ARNI 35.3%, BB 92.9%, MRA 57.1% Note ACEI/ARB>50%

Placebo (N = 157)

Background therapy: ACEI 29.9%, ARB 26.8%, ARNI 36.9%, BB 98.1%, MRA 59.9% Note ACEI/ARB>50%

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (dapaglifloxin) (N = 156)	Placebo (N = 157)
% Female Sample size	n = 45 ; % = 28.8	n = 35 ; % = 22.3
Age Median (IQR)	69 (62 to 76)	69 (60 to 76)
Ethnicity - white Sample size	n = 100 ; % = 64.1	n = 98 ; % = 62.4

Characteristic	SGLT2i (dapaglifloxin) (N = 156)	Placebo (N = 157)
Ethnicity - Black Sample size	n = 25 ; % = 16	n = 22 ; % = 14
Ethnicity - Other Sample size	n = 31 ; % = 19.9	n = 37 ; % = 23.6
NYHA class - II NYHA Sample size	n = 130 ; % = 83.3	n = 125 ; % = 79.6
NYHA class - III NYHA Sample size	n = 25 ; % = 16	n = 32 ; % = 20.4
NYHA class - IV NYHA Sample size	n = 1 ; % = 0.6	n = 0 ; % = 0
LVEF Median (IQR)	30 (24 to 35)	29 (23 to 35)
Type 2 diabetes Sample size	n = 72 ; % = 46.2	n = 73 ; % = 46.5
Atrial fibrillation Sample size	n = 55 ; % = 35.3	n = 62 ; % = 39.5
Background (non-randomised) heart failure medications - ACEI	n = 56 ; % = 35.9	n = 47 ; % = 29.9

Characteristic	SGLT2i (dapaglifloxin) (N = 156)	Placebo (N = 157)
Sample size		
Background (non-randomised) heart failure medications - ARB Sample size	n = 37 ; % = 23.7	n = 42 ; % = 26.8
Background (non-randomised) heart failure medications - ARNI Sample size	n = 55 ; % = 35.3	n = 58 ; % = 36.9
Background (non-randomised) heart failure medications - Beta-blocker Sample size	n = 145 ; % = 92.9	n = 154 ; % = 98.1
Background (non-randomised) heart failure medications - MRA Sample size	n = 89 ; % = 57.1	n = 94 ; % = 59.9
Background (non-randomised) heart failure medications - ACEI/ARB Sample size	n = 93 ; % = 59.6	n = 87 ; % = 55.4
Device therapy cardiac resynchronization therapy Sample size	n = 20 ; % = 12.8	n = 26 ; % = 16.6

Outcomes

Study timepoints

16 week

Dichotomous outcomes

Outcome	SGLT2i (dapaglifloxin), 16 week, N = 156	Placebo, 16 week, N = 157
All-cause mortality No of events	n = 3 ; % = 1.9	n = 2 ; % = 1.3
Withdrawal due to drug-related adverse events (adverse events leading to discontinuation of study drug) No of events	n = 9 ; % = 5.8	n = 12 ; % = 7.6

All-cause mortality - Polarity - Lower values are better

Withdrawal due to drug-related adverse events (adverse events leading to discontinuation of study drug) - Polarity - Lower values are better

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

All-cause mortality - No of events-FUP 16 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Mortality is not a pre-specified outcome in the paper)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Withdrawal due to drug-related adverse events (adverse events leading to discontinuation of study drug) - No of events-FUP 16 weeks

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

McMurray, 2003

Bibliographic Reference	McMurray, John J V; Ostergren, Jan; Swedberg, Karl; Granger, Christopher B; Held, Peter; Michelson, Eric L; Olofsson, Bertil; Yusuf, Salim; Pfeffer, Marc A; 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); 2003; vol. 362 (no. 9386); 767-71

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with this study included in review	Swedberg K, Pfeffer M, Granger C, et al, for the CHARM Programme Investigators. Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM)—rationale and design. J Card Fail 1999; 5: 276-82

	McMurray J, Östergren J, Pfeffer M, et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) Programme. Eur J Heart Fail 2003; 5: 261–70
Trial name / registration number	CHARM-added
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study - 618 centres in 26 countries
Study setting	NR
Study dates	Patients enrolled between March, 1999, and November, 1999.
Sources of funding	This study was supported by AstraZeneca R&D, Mölndal, Sweden.
Inclusion criteria	Patients were aged 18 years or older, had left ventricular ejection fraction 40% or lower measured within the past 6 months, New York Heart Association functional class II–IV (if class II, patients had to have admission to hospital for a cardiac reason in the previous 6 months), and treatment with an ACE inhibitor at a constant dose for 30 days or longer.
Exclusion criteria	Current serum-creatinine/> 265mmol/L (~>3 mg/dL); current serum-potassium >/5.5 mmol/L (/>5.5 mEq/L) or a history of marked ACE inhibitor-induced hyperkalemia resulting in either a serum potassium greater than or equal to 6.0t mmol/L (/>6.0 mEq/L) or a life-threatening adverse event; known bilateral renal artery stenosis; current symptomatic hypotension; persistent systolic or diastolic hypertension; stroke, acute myocardial infarction, or open heart surgery within the last 4 weeks; previous heart transplant or heart transplant expected to be performed within the next 6 months; presence of any noncardiac disease (eg, cancer) that is likely to significantly shorten life expectancy to less than 2 years
Recruitment / selection of participants	NR

Intervention(s)	Starting dose 4 or 8 mg once daily; dose was doubled every 2 weeks, as tolerated, to the target dose of 32 mg once daily from 6 weeks onwards. Background treatment: ACEI 100%, BB 55%, MRA 17.4%
Comparator	Matching placebo Background treatment: ACEI 99.8%, BB 55.9%, MRA 16.9%
Number of participants	2548
Duration of follow-up	Median 41 months
Method of analysis	ITT analysis

Study arms

ARB (Candesartan) (N = 1276)

Starting dose 4 or 8 mg once daily; dose was doubled every 2 weeks, as tolerated, to the target dose of 32 mg once daily from 6 weeks onwards
Background treatment: ACEI 100%, BB 55%, MRA 17.4%

Placebo (N = 1272)

Background treatment: ACEI 99.8%, BB 55.9%, MRA 16.9%

Characteristics

Arm-level characteristics

Characteristic	ARB (Candesartan) (N = 1276)	Placebo (N = 1272)
% Female Sample size	n = 270 ; % = 21.2	n = 272 ; % = 21.4
Age Mean (SD)	64 (10.7)	64.1 (11.3)
European Sample size	n = 1143 ; % = 89.6	n = 1164 ; % = 91.5
Black Sample size	n = 65 ; % = 5.1	n = 62 ; % = 4.9
Other Sample size	n = 68 ; % = 5.3	n = 46 ; % = 3.6
II Sample size	n = 312 ; % = 24.5	n = 302 ; % = 23.7
III Sample size	n = 931 ; % = 73	n = 925 ; % = 72.7

Characteristic	ARB (Candesartan) (N = 1276)	Placebo (N = 1272)
IV Sample size	n = 33 ; % = 2.6	n = 45 ; % = 3.5
Ischaemic Sample size	n = 794 ; % = 62.2	n = 796 ; % = 62.6
Idiopathic Sample size	n = 340 ; % = 26.6	n = 328 ; % = 25.8
Hypertensive Sample size	n = 87 ; % = 6.8	n = 79 ; % = 6.2
LVEF Mean (SD)	28 (7.5)	28 (7.5)
Type 2 diabetes Not specified if T1 or T2 Sample size	n = 376 ; % = 29.5	n = 382 ; % = 30
Atrial fibrillation Sample size	n = 346 ; % = 27.1	n = 341 ; % = 26.8
Previous heart failure hospitalisation Sample size	n = 975 ; % = 76.4	n = 990 ; % = 77.8

Characteristic	ARB (Candesartan) (N = 1276)	Placebo (N = 1272)
ACE-inhibitor Sample size	n = 1276 ; % = 100	n = 1270 ; % = 99.8
Diuretic Sample size	n = 1148 ; % = 90	n = 1146 ; % = 90.1
Beta-blocker Sample size	n = 702 ; % = 55	n = 711 ; % = 55.9
Spironolactone Sample size	n = 222 ; % = 17.4	n = 215 ; % = 16.9
Digoxin/digitalis glycoside Sample size	n = 735 ; % = 57.6	n = 753 ; % = 59.2
Calcium-antagonists Sample size	n = 123 ; % = 9.6	n = 144 ; % = 11.3
Other vasodilators Sample size	n = 444 ; % = 34.8	n = 492 ; % = 38.7
Oral anti-coagulant Sample size	n = 484 ; % = 37.9	n = 487 ; % = 38.3
Antiarrhythmic agent	n = 166 ; % = 13	n = 154 ; % = 12.1

Characteristic	ARB (Candesartan) (N = 1276)	Placebo (N = 1272)
Sample size		
Aspirin Sample size	n = 652 ; % = 51.1	n = 659 ; % = 51.8
Other antiplatelet agent Sample size	n = 40 ; % = 3.1	n = 45 ; % = 3.5
Lipid-lowering drug Sample size	n = 528 ; % = 41.4	n = 521 ; % = 41
Implantable cardioverter defibrillator Sample size	n = 47 ; % = 3.7	n = 53 ; % = 4.2

Outcomes

Study timepoints

41 month (median)

Dichotomous outcomes

Outcome	ARB (Candesartan), 41 month, N = 1276	Placebo, 41 month, N = 1272
All-cause mortality No of events	n = 377 ; % = 30	n = 412 ; % = 32
CV mortality all deaths classified as CV unless unequivocal non-CV cause established No of events	n = 302 ; % = 23.7	n = 347 ; % = 27.3
Unplanned hospitalisation or visits (HF-related) (admission to hospital necessitated by heart failure and primarily for its treatment) No of events	n = 309 ; % = 24.2	n = 356 ; % = 28
Withdrawal due to drug-related adverse events No of events	n = 309 ; % = 24.2	n = 233 ; % = 18.3
Hyperkalaemia (causing discontinuation) causing discontinuation No of events	n = 44 ; % = 3.4	n = 9 ; % = 0.7

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (admission to hospital necessitated by heart failure and primarily for its treatment) - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Hyperkalaemia (causing discontinuation) - Polarity - Lower values are better

Hazard ratios

Outcome	ARB (Candesartan) vs Placebo, 41 month, N2 = 1276, N1 = 1272
All-cause mortality Hazard ratio/95% CI	0.89 (0.77 to 1.02)
CV morality all deaths classified as CV unless unequivocal non-CV cause established Hazard ratio/95% CI	0.83 (0.71 to 0.97)
Unplanned hospitalisation or visits (HF-related) (admission to hospital necessitated by heart failure and primarily for its treatment) Hazard ratio/95% CI	0.83 (0.71 to 0.97)

All-cause mortality - Polarity - Lower values are better

CV morality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (admission to hospital necessitated by heart failure and primarily for its treatment) - Polarity - Lower values are better

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

All-cause mortality - dichotomous - 41 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

CV mortality - dichotomous - 41 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits (HF-related) (admission to hospital necessitated by heart failure and primarily for its treatment) - dichotomous - 41 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Withdrawal due to drug-related adverse events - dichotomous - 41 months

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

Hyperkalaemia (causing discontinuation) - 41 months

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

All-cause mortality - HR- 41 months

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

CV mortality - HR- 41 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits (HF-related) (admission to hospital necessitated by heart failure and primarily for its treatment) - HR - 41 months

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

McMurray, 2014

Bibliographic Reference	McMurray, John J V; Packer, Milton; Desai, Akshay S; Gong, Jianjian; Lefkowitz, Martin P; Rizkala, Adel R; Rouleau, Jean L; Shi, Victor C; Solomon, Scott D; Swedberg, Karl; Zile, Michael R; Angiotensin-neprilysin inhibition versus enalapril in heart failure.; The New England journal of medicine; 2014; vol. 371 (no. 11); 993-1004

Study details

Secondary publication of another included study – see primary study for details	NA

Other publications associated with this study included in review	McMurray 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 **ACE**I to Determine Impact on Global Mortality and morbidity in **Heart Failure** trial (PARADIGM-HF).European journal of **heart failure**; 2013; vol. 15 (no. 9); 1062-73. McMurray et al (2014). Baseline characteristics and treatment of patients in prospective comparison of **ARNI** with **ACE**I to determine impact on global mortality and morbidity in **heart failure** trial (PARADIGM-HF). European journal of **heart failure**; 2014; vol. 16 (no. 7); 817-25 Lewis 2017
Trial name / registration number	PARADIGM-HF
Study type	Randomised controlled trial (RCT)
Study location	Multi-centre study
Study setting	Multi-centre study
Study dates	From December 8, 2009, through November 23, 2012, a total of 10,521 patients at 1043 centers in 47 countries entered the run-in period.
Sources of funding	Novartis

Inclusion criteria	(i) age 18 years or older and able to give written informed consent; (ii) NYHA functional class II–IV; (iii) LVEF ≤ 35% (initially this was ≤ 40% but changed in a protocol amendment dated 15 December 2010); (iv) plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL) at the screening visit (Visit 1) or a BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) and a hospitalization for heart failure within the last 12 months; (v) treatment with a stable dose of an ACE inhibitor or an ARB equivalent to enalapril 10 mg/day (see Table 1) for at least 4 weeks before the screening visit; and (vi) treatment with a stable dose of a beta-blocker for at least 4 weeks prior to the screening visit, unless contraindicated or not tolerated.
Exclusion criteria	1. History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACE inhibitors (ACEIs), ARBs, or neprilysin inhibitors, as well as known or suspected contraindications to the study drugs. 2. Previous history of intolerance to recommended target doses of ACEIs or ARBs. 3. Known history of angioedema. 4. Requirement for treatment with both ACEIs and ARBs. 5. Current acute decompensated heart failure (exacerbation of chronic heart failure manifested by signs and symptoms that may require intravenous therapy). 6. Symptomatic hypotension and/or a systolic blood pressure ,100 mmHg at Visit 1 (screening) or ,95 mmHg at Visit 3 or at Visit 5 (randomization). 7. Estimated glomerular filtration rate (eGFR) ,30 mL/min/1.73 m2 at Visit 1 (screening), Visit 3 (end of enalapril run-in), or Visit 5 (end of LCZ696 run-in and randomization) or .35% decline in eGFR between Visit 1 and Visit 3 or between Visit 1 and Visit 5. 8. Serum potassium .5.2 mmol/L at Visit 1 (screening) or .5.4 mmol/L at Visit 3 or Visit 5 (randomization).

	9. Acute coronary syndrome, stroke, transient ischaemic attack, cardiac, carotid, or other major cardiovascular surgery, PCI, or carotid angioplasty within the 3 months prior to Visit 1. 10. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1. 11. Implantation of a CRT device within 3 months prior Visit 1 or intent to implant a CRT. 12. History of heart transplant or on a transplant list or with LV assistance device. 13. History of severe pulmonary disease. 14. Diagnosis of peripartum- or chemotherapy-induced cardiomyopathy within the 12 months prior to Visit 1. 15. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1. 16. Symptomatic bradycardia or second- or third-degree atrioventricular block without a pacemaker. 17. Presence of haemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to LV dilatation. 18. Presence of other haemodynamically significant obstructive lesions of the LV outflow tract, including aortic and subaortic stenosis. 19. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including, but not limited to, any of the following: History of active inflammatory bowel disease during the 12 months before Visit 1. Active duodenal or gastric ulcers during the 3 months prior to Visit 1. Evidence of hepatic disease as determined by any one of the following: aspartate aminotransferase or alanine aminotransferase values exceeding 2× upper limit of normal at Visit 1, history of hepatic encephalopathy, history of oesophageal varices, or history of porto-caval shunt. Current treatment with cholestyramine or colestipol resins. 20. Presence of any other disease with a life expectancy of ,5 years.
Recruitment / selection of participants	A total of 10,521 patients at 1043 centers in 47 countries entered the run-in period. Of these patients, 2079 did not fulfill the criteria for randomization, and 43 patients underwent randomization erroneously or were enrolled at sites that were closed

	owing to serious Good Clinical Practice violations; these patients were prospectively omitted from all analyses before the end of the trial. Accordingly, 4187 patients were randomly assigned to receive Sacubril/valsartan and 4212 to receive enalapril. After screening there was a 2 stage run-in period prior to randomisation: **Enalapril active run-in period (Visit 2)** At Visit 2, most eligible patients started 2 weeks of single-blind treatment with enalapril 10 mg twice daily. A lower dose of enalapril (5 mg twice daily.) was allowed for patients currently treated with an ARB and for those taking a low dose of ACE inhibitor if the investigator was concerned that switching directly to enalapril 10 mg twice daily. might not be tolerated (e.g. because of hypotension, renal dysfunction, and/or hyperkalaemia). These patients were up-titrated to enalapril 10 mg twice daily. after 1–2 weeks. Patients tolerating enalapril 10 mg twice daily. as defined by specific criteria (available in paper) were eligible for Visit 3. **Sacubitril/valsartan active run-in period (Visits 3 and 4)** At Visit 3, patients started single-blind treatment with Sacubitril/valsartan 100 mg twice daily. After 1–2 weeks, the dose was up-titrated to 200 mg twice daily, for a further 2–4 weeks. Other heart failure medication (except for an ACE inhibitor or ARB) was continued during the run-in periods. Patients tolerating both enalapril 10 mg twice daily and Sacubitril/valsartan 200 mg twice went on to randomisation.
Intervention(s)	ARNI (Sacubitril/valsartan) N=4187 Also known as LCZ696, 200mg twice daily.

	Concomitant treatment: Beta-blocker 93.1% MRA 54.2%
Comparator	ACEI (Enalapril) N=4212 10mg twice daily Concomitant treatment: Beta-blocker 92.9% MRA 57.0%
Population subgroups	Age: <75y and ≥75y Ethnicity: White /Black /Asian/ Native American/ Other Renal function: Estimated GFR <60 ml/min/1.73 m2 and ≥60 ml/min/1.73 m2 T2DM: presence or absence (not relevant to this intervention?) Above available for CV mortality but only graphically so not extracted (Fig 3)
Number of participants	8339 successfully randomised and allocated treatment.

Duration of follow-up	Median duration of follow-up was 27 months
Indirectness	
Additional comments	Intention-to-treat analysis

Study arms

ARNI (Sacubitril/valsartan) (N = 4187)

Also known as LCZ696, 200mg twice daily. Concomitant treatment: Beta-blocker 93.1% MRA 54.2%

ACEI (Enalapril) (N = 4212)

10mg twice daily Concomitant treatment: Beta-blocker 92.9% MRA 57.0%

Characteristics

Arm-level characteristics

Characteristic	ARNI (Sacubitril/valsartan) (N = 4187)	ACEI (Enalapril) (N = 4212)
% Female Sample size	n = 879 ; % = 21	n = 953 ; % = 22.6
Age (years)	63.8 (11.5)	63.8 (11.3)

Characteristic	ARNI (Sacubitril/valsartan) (N = 4187)	ACEI (Enalapril) (N = 4212)
Mean (SD)		
White Sample size	n = 2763 ; % = 66	n = 2781 ; % = 66
Black Sample size	n = 213 ; % = 5.1	n = 215 ; % = 5.1
Asian Sample size	n = 759 ; % = 18.1	n = 750 ; % = 17.8
Other Sample size	n = 452 ; % = 10.8	n = 466 ; % = 11.1
NYHA Class I Sample size	n = 180 ; % = 4.3	n = 209 ; % = 5
NYHA Class II Sample size	n = 2998 ; % = 71.6	n = 2921 ; % = 69.3
NYHA Class III Sample size	n = 969 ; % = 23.1	n = 1049 ; % = 24.9
NYHA class IV Sample size	n = 33 ; % = 0.8	n = 27 ; % = 0.6

Characteristic	ARNI (Sacubitril/valsartan) (N = 4187)	ACEI (Enalapril) (N = 4212)
Missing data Sample size	n = 7 ; % = 0.2	n = 6 ; % = 0.1
Ischemic cardiomyopathy Sample size	n = 2506 ; % = 59.9	n = 2530 ; % = 60.1
LVEF (%) Mean (SD)	29.6 (6.1)	29.4 (6.3)
Type 2 diabetes Sample size	n = 1451 ; % = 34.7	n = 1456 ; % = 34.6
Atrial fibrillation Sample size	n = 1517 ; % = 36.2	n = 1574 ; % = 37.4
Previous heart failure hospitalisation Hospitalisation for HF Sample size	n = 2607 ; % = 62.3	n = 2667 ; % = 63.3
Diuretic Sample size	n = 3363 ; % = 80.3	n = 3375 ; % = 80.1
Digitalis Sample size	n = 1223 ; % = 29.2	n = 1316 ; % = 31.2

Characteristic	ARNI (Sacubitril/valsartan) (N = 4187)	ACEI (Enalapril) (N = 4212)
Beta-blocker Sample size	n = 3899 ; % = 93.1	n = 3912 ; % = 92.9
MRA Sample size	n = 2271 ; % = 54.2	n = 2400 ; % = 57
Implantable cardioverter defibrillator Sample size	n = 623 ; % = 14.9	n = 620 ; % = 14.7
Cardiac resynchronization therapy Sample size	n = 292 ; % = 7	n = 282 ; % = 6.7

Outcomes

Study timepoints

27 month (Median FUP 27 months)

8 month (For QoL only)

Contrast outcomes

Outcome	ARNI (Sacubitril/valsartan) vs ACEI (Enalapril), 27 month, N2 = 4187, N1 = 4212	ARNI (Sacubitril/valsartan) vs ACEI (Enalapril), 8 month, N2 = NR, N1 = NR
CV mortality	0.8 (0.71 to 0.89)	NR

Outcome	ARNI (Sacubitril/valsartan) vs ACEI (Enalapril), 27 month, N2 = 4187, N1 = 4212	ARNI (Sacubitril/valsartan) vs ACEI (Enalapril), 8 month, N2 = NR, N1 = NR
Hazard ratio/95% CI		
Unplanned hospitalisation or visits (HF-related) (first hospitalisation for worsening HF) Hazard ratio/95% CI	0.79 (0.71 to 0.89)	NR
All-cause mortality Hazard ratio/95% CI	0.84 (0.76 to 0.93)	NR
Health-related quality of life (KCCQ clinical summary score) range 0-100, change score Hazard ratio/95% CI	NR	1.64 (0.63 to 2.65)

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (first hospitalisation for worsening HF) - Polarity - Lower values are better

All-cause mortality - Polarity - Lower values are better

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons. Extracted HR for KCCQ-CSS for now but arm-based data likely to be better.

Continuous outcomes

Outcome	ARNI (Sacubitril/valsartan), 27 month, N = NR	ARNI (Sacubitril/valsartan), 8 month, N = 4187	ACEI (Enalapril), 27 month, N = NR	ACEI (Enalapril), 8 month, N = 4212
Health-related quality of life (KCCQ clinical summary score) range 0-100, change score Mean (SE)	NR	-2.99 (0.36)	NR	-4.63 (0.36)

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

Dichotomous outcomes

Outcome	ARNI (Sacubitril/valsartan), 27 month, N = 4187	ACEI (Enalapril), 27 month, N = 4212
All-cause mortality No of events	n = 711 ; % = 17	n = 835 ; % = 19.8
CV mortality No of events	n = 558 ; % = 13.3	n = 693 ; % = 16.5
Unplanned hospitalisation or visits (HF-related) (first hospitalization for worsening heart failure) No of events	n = 537 ; % = 12.8	n = 658 ; % = 15.6
Hyperkalaemia (serum potassium concentration>5.5 mmol/l) Calculated by adding event data for >5.5nmol/l and >6 nmol/l since both categories meet the criteria in the protocol No of events	n = 855 ; % = 20.4	n = 963 ; % = 22.9

Outcome	ARNI (Sacubitril/valsartan), 27 month, N = 4187	ACEI (Enalapril), 27 month, N = 4212
Withdrawal due to drug-related adverse events No of events	n = 448 ; % = 10.7	n = 518 ; % = 12.3
Acute kidney injury (renal failure acute) n= 4203/4229 No of events	n = 95 ; % = 2.26	n = 93 ; % = 2.23
Falls (symptomatic hypotension as a surrogate) No of events	n = 588 ; % = 14	n = 388 ; % = 9.2

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (first hospitalization for worsening heart failure) - Polarity - Lower values are better

Hyperkalaemia (serum potassium concentration>5.5 mmol/liter) - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Acute kidney injury (renal failure acute) - Polarity - Lower values are better

Falls (symptomatic hypotension as a surrogate) - Polarity - Lower values are better

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

CV mortality - Hazard Ratio (median FUP 27 months)

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

Unplanned hospitalisation or visits (HF-related) (first hospitalisation for worsening HF)-Hazard Ratio at median FUP 27 months

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

All-cause mortality - Hazard Ratio at median FUP 27 months

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

Health-related quality of life (KCCQ clinical summary score) - Hazard Ratio at 8 months (new)

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Health-related quality of life (KCCQ clinical summary score) - arm based data at 8 months (change score)

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

Hyperkalaemia (serum potassium concentration >5.5mmol/liter)-arm based events-at median FUP 27 months

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

All-cause mortality - arm based events, median FUP 27 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

CV mortality - arm based events-median FUP 27 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits (HF related) (first hospitalization for worsening heart failure)-arm based events-median FUP 27 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Falls (symptomatic hypotension as a surrogate)- events -median FUP 27 mo

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

Withdrawal due to drug-related adverse events - events - FUP 27 mo

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

McMurray, 2014

Bibliographic Reference	McMurray, John J V; Packer, Milton; Desai, Akshay S; Gong, Jianjian; Lefkowitz, Martin; Rizkala, Adel R; Rouleau, Jean L; Shi, Victor C; Solomon, Scott D; Swedberg, Karl; Zile, Michael R; 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; 2014; vol. 16 (no. 7); 817-25

Study details

Secondary publication of another included study – see primary study for details	Baseline characteristics for PARADIGM-HF See main report for details: McMurray 2014
Other publications associated with this study included in review	Lewis 2017: quality of life outcomes

McMurray, 2013

Bibliographic Reference	McMurray, John J V; Packer, Milton; Desai, Akshay S; Gong, Jim; Lefkowitz, Martin P; Rizkala, Adel R; Rouleau, Jean; Shi, Victor C; Solomon, Scott D; Swedberg, Karl; Zile, Michael R; 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; 2013; vol. 15 (no. 9); 1062-73

Study details

Secondary publication of another included study – see primary study for details	Rationale and design of PARADIGM-HF See main report for details: McMurray 2014

McMurray, 2019

Bibliographic Reference	McMurray, John J V; Solomon, Scott D; Inzucchi, Silvio E; Kober, Lars; Kosiborod, Mikhail N; Martinez, Felipe A; Ponikowski, Piotr; Sabatine, Marc S; Anand, Inder S; Belohlavek, Jan; Bohm, Michael; Chiang, Chern-En; Chopra, Vijay K; de Boer, Rudolf A; Desai, Akshay S; Diez, Mirta; Drozdz, Jaroslaw; Dukat, Andrej; Ge, Junbo; Howlett, Jonathan G; Katova, Tzvetana; Kitakaze, Masafumi; Ljungman, Charlotta E A; Merkely, Bela; Nicolau, Jose C; O'Meara, Eileen; Petrie, Mark C; Vinh, Pham N; Schou, Morten; Tereshchenko, Sergey; Verma, Subodh; Held, Claes; DeMets, David L; Docherty, Kieran F; Jhund, Pardeep S; Bengtsson, Olof; Sjostrand, Mikaela; Langkilde, Anna-Maria; Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction.; The New England journal of medicine; 2019; vol. 381 (no. 21); 1995-2008

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with this study included in review	Trial design paper: McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD; DAPA-HF Committees and Investigators. 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). Eur J Heart Fail. 2019 May;21(5):665-675. doi: 10.1002/ejhf.1432. Epub 2019 Mar 21. PMID: 30895697; PMCID: PMC6607736.
Trial name / registration number	DAPA-HF NCT03036124
Study type	Randomised controlled trial (RCT)
Study location	20 countries
Study setting	NR
Study dates	February 15 2017 to August 17 2018
Sources of funding	AstraZeneca
Inclusion criteria	1. Provision of signed informed consent prior to any study specific procedures 2. Male or female, aged ≥18 years at the time of consent

	3. Established documented diagnosis of symptomatic HFrEF (New York Heart Association (NYHA) functional class II-IV), which has been present for at least 2 months and is optimally treated with pharmacological and/or device therapy, as indicated NB: Patients in which additional pharmacological or device therapy is contemplated, or should be considered, must not be enrolled until therapy has been optimized and is stable for ≥1 month. 4. Left ventricular ejection fraction (LVEF) ≤40% (echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI) within the last 12 months prior to enrolment (Visit 1): a) If there is more than one assessment of LVEF the value from the most recent measurement should be used in assessing eligibility. b) Patients undergoing coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), valve repair/replacement or implantation of a cardiac resynchronization therapy (CRT) device or any other surgical, device or pharmacological intervention (ie initiation of a beta-blocker) that might improve LVEF must have a measurement of LVEF at least 3 months after the intervention in order to be eligible. NB: Patients with known HFrEF but without a recent (≤12 months) assessment of left ventricular (LV) function will undergo a local echocardiogram at the time of enrolment. 5. N-terminal pro b-type natriuretic peptide (NT-proBNP) >600 pg/ml (or if hospitalised for heart failure within the previous 12 months, NT-proBNP ≥400 pg/ml) at enrolment (visit 1). If concomitant atrial fibrillation or atrial flutter at Visit 1, NT-proBNP must be ≥900 pg/ml (irrespective of history of heart failure hospitalisation) 6. Patients should receive background standard of care for HFrEF and be treated according to locally recognized guidelines with both drugs and devices, as appropriate. Guideline-recommended medications should be used at recommended doses unless contraindicated or not tolerated. Therapy should have been individually optimized and stable for ≥4 weeks (this does not apply to diuretics – see NB below) before visit 1 and include (unless contraindicated or not tolerated): a) an ACE inhibitor, or ARB or sacubitril/valsartan and b) a beta-blocker and c) if considered appropriate by the patient's treating physician; a mineralocorticoid receptor antagonist (MRA). NB: Most patients with heart failure require treatment with a diuretic to control sodium and water retention leading to volume overload. It is recognized that diuretic dosing may be titrated to symptoms, signs, weight and other information and may thus vary. Each patient should, however, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual. 7. eGFR ≥30 ml/min/1.73 m2 (CKD-EPI formula) at enrolment (visit 1)

Exclusion criteria	Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor
	Type 1 diabetes mellitus
	Symptomatic hypotension or systolic blood pressure < 95 mmHg at two out of three measurements either at Visit 1 or Visit 2
	Current acute decompensated HF or hospitalization due to decompensated HF < 4 weeks prior to enrolment
	Myocardial infarction, unstable angina, stroke or transient ischemic attack within 12 weeks prior to enrolment
	Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo any of these operations after randomization
	Implantation of a CRT device within 12 weeks prior to enrolment or intent to implant a CRT device
	Previous cardiac transplantation or implantation of a ventricular assistance device or similar device, or implantation expected after randomization
	HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, or uncorrected primary valvular disease
	Symptomatic bradycardia or second or third-degree heart block without a pacemaker
	Any condition outside the cardiovascular and renal disease area, such as but not limited to malignancy, with a life expectancy of < 2 years based on investigator's clinical judgement
	Active malignancy requiring treatment at the time of Visit 1(with the exception of successfully treated basal cell or treated squamous cell carcinoma)
	Hepatic impairment (aspartate transaminase or alanine transaminase > 3 × the ULN, or total bilirubin > 2 × ULN at time of enrolment). An isolated increase in bilirubin in patients with known Gilbert's syndrome is not a reason for exclusion
	Known blood-borne diseases representing a shipping/transportation biohazard
	Severe (eGFR < 30 mL/min/1.73 m2 by CKD-EPI equation), unstable or rapidly progressing renal disease at the time of randomization

	Women of child-bearing potential (i.e. those who are not chemically or surgically sterilised or who are not post-menopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgement of the investigator, from the time of signing the informed consent throughout the study and 4 weeks thereafter, or women who have a positive pregnancy test at enrolment or randomization, or women who are breast-feeding Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site) Previous randomization in the present study Participation in another clinical study with an IP during the last month prior to enrolment Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up, or any conditions that, in the opinion of the investigator, may render the patient unable to complete the study
Recruitment / selection of participants	NR
Intervention(s)	SGLT2i (dapagliflozin); Patients 10mg once daily dapagliflozin in addition to recommended therapy Concomitant treatment: Beta-blocker (96.0%), ACEI (56.1%), ARB (28.4%), Sacubitril-valsartan (10.5%), MRA (71.5%)
Comparator	Placebo; Patients received once daily matched placebo in addition to recommended therapy Concomitant treatment:

	Beta-blocker (96.2%), ACEI (56.1%), ARB (26.7%), Sacubitril-valsartan (10.9%), MRA (70.6%)
Population subgroups	
Number of participants	4744
Duration of follow-up	Median 18.2 months
Indirectness	NA
Additional comments	Intention-to-treat

Study arms

SGLT2i (dapagliflozin) (N = 2373)

Patients received 10 mg dapagliflozin daily in addition to recommended therapy. Patients also received Beta-blocker (96.0%), ACEI (56.1%), ARB (28.4%), Sacubitril-valsartan (10.5%), MRA (71.5%)

Placebo (N = 2371)

Patients received daily placebo in addition to recommended therapy Patients also received Beta-blocker (96.2%), ACEI (56.1%), ARB (26.7%), Sacubitril-valsartan (10.9%), MRA (70.6%)

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (dapagliflozin) (N = 2373)	Placebo (N = 2371)
% Female Sample size	n = 564 ; % = 23.8	n = 545 ; % = 23
Age (Years (mean, SD)) Mean (SD)	66.2 (11)	66.5 (10.8)
Ethnicity Sample size	n = NA	n = NA
White Sample size	n = 1662 ; % = 70	n = 1671 ; % = 70.5
Black Sample size	n = 122 ; % = 5.1	n = 104 ; % = 4.4
Asian Sample size	n = 552 ; % = 23.3	n = 564 ; % = 23.8
Other Sample size	n = 37 ; % = 1.6	n = 32 ; % = 1.3
NYHA class Sample size	n = NA	n = NA

Characteristic	SGLT2i (dapagliflozin) (N = 2373)	Placebo (N = 2371)
Class II Sample size	n = 1606 ; % = 67.7	n = 1597 ; % = 67.4
Class III Sample size	n = 747 ; % = 31.5	n = 751 ; % = 31.7
Class IV Sample size	n = 20 ; % = 0.8	n = 23 ; % = 1
Heart failure aetiology Sample size	n = NA	n = NA
Ischaemic Sample size	n = 1316 ; % = 55.5	n = 1358 ; % = 57.3
Non-ischaemic Sample size	n = 857 ; % = 36.1	n = 830 ; % = 35
Unknown Sample size	n = 200 ; % = 8.4	n = 183 ; % = 7.7
LVEF (Percentage) Mean (SD)	31.2 (6.7)	30.9 (6.9)
Type 2 diabetes	n = 993 ; % = 41.8	n = 990 ; % = 41.8

Characteristic	SGLT2i (dapagliflozin) (N = 2373)	Placebo (N = 2371)
Sample size		
Atrial fibrillation Sample size	n = 916 ; % = 38.6	n = 902 ; % = 38
Previous heart failure hospitalisation Sample size	n = 1124 ; % = 47.4	n = 1127 ; % = 47.5
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	66 (19.6)	65.5 (19.3)
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
Diuretic Sample size	n = 2216 ; % = 93.4	n = 2217 ; % = 93.5
ACE inhibitor Sample size	n = 1332 ; % = 56.1	n = 1329 ; % = 56.1
ARB Sample size	n = 675 ; % = 28.4	n = 632 ; % = 26.7
Sacubitril-valsartan Sample size	n = 250 ; % = 10.5	n = 258 ; % = 10.9

Characteristic	SGLT2i (dapagliflozin) (N = 2373)	Placebo (N = 2371)
Beta-blocker Sample size	n = 2278 ; % = 96	n = 2280 ; % = 96.2
Mineralocorticoid receptor antagonist Sample size	n = 1696 ; % = 71.5	n = 1674 ; % = 70.6
Digitalis Sample size	n = 445 ; % = 18.8	n = 442 ; % = 18.6
Device therapy Sample size	n = NA	n = NA
Inplantable cardioverter-defibrillator Sample size	n = 622 ; % = 26.2	n = 620 ; % = 26.1
Cardiac resynchronisation therapy Sample size	n = 190 ; % = 8	n = 164 ; % = 6.9

Outcomes

Study timepoints

18.2 month

8 month (for KCCQ only)

Dichotomous outcomes

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = 2373	Placebo, 18.2 month, N = 2371
All-cause mortality No of events	n = 276 ; % = 11.6	n = 329 ; % = 13.9
All-cause mortality events/100 patient yr	7.9	9.5
CV mortality No of events	n = 227 ; % = 9.6	n = 273 ; % = 11.5
CV mortality events/100 patient yr	6.5	7.9
Unplanned hospitalisation or visits HF related (hospitalisation or an urgent visit for HF) No of events	n = 237 ; % = 10	n = 326 ; % = 13.7
Unplanned hospitalisation or visits HF related (hospitalisation or an urgent visit for HF) events/100 patient yr	7.1	10.1
Unplanned hospitalisation or visits HF related (hospitalisation for Hf)	n = 231 ; % = 9.7	n = 318 ; % = 13.4

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = 2373	Placebo, 18.2 month, N = 2371
No of events		
Unplanned hospitalisation or visits HF related (hospitalisation for Hf) events/100 patient yr	6.9	9.8
Acute kidney injury (undefined) No of events	n = 23 ; % = 1	n = 46 ; % = 1.9
Withdrawal due to drug-related adverse events In suppl material AE table, n=2368 for both arms No of events	n = 111 ; % = 4.7	n = 116 ; % = 4.9

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits HF related (hospitalisation or an urgent visit for HF) - Polarity - Lower values are better

Unplanned hospitalisation or visits HF related (hospitalisation for Hf) - Polarity - Lower values are better

Acute kidney injury (undefined) - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Hazard ratios

Outcome	SGLT2i (dapagliflozin) vs Placebo, 18.2 month, N2 = 2373, N1 = 2371
All-cause mortality Hazard ratio/95% CI	0.83 (0.71 to 0.97)
CV mortality Hazard ratio/95% CI	0.82 (0.69 to 0.98)
Unplanned hospitalisation or visits HF-related (hospitalisation or an urgent visit for HF) Hazard ratio/95% CI	0.7 (0.59 to 0.83)
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) Hazard ratio/95% CI	0.7 (0.59 to 0.83)

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits HF-related (hospitalisation or an urgent visit for HF) - Polarity - Lower values are better

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

Continuous outcomes

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = NR	SGLT2i (dapagliflozin), 8 month, N = 2373	Placebo, 18.2 month, N = NR	Placebo, 8 month, N = 2371
Health-related quality of life (KCCQ overall summary score) range 0-100, change score	NR	6.1 (18.6)	NR	3.3 (19.2)

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = NR	SGLT2i (dapagliflozin), 8 month, N = 2373	Placebo, 18.2 month, N = NR	Placebo, 8 month, N = 2371
Mean (SD)				

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

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

All-cause mortality - Hazard Ratio FUP median 18.2 months

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

All cause mortality - Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

All-cause mortality - Events/100 patient year-FUP 18.2 months

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

CV mortality - Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

CV mortality - Events/100 patient year-FUP 18.2 months

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

Unplanned hospitalisation or visits (HF related) (hospitalisation or an urgent visit for HF) - Events-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits (HF related) (hospitalisation or an urgent visit for HF) - Events/100 patient year-FUP 18.2 months

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

Unplanned hospitalisation or visits (HF related) (hospitalisation for HF) - Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits (HF related) (hospitalisation for HF) - Events/100 patient year-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Acute kidney injury (undefined) - Events-FUP 18.2 months

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

Withdrawal due to drug-related adverse events - Events-FUP 18.2 months

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

CV mortality - Hazard Ratio-FUP 18.2 months

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

Unplanned hospitalisation or visits (HF-related) (hospitalisation or an urgent visit for HF) - Hazard Ratio-FUP 18.2 months

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

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF) - Hazard Ratio-FUP 18.2 months

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

Health-related quality of life (KCCQ overall summary score) - Mean SD-change score at 8 months

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

Mebazaa, 2022

Bibliographic Reference	Mebazaa, Alexandre; Davison, Beth; Chioncel, Ovidiu; Cohen-Solal, Alain; Diaz, Rafael; Filippatos, Gerasimos; Metra, Marco; Ponikowski, Piotr; Sliwa, Karen; Voors, Adriaan A; Edwards, Christopher; Novosadova, Maria; Takagi, Koji; Damasceno, Albertino; Saidu, Hadiza; Gayat, Etienne; Pang, Peter S; Celutkiene, Jelena; Cotter, Gad; 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); 2022; vol. 400 (no. 10367); 1938-1952

Study details

Secondary publication of another included study – see primary study for details	Although this is the primary study report, results by LVEF (Pagnesi 2023) matching the review protocol were prioritised for analysis.
Other publications associated with this study included in review	Kimmoun 2019 - study rationale and design Cotter 2021 - amended study design Pagnesi 2023 - results by LVEF category
Trial name / registration number	STRONG-HF: NCT03412201.
Study type	Randomised controlled trial (RCT)
Study location	14 countries (Argentina, Austria, Bulgaria, Columbia, France, Hungary, Israel, Mozambique, Nigeria, Russia, Serbia, Slovakia, South Africa, and Tunisia).
Study setting	87 hospitals, with follow up after discharge

Study dates	Recruitment: May 10, 2018, and Sept 23, 2022 Follow-up ended: Oct 13, 2022 (study was stopped early per the data and safety monitoring board's recommendation because of greater than expected between-group differences)
Sources of funding	Roche Diagnostics
Inclusion criteria	1. Hospital admission within the 72 hours prior to screening for AHF with dyspnea at rest and pulmonary congestion on chest X-ray, and other signs and/or symptoms of HF. 2. All measures within 24 hours prior to randomization of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm. 3. All measures within 24 hours prior to randomization of serum potassium ≤ 5.0 mEq/L (mmol/L). 4. Biomarker criteria for persistent congestion: At screening, NT-proBNP > 2,500 pg/mL. At the time of randomisation (1-2 days prior to discharge), NT-proBNP > 1,500 pg/mL (to ensure the persistence of congestion) that has decreased by more than 10% compared to screening (to ensure the acuity of the index episode). 5. At 1 week prior to admission, at screening, and at visit 2 (just prior to randomization) either: a. half the recommended dose of ACEI/ARB/ARNI prescribed, no beta-blocker prescribed, and half the recommended dose of MRA prescribed; or b. no ACEI/ARB/ARNI prescribed, half the recommended dose of beta-blocker prescribed, and half the recommended dose of MRA prescribed.
Exclusion criteria	1. Age < 18 or > 85 years. 2. Clearly documented intolerance to high doses of beta-blockers. 3. Clearly documented intolerance to high doses of RAAS inhibitor (both ACEI /ARB).

	4. Mechanical ventilation (not including CPAP/BiPAP) in the 24 hours prior to screening. 5. Significant pulmonary disease contributing substantially to the patients' dyspnea such as FEV1< 1 liter or need for chronic systemic or non-systemic steroid therapy, or any kind of primary right HF such as primary pulmonary hypertension or recurrent pulmonary embolism. 6. Myocardial infarction, unstable angina or cardiac surgery within 3 months, or cardiac resynchronization therapy device implantation within 3 months, or percutaneous transluminal coronary intervention, within 1 month prior to screening. 7. Index event (admission for AHF) triggered primarily by a correctable aetiology such as significant arrhythmia (e.g., sustained ventricular tachycardia, or atrial fibrillation/flutter with sustained ventricular response >130 beats per minute, or bradycardia with sustained ventricular arrhythmia <45 beats per minute), infection, severe anaemia, acute coronary syndrome, pulmonary embolism, exacerbation of COPD, planned admission for device implantation or severe non-adherence leading to very significant fluid accumulation prior to admission and brisk diuresis after admission. Troponin elevations without other evidence of an acute coronary syndrome are not an exclusion. 8. Uncorrected thyroid disease, active myocarditis, or known amyloid or hypertrophic obstructive cardiomyopathy. 9. History of heart transplant or on a transplant list, or using or planned to be implanted with a ventricular assist device. 10. Sustained ventricular arrhythmia with syncopal episodes within the 3 months prior to screening that is untreated. 11. Presence at screening of any hemodynamically significant valvular stenosis or regurgitation, except mitral or tricuspid regurgitation secondary to left ventricular dilatation, or the presence of any hemodynamically significant obstructive lesion of the left ventricular outflow tract. 12. Active infection at any time during the AHF hospitalization prior to randomization based on abnormal temperature and elevated whole blood count or need for intravenous antibiotics. 13. Stroke or TIA within the 3 months prior to screening. 14. Primary liver disease considered to be life threatening. 15. Renal disease or eGFR < 30 mL/min/1.73m2 (as estimated by the simplified MDRD formula) at screening or history of dialysis. 16. Psychiatric or neurological disorder, cirrhosis, or active malignancy leading to a life expectancy < 6 months.

	17. Prior (defined as less than 30 days from screening) or current enrolment in a CHF trial or participation in an investigational drug or device study within the 30 days prior to screening. 18. Discharge for the AHF hospitalization anticipated to be > 14 days from admission, or to a long-term care facility. Randomization must occur within 12 days following admission and at 1-2 days prior to anticipated discharge. 19. Inability to comply with all study requirements, due to major co-morbidities, social or financial issues, or a history of noncompliance with medical regimens, that might compromise the patient's ability to understand and/or comply with the protocol instructions or follow-up procedures 20. Pregnant or nursing (lactating) women.
Recruitment / selection of participants	Screened patients admitted for acute heart failure who were not optimally treated with oral heart failure medications
Intervention(s)	Optimisation of oral heart failure therapies and frequent visits, including circulating NT-proBNP measures, to assess congestion. For patients in this group, the first dose adjustment occurred just after randomisation (within 2 days before anticipated hospital discharge), when patients were prescribed medical therapy with β blockers, renin-angiotensin blockers (ACE inhibitors [or ARBs if intolerant to ACE inhibitors] or ARN inhibitors), and mineralocorticoid receptor antagonists adjusted to at least half the optimal doses. Two weeks following randomisation, up-titration to full optimal doses of BBs, ACEI/ARB/ARNI, and MRA was performed given adequate safety. In haemodynamically stable patients, doses of all three classes of HF therapies were increased on the same day when possible, but dose adjustments could also span several days (e.g., BBs and MRA up-titrated on 1 day and ACEI (or ARB or ARNI) on the following day). At each visit more than 1 week following randomisation, if the patient was not on maximally tolerated doses of BBs and/or ACEI/ARBs/ARNI and it was deemed safe to further up-titrations were encouraged. Additional visits 1 week after any up-titration to assess safety and tolerability. By day 90, the following numbers of participants were up-titrated to full doses of each of the three oral heart failure medication classes (renin-angiotensin blockers 278 [55%] of 505; beta-blockers 249 [49%]; mineralocorticoid receptor antagonists 423 [84%]).

	SGLT-2 inhibitor use was only between Jan 25, 2021 and Oct 13, 2022; after approval and recommendation for heart failure). They were prescribed at day 90 in 48 (10%) of 505 patients in the high-intensity care group. Biomarker results and clinical assessments guide the safety of up-titrations of oral HF medications. Guidance for delaying up-titrations was follows: • ACEI/ARB/ARNI and/or MRAs not up-titrated if systolic blood pressure <95 mmHg, serum potassium >5.0 mmol/L, or eGFR <30 mL/min/1.73m2. • If eGFR alone is <30 mL/min/1.73m2, reduce the dose of diuretics, if those are deemed high or have been recently up-titrated. • BBs not up-titrated if heart rate <55 bpm or systolic blood pressure is <95 mmHg. If the NT-proBNP level is >10% higher than the pre-discharge level, physicians should consider not up-titrating BBs and consider increasing diuretics. • If GDF-15 >2500 pg/mL, consider correcting comorbidities, including diabetes or hypertension for instance, if needed.
Comparator	Follow-up schedule and medication management at the discretion of the treating physician according to local practice at the site. By day 90, the following numbers of participants were up-titrated to full doses of each of the three oral heart failure medication classes (renin-angiotensin blockers 11 [2%] of 497; β blockers 20 [4%]; mineralocorticoid receptor antagonists 231 [46%]). SGLT-2 inhibitor use was only between Jan 25, 2021 and Oct 13, 2022; after approval and recommendation for heart failure). They were prescribed at day 90 in 27 (5%) of 497 in the usual care group.
Population subgroups	LVEF categories for primary endpoint

Number of participants	1078
Duration of follow-up	180 days (average not stated) - 1017 completed 90-day visit; 860 completed 180-day visit
Indirectness	Population indirectness - acute heart failure and mixed LVEF (68% ≤40%)
Additional comments	Efficacy outcomes: ITT - analysed according to the arm to which they were assigned Safety outcomes analysis: any patient assigned to the high-intensity care arm who failed to attend at least one post-randomisation titration visit was included in the usual care arm

Study arms

High intensity care (N = 542)

The first dose adjustment occurred just after randomisation (within 2 days before anticipated hospital discharge), when patients were prescribed medical therapy with β blockers, renin-angiotensin blockers (ie, ACE inhibitors [or ARBs if intolerant to ACE inhibitors] or ARN inhibitors), and mineralocorticoid receptor antagonists adjusted to at least half the optimal doses. Doses were optimised at visit 4 (week 2)

Usual care (N = 536)

Follow up and therapy adjustments after discharge were according to the local practice.

Characteristics

Arm-level characteristics

Characteristic	High intensity care (N = 542)	Usual care (N = 536)
% Female Sample size	n = 216 ; % = 40	n = 200 ; % = 37
Age Mean (SD)	62.9 (13.5)	63 (13.7)
Black Sample size	n = 115 ; % = 21	n = 115 ; % = 21
White or Caucasian Sample size	n = 418 ; % = 77	n = 414 ; % = 77
Native American Sample size	n = 1 ; % = 0.002	n = 0 ; % = 0
Other Other reported races were African (n=2), Europiod (n=2), Latin American (n=1), Berber (n=1), Gipsy (n=1), and not specified (n=5). Sample size	n = 7 ; % = 1	n = 5 ; % = 1
Pacific Islander Sample size	n = 1 ; % = 0.002	n = 0 ; % = 0
NYHA I	n = 29 ; % = 6	n = 34 ; % = 7

Characteristic	High intensity care (N = 542)	Usual care (N = 536)
Sample size		
NYHA II Sample size	n = 147 ; % = 29	n = 160 ; % = 33
NYHA III Sample size	n = 216 ; % = 43	n = 199 ; % = 40
NYHA IV Sample size	n = 116 ; % = 23	n = 99 ; % = 20
Ischaemic Sample size	n = 260 ; % = 48	n = 254 ; % = 48
Non-ischaemic Sample size	n = 281 ; % = 52	n = 280 ; % = 52
LVEF Most recent value within 6 months before screening, including during the index hospitalisation Mean (SD)	36.7 (12.57)	35.9 (12.47)
</= 40 Sample size	n = 365 ; % = 67	n = 366 ; % = 68
Over 40%	n = 177 ; % = 33	n = 170 ; % = 32

Characteristic	High intensity care (N = 542)	Usual care (N = 536)
Sample size		
Type 2 diabetes 'Diabetes' Sample size	n = 152 ; % = 28	n = 161 ; % = 30
Atrial fibrillation History of atrial fibrillation or atrial flutter Sample size	n = 238 ; % = 44	n = 258 ; % = 48
Previous heart failure hospitalisation Hospitalised for heart failure in the past year Sample size	n = 140 ; % = 26	n = 133 ; % = 25
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	61.92 (19.92)	62.89 (21.83)
Cardiac resynchronisation therapy Sample size	n = 3 ; % = 1	n = 3 ; % = 1
Automatic internal cardiac defibrillator Sample size	n = 3 ; % = 1	n = 6 ; % = 1
History of heart failure Sample size	n = 465 ; % = 86	n = 451 ; % = 84

Outcomes

Study timepoints

Baseline

90 day

180 day

Dichotomous and continuous outcomes

Outcome	High intensity care, 90 day, N = 542	High intensity care, 180 day, N = 506	Usual care, 90 day, N = 536	Usual care, 180 day, N = 502
All-cause mortality No of events	-	n = 39 ; % = 8.5	-	n = 48 ; % = 10
CV mortality Kaplan-Meier estimated cumulative risks adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights are shown for each treatment group. No of events	-	n = 32 ; % = 6.9	-	n = 44 ; % = 9.3
Unplanned hospitalisation or visits (HF-related) (HF re-admission) No of events	-	n = 47 ; % = 9.5	-	n = 74 ; % = 17.1

Outcome	High intensity care, 90 day, N = 542	High intensity care, 180 day, N = 506	Usual care, 90 day, N = 536	Usual care, 180 day, N = 502
Health-related quality of life EQ-5D VAS) range -0.59 to 1, change score; baseline values not reported. Analysis includes n=461 from the high-intensity care group and n=454 the from usual care group Mean (SD)	10.72 (0.88)	-	-	7.22
Acute kidney injury (undefined) No of events	n = 3 ; % = 0.6	-	n = 0 ; % = 0	-
Hyperkalaemia (undefined) No of events	n = 18 ; % = 3.3	-	n = 0 ; % = 0	-
Falls (undefined) No of events	n = 1 ; % = 0.2	-	n = 0 ; % = 0	-

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (HF re-admission) - Polarity - Lower values are better

Health-related quality of life EQ-5D VAS) - Polarity - Higher values are better

Acute kidney injury (undefined) - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

Falls (undefined) - Polarity - Lower values are better

Between-group differences

Outcome	High intensity care vs Usual care, 90 day, N2 = 542, N1 = 536	High intensity care vs Usual care, 180 day, N2 = 506, N1 = 502
All-cause mortality Kaplan-Meier estimated cumulative risks adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights are shown for each treatment group Relative risk/95% CI	-	0.84 (0.56 to 1.26)
CV mortality Kaplan-Meier estimated cumulative risks adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights are shown for each treatment group Relative risk/95% CI	-	0.74 (0.47 to 1.16)
Unplanned hospitalisation or visits (HF-related) (HF re-admission) Kaplan-Meier estimated cumulative risks adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights are shown for each treatment group Relative risk/95% CI	-	0.56 (0.38 to 0.81)
Health-related quality of life EQ-5D VAS) range -0.59 to 1; change score. Statistics are estimated from an ANCOVA model with fixed terms for treatment, LVEF (≤40% vs >40%), geographical region, and baseline value. Treatment effect is the adjusted mean difference between treatment groups. Analysis includes n=461 from the high-intensity care group and n=454 the from usual care group Mean (95% CI)	3.49 (1.74 to 5.24)	-

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (HF re-admission) - Polarity - Lower values are better

Health-related quality of life EQ-5D VAS) - Polarity - Higher values are better

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

All-cause mortality - 180 days - dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and TTE reported as number of events)*

CV mortality - 180 days - dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and TTE reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (HF re-admission) - 180 days - dichotomous

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and TTE reported as number of events)*

Health-related quality of life (EQ-5D VAS) change from baseline to 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unblinded and subjective outcome; plus possible selection of outcome data from multiple scales)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: mixed LVEF)*

Acute kidney injury (undefined) - 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and outcome not defined)*

Hyperkalaemia (undefined) - 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and outcome not defined)*

Falls (undefined) - 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and outcome not defined)*

All-cause mortality - 180 days - HR

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: mixed LVEF)*

CV mortality - 180 days - HR

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and TTE reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (HF re-admission) - 180 days - HR

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness: mixed LVEF and TTE reported as number of events)*

Health-related quality of life (EQ-5D) - mean difference between groups - 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unblinded and subjective outcome; plus possible selection of outcome data from multiple scales)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: mixed LVEF)*

Nagele, 2024

Bibliographic Reference	Nagele, Matthias P; Haider, Thomas; Kreysing, Leonie; Barthelmes, Jens; Nebunu, Delia; Rossi, Valentina A; Hebeisen, Monika; Sudano, Isabella; Ruschitzka, Frank; Flammer, Andreas J; Vascular Endothelial Effects of Sacubitril/Valsartan in Heart Failure With Reduced Ejection Fraction: Randomized Controlled Trial.; JACC. Advances; 2024; vol. 3 (no. 12); 101392

Study details

Secondary publication of another included study – see primary study for details	NA
Trial name / registration number	VASCEND NCT03168568
Study location	Switzerland
Study setting	Cardiology clinic
Study dates	Recruitment between 2017 and 2020.
Sources of funding	The trial was funded by a grant from Novartis and the University of Zurich.
Inclusion criteria	Patients ≥18 years of age, diagnosis of symptomatic heart failure (NYHA functional class II-IV) per European Society of Cardiology heart failure guidelines, left ventricular ejection fraction ≤40% (any one measurement made within the past 12 months using echocardiography or MRI was acceptable), and established guideline-recommended therapy with an ACE-inhibitor, angiotensin receptor blocker, and a beta-blocker, as clinically indicated and tolerated, at stable doses for at least 3 weeks prior to inclusion

Exclusion criteria	history of angioedema, sitting systolic blood pressure <90 mm Hg at visit 1 (screening) or visit 2 (randomization), concurrent or planned treatment with valsartan/sacubitril, any ACEI, any angiotensin receptor blocker or renin inhibitor during the study period, current acute decompensated HF, estimated GFR <20 mL/min/1.73 m2 as measured by the Chronic Kidney Disease Epidemiology Collaboration formula at visit 1 (screening) or visit 2 (randomization), serum potassium >5.5 mmol/L at visit 1 (screening) or visit 2 (randomization), acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention or carotid angioplasty within the 3 months prior to visit 1, coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 3 months after visit 1, implantation of a cardiac resynchronization therapy device within 2 months prior visit 1 or intent to implant a cardiac resynchronization therapy device within next 3 months, history of heart transplant, on a transplant list or with ventricular assistance device, presence of any other disease with a life expectancy of <6 months, presence of significant endocrine diseases, including primary hyperparathyroidism, Cushing's disease, adrenal insufficiency, pituitary tumors, primary hyperaldosteronism, manifest hyperthyroidism or genetic endocrine disorders, presence of active acute infectious diseases, inability to follow the procedures of the study, lack of safe contraception, participation in another study with investigational drugs or device within the 30 days preceding and during the study, narrow-angle glaucoma, epilepsy, cimino-shunt on both arms.
Recruitment / selection of participants	Patients were recruited at the Clinic of Cardiology at the University Hospital Zurich between 2017 and 2020.
Intervention(s)	ARNI (sacubitril/valsartan) N=37 Dose uptitrated in 2-week intervals starting with 50 mg sacubitril/valsartan twice daily up to the target dose of 200 mg twice daily. Background therapy: ACEI 82.1%, ARB 17.9%, BB 97.4%, MRA 74.4%, SGLT2i 15.4%
Comparator	ARB (valsartan) N=35 Dose uptitrated in 2-week intervals starting with 40 mg valsartan twice daily up to the target dose of 160 mg twice daily.

	Background therapy: ACEI 61.5%, ARB 38.5%, BB 100%, MRA 76.9%, SGLT2i 7.7%
Number of participants	79 randomised
Duration of follow-up	3 months
Method of analysis	Modified ITT analysis
Additional comments	Analyses were carried out with the intention to treat principle. AE and mortality data in text (assumed out of total n randomised)

Study arms

ARNI (sacubitril/valsartan) (N = 40)

Dose uptitrated in 2-week intervals starting with 50 mg sacubitril/valsartan twice daily up to the target dose of 200 mg twice daily. Background therapy: BB 97.4%, MRA 74.4%, SGLT2i 15.4%

ARB (valsartan) (N = 39)

Dose uptitrated in 2-week intervals starting with 40 mg valsartan twice daily up to the target dose of 160 mg twice daily. Background therapy: BB 100%, MRA 76.9%, SGLT2i 7.7%

Characteristics

Arm-level characteristics

Characteristic	ARNI (sacubitril/valsartan) (N = 40)	ARB (valsartan) (N = 39)
% Female Sample size	n = 5 ; % = 12.8	n = 1 ; % = 2.6
Age Mean (SD)	60 (10)	59 (13)
NYHA class - II NYHA Sample size	n = 34 ; % = 87.2	n = 35 ; % = 89.7
NYHA class - III NYHA Sample size	n = 5 ; % = 12.8	n = 3 ; % = 7.7
NYHA class - IV NYHA Sample size	n = 0 ; % = 0	n = 1 ; % = 2.6
Heart failure aetiology - Ischemic HF Sample size	n = 28 ; % = 71.8	n = 25 ; % = 64.1
LVEF Mean (SD)	29 (8)	31 (6)
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	68 (19)	75 (19)
Background (non-randomised) heart failure medications - ACEI	n = 32 ; % = 82.1	n = 24 ; % = 61.5

Characteristic	ARNI (sacubitril/valsartan) (N = 40)	ARB (valsartan) (N = 39)
Sample size		
Background (non-randomised) heart failure medications - ARB Sample size	n = 7 ; % = 17.9	n = 15 ; % = 38.5
Background (non-randomised) heart failure medications - Bet ablocker Sample size	n = 38 ; % = 97.4	n = 39 ; % = 100
Background (non-randomised) heart failure medications - MRA Sample size	n = 29 ; % = 74.4	n = 30 ; % = 76.9
Background (non-randomised) heart failure medications - SGLT2i Sample size	n = 6 ; % = 15.4	n = 3 ; % = 7.7

Outcomes

Study timepoints

3 month

Dichotomous outcomes

Outcome	ARNI (sacubitril/valsartan), 3 month, N = 40	ARB (valsartan), 3 month, N = 39
All-cause mortality	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	ARNI (sacubitril/valsartan), 3 month, N = 40	ARB (valsartan), 3 month, N = 39
No of events		
Withdrawal due to drug-related adverse events No of events	n = 1 ; % = 2.5	n = 2 ; % = 5.1

All-cause mortality - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

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

All-cause mortality - No of events-FUP 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adverse events and mortality not pre-specified outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to drug-related adverse events - No of events-FUP 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adverse events and mortality not pre-specified outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Nassif, 2019

Bibliographic Reference	Nassif, Michael E; Windsor, Sheryl L; Tang, Fengming; Khariton, Yevgeniy; Husain, Mansoor; Inzucchi, Silvio E; McGuire, Darren K; Pitt, Bertram; Scirica, Benjamin M; Austin, Bethany; Drazner, Mark H; Fong, Michael W; Givertz, Michael M; Gordon, Robert A; Jermyn, Rita; Katz, Stuart D; Lamba, Sumant; Lanfear, David E; LaRue, Shane J; Lindenfeld, JoAnn; Malone, Michael; Margulies, Kenneth; Mentz, Robert J; Mutharasan, R Kannan; Pursley, Michael; Umpierrez, Guillermo; Kosiborod, Mikhail; Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial.; Circulation; 2019; vol. 140 (no. 18); 1463-1476

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with this study included in review	Nassif ME, Windsor SL, Gosch K, Borlaug BA, Husain M, Inzucchi SE, Kitzman DW, McGuire DK, Pitt B, Scirica BM, Shah SJ, Umpierrez G, Austin BA, Lamba S, Khumri T, Sharma K, Kosiborod MN. 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. Circ Heart Fail. 2023 Jul;16(7):e009837. doi: 10.1161/CIRCHEARTFAILURE.122.009837. Epub 2023 May 19. PMID: 37203441; PMCID: PMC10348645.
Trial name / registration number	DEFINE-HF / NCT02653482
Study type	Randomised controlled trial (RCT)

Study location	United States
Study setting	NR
Study dates	NR
Sources of funding	AstraZeneca Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Inclusion criteria	• Age > 18 and < 120 at the screening visit • Established diagnosis of heart failure (for at least 16 weeks prior to the screening visit) with reduced systolic function (LVEF≤40% due to either ischemic or nonischaemic aetiology) documented by an imaging modality (echocardiography, nuclear imaging, LV angiography, magnetic resonance imaging) within the past 24 months. Any local measurement of LVEF by any modality within the eligibility range made within the past 24 months is acceptable provided there has been no subsequent LVEF measurement above 40%. • No change in diuretic management for 1 week prior to screening visit or between the screening and randomization visit • NYHA class II or III heart failure symptoms at the screening and randomization visit • BNP ≥100 pg/mL and/or NT pro-BNP ≥ 400 pg/mL at the screening visit (For patients with permanent atrial fibrillation inclusion thresholds will be BNP ≥ 125 pg/mL or NTproBNP ≥ 600 pg/mL) • Ability to provide informed consent prior to initiating screening visit procedures
Exclusion criteria	• Decompensated heart failure (hospitalization for heart failure within the 30 days prior to screening or NYHA class IV heart failure symptoms at screening) • History of type 1 diabetes • Estimated glomerular filtration rate (eGFR) < 30 at the screening visit by modified MDRD equation GFR in mL/min per 1.73 m2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if patient is African American) x 0.742 (if female)

	• Admission for an acute coronary syndrome (ST-elevation MI, non-ST-elevation MI, or unstable angina), percutaneous coronary intervention, or cardiac surgery within 30 days prior to the screening visit. • Admission for cardiac resynchronization therapy (CRT) within 90 days prior to the screening visit • Planned cardiovascular revascularization (percutaneous intervention or surgical) or major cardiac surgery (coronary artery bypass grafting, valve replacement, ventricular assist device, cardiac transplantation, or any other surgery requiring thoracotomy) or CRT within the 90 days after the screening visit. 8 • Participation in any interventional clinical trial (with an investigational drug or device) that is not an observational registry within the 8 weeks prior to the screening visit. • History of hypersensitivity to dapagliflozin • For women of child-bearing potential: Current or planned pregnancy or currently lactating. • Women who are surgically sterile or those who are postmenopausal for at least 1 year are not considered to be of child-bearing potential. Women of child-bearing potential, who are sexually active, must agree to use a medically-accepted method of birth control for the duration of the study. Acceptable birth control methods include: (1) surgical sterilization (such as a hysterectomy or bilateral tubal ligation), (2) progesterone hormonal contraceptives (birth control pills or implants), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Women of child-bearing potential will have a urine pregnancy test at every clinic visit and it must be negative to continue study participation. • Life expectancy <1 year at the screening visit • Patients who are volume depleted based upon physical examination at the time of the screening or randomization visit • BNP <100 pg/mL and NT pro-BNP<400 pg/mL at the screening visit (For patients with permanent atrial fibrillation exclusion thresholds will be BNP<125 pg/mL and NT-proBNP<600 pg/mL) • Patients currently being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or having received treatment with any SGLT-2 inhibitor within the 12 weeks prior to the screening visit. • Average supine systolic BP <90 mmHg at the screening or randomization visit • Past or current history of bladder cancer • Active hematuria

	• Donation of blood or bone marrow 12 weeks prior to the screening visit and no planned donations during the study period • Heart failure due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valve disease, and HOCM (hypertrophic obstructive cardiomyopathy).
Recruitment / selection of participants	NR
Intervention(s)	SGLT2i (Dapagliflozin); Patients received 10 mg oral dapagliflozin daily in addition to guideline directed standard of care therapy for chronic heart failure with reduced systolic function for 12 weeks
Comparator	Placebo; Patients received oral placebo daily in addition to guideline directed standard of care therapy for chronic heart failure with reduced systolic function for 12 weeks
Population subgroups	
Number of participants	n=263
Duration of follow-up	12 weeks
Indirectness	NA
Method of analysis	Modified ITT analysis

Study arms

SGLT2i (dapagliflozin) (N = 131)

Patients received 10 mg dapagliflozin daily for 12 weeks. Additionally receiving Beta-blockers (99.2%), MRA (58%) ACEI/ARB (58%) ARNI (35.9%)

Placebo (N = 132)

Patients received matching placebo for 12 weeks. Additionally receiving Beta-blockers (93.9%), MRA (63.6%) ACEI/ARB (60.6%) ARNI (28.8%)

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (dapagliflozin) (N = 131)	Placebo (N = 132)
% Female Sample size	n = 36 ; % = 27.5	n = 34 ; % = 25.8
Age Mean (SD)	62.2 (11)	60.4 (12)
Ethnicity Sample size	n = NA	n = NA
White Sample size	n = 74 ; % = 59.7	n = 70 ; % = 55.6

Characteristic	SGLT2i (dapagliflozin) (N = 131)	Placebo (N = 132)
African American Sample size	n = 47 ; % = 37.9	n = 52 ; % = 41.3
NYHA class Sample size	n = NA	n = NA
NYHA Class II Sample size	n = 91 ; % = 69.5	n = 82 ; % = 62.1
NYHA Class III Sample size	n = 40 ; % = 30.5	n = 50 ; % = 37.9
Heart failure aetiology Sample size	n = NA	n = NA
Ischaemic heart disease Sample size	n = 70 ; % = 53.4	n = 69 ; % = 52.3
LVEF (%) Listed as ejection fraction Mean (SD)	27.2 (8)	25.7 (8.2)
Type 2 diabetes Sample size	n = 81 ; % = 61.8	n = 85 ; % = 64.4

Characteristic	SGLT2i (dapagliflozin) (N = 131)	Placebo (N = 132)
Atrial fibrillation Sample size	n = 57 ; % = 43.5	n = 49 ; % = 37.1
Previous heart failure hospitalisation Sample size	n = 101 ; % = 77.1	n = 108 ; % = 81.8
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	66.9 (21.1)	71.2 (23.1)
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACEI/ARB Sample size	n = 76 ; % = 58	n = 80 ; % = 60.6
ARNI Sample size	n = 47 ; % = 35.9	n = 38 ; % = 28.8
Beta-blockers Sample size	n = 130 ; % = 99.2	n = 124 ; % = 93.9
Hydralazine Sample size	n = 19 ; % = 14.5	n = 26 ; % = 19.7
Long-acting nitrates	n = 17 ; % = 13	n = 22 ; % = 16.7

Characteristic	SGLT2i (dapagliflozin) (N = 131)	Placebo (N = 132)
Sample size		
MRA Sample size	n = 76 ; % = 58	n = 84 ; % = 63.6
Loop diuretics Sample size	n = 114 ; % = 87	n = 111 ; % = 84.1
Digoxin Sample size	n = 25 ; % = 19.1	n = 21 ; % = 15.9
Lipid-lowering agents Sample size	n = 107 ; % = 81.7	n = 104 ; % = 78.8
Anticoagulant agent Sample size	n = 58 ; % = 44.3	n = 42 ; % = 31.8
Device therapy Sample size	n = NA	n = NA
ICD Sample size	n = 88 ; % = 67.2	n = 75 ; % = 56.8
CRT Sample size	n = 43 ; % = 32.8	n = 25 ; % = 18.9

Outcomes

Study timepoints

Baseline

12 week

Dichotomous and continuous outcomes

Outcome	SGLT2i (dapagliflozin), Baseline, N = 131	SGLT2i (dapagliflozin), 12 week, N = 131	Placebo, Baseline, N = 132	Placebo, 12 week, N = 132
All-cause mortality No of events	n = NA	n = 1 ; % = 0.8	n = NA	n = 1 ; % = 0.8
CV mortality No of events	n = NA	n = 1 ; % = 0.8	n = NA	n = 1 ; % = 0.8
Health-related quality of life (KCCQ clinical summary score) - no diabetes range 0-100, baseline and adjusted final score Standardised Mean (95% CI)	NA	75.4 (73 to 77.8)	NA	71.4 (69 to 73.7)
Health-related quality of life (KCCQ clinical summary score) - no diabetes range 0-100, baseline and adjusted final score Mean (SD)	70.8 (21.9)	NA (NA)	69.9 (21.4)	NA (NA)

Outcome	SGLT2i (dapagliflozin), Baseline, N = 131	SGLT2i (dapagliflozin), 12 week, N = 131	Placebo, Baseline, N = 132	Placebo, 12 week, N = 132
Health-related quality of life (KCCQ overall summary score) range 0-100, baseline and adjusted final score Standardised Mean (95% CI)	NA	73.2 (70.8 to 75.6)	NA	70 (67.6 to 72.5)
Health-related quality of life (KCCQ overall summary score) range 0-100, baseline and adjusted final score Mean (SD)	67.4 (22)	NA (NA)	67 (21.1)	NA (NA)
Unplanned hospitalisation or visits (HF-related) (adjudicated events of exacerbations of HF including HF hospitalisation or urgent HF) No of events	n = NA	n = 12 ; % = 9.1	n = NA	n = 13 ; % = 9.8
Withdrawal due to drug-related adverse events No of events	n = NA	n = 11 ; % = 8.4	n = NA	n = 12 ; % = 9.1
Acute kidney injury (undefined) No of events	n = NA	n = 1 ; % = 0.8	n = NA	n = 1 ; % = 0.8

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Health-related quality of life (KCCQ clinical summary score) - no diabetes - Polarity - Higher values are better

Health-related quality of life (KCCQ overall summary score) - Polarity - Higher values are better

Unplanned hospitalisation or visits (HF-related) (adjudicated events of exacerbations of HF including HF hospitalisation or urgent HF) - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Acute kidney injury (undefined) - Polarity - Lower values are better

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

All-cause mortality - number of events. SGLT2i (dapagliflozin) v placebo after 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality - Number of events. SGLT2i (dapagliflozin) v placebo after 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Health-related quality of life (KCCQ clinical summary score) final score. SGLT2i (dapagliflozin) v placebo after 12 weeks

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

Health-related quality of life (KCCQ overall summary score) final score. SGLT2i (dapagliflozin) v placebo after 12 weeks

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

Unplanned hospitalisation or visits (HF-related) (adjudicated events of exacerbations of HF including HF hospitalisation or urgent HF) - number of events. SGLT2i (dapagliflozin) v placebo after 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Withdrawal due to drug-related adverse events - number of events. SGLT2i (dapagliflozin) v Placebo after 12 weeks

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

Acute kidney injury (doubling of serum creatinine) - number of events. SGLT2i (dapagliflozin) v Placebo after 12 weeks

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

Packer, 2020

Bibliographic Reference	Packer, Milton; Anker, Stefan D; Butler, Javed; Filippatos, Gerasimos; Pocock, Stuart J; Carson, Peter; Januzzi, James; Verma, Subodh; Tsutsui, Hiroyuki; Brueckmann, Martina; Jamal, Waheed; Kimura, Karen; Schnee, Janet; Zeller, Cordula; Cotton, Daniel; Bocchi, Edimar; Bohm, Michael; Choi, Dong-Ju; Chopra, Vijay; Chuquiure, Eduardo; Giannetti, Nadia; Janssens, Stefan; Zhang, Jian; Gonzalez Juanatey, Jose R; Kaul, Sanjay; Brunner-La Rocca, Hans-Peter; Merkely, Bela; Nicholls, Stephen J; Perrone, Sergio; Pina, Ileana; Ponikowski, Piotr; Sattar, Naveed; Senni, Michele; Seronde, Marie-France; Spinar, Jindrich; Squire, Iain; Taddei, Stefano; Wanner, Christoph; Zannad, Faiez; Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure.; The New England journal of medicine; 2020; vol. 383 (no. 15); 1413-1424

Study details

Secondary publication of	N/A

another included study – see primary study for details	
Other publications associated with this study included in review	Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J, Filippatos G, Hauske SJ, Brueckmann M, Pfarr E, Schnee J, Wanner C, Packer M. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. Circulation. 2021 Jan 26;143(4):310-321. doi: Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, Schnaidt S, Ofstad AP, Brueckmann M, Jamal W, Bocchi EA, Ponikowski P, Perrone SV, Januzzi JL, Verma S, Böhm M, Ferreira JP, Pocock SJ, Zannad F, Packer M. Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. Circulation. 2021 Jan 26;143(4):337-349. doi: 10.1161/CIRCULATIONAHA.120.051824. Epub 2020 Nov 11. PMID: 33175585; PMCID: PMC7834911. Lam CSP, Ferreira JP, Pfarr E, Sim D, Tsutsui H, Anker SD, Butler J, Filippatos G, Pocock SJ, Sattar N, Verma S, Brueckmann M, Schnee J, Cotton D, Zannad F, Packer M. Regional and ethnic influences on the response to empagliflozin in patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. Eur Heart J. 2021 Nov 14;42(43):4442-4451. doi: 10.1093/eurheartj/ehab360. PMID: 34184057; PMCID: PMC8599078.
Trial name / registration number	EMPEROR-Reduced / NCT03057977
Study type	Randomised controlled trial (RCT)
Study location	Multinational - 20 countries
Study setting	
Study dates	From April 2017 to April 29 2020

Sources of funding	Funded by Boehringer Ingelheim and Eli Lilly
Inclusion criteria	Age ≥ 18 years at screening. For Japan only: Age ≥ 20 years at screening Male or female patients. WOCBPa must be ready and able to use highly effective methods of birth control per ICH M3that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information Patients with chronic HF diagnosed for at least 3 months before Visit 1 and currently in HF NYHA class II-IV Chronic HF with reduced EF defined as LVEF ≤ 40% per local reading (obtained under stable condition by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT). The EF must have been obtained and documented at Visit 1 or within 6 months prior to Visit 1. Patient must have at least one of the following evidence of HF: - If EF ≥36 to ≤40: Elevated NT-proBNP at Visit 1 ≥2500 pg/ml for patients without AF, OR ≥5000 pg/ml for patients with AF, analysed at the Central Laboratory, - If EF ≥31 to ≤35: Elevated NT-proBNP at Visit 1 ≥1000 pg/ml for patients without AF, OR ≥2000 pg/ml for patients with AF, analysed at the Central Laboratory, - If EF≤30%: Elevated NT-proBNP at Visit 1 ≥600 pg/ml for patients without AF, OR ≥1200 pg/ml for patients with AF, analysed at the Central Laboratory Appropriate dose of medical therapy for HF (such as ACEI, ARB, βablocker, oral diuretics, MRA, ARNI, ivabradine) and appropriate device therapy, consistent with prevailing CV guidelines, stable for at least 1 week prior to Visit 1(screening) and during screening period until Visit 2 (Randomisation) with the exception of diuretics stable for only one week prior to Visit 2 to control symptoms. The investigator must document the reason why patient not on target dose per local guidelines. Appropriate use of medical devices such as cardioverter defibrillator (ICD) or a cardiac resynchronization therapy (CRT) consistent with prevailing local or international CV guidelines, unless it is implanted within 3 months prior to Visit 1, or if there is an intent to implant ICD or CRT eGFR ≥ 20 mL/min/1.73m2 at Visit 1

Exclusion criteria	Myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischaemia or newly developed ischaemic ECG changes), coronary artery bypass graft surgery, or other major cardiovascular surgery, stroke or TIA in past 90 days prior to Visit 1 Heart transplant recipient, or listed for heart transplant Currently implanted left ventricular assist device (LVAD) Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction Any severe (obstructive or regurgitant) valvular heart disease, expected to lead to surgery during the trial in the investigator's opinion Acute decompensated HF (exacerbation of chronic HF) requiring i.v. diuretics, i.v. inotropes, or i.v. vasodilators, or LVAD within 1 week from discharge to Visit 1 (Screening) and during screening period until Visit 2 (Randomisation) Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm documented by ECG at Visit 1 (Screening) Untreated ventricular arrhythmia with syncope in patients without ICD documented within the 3 months prior to Visit 1 Diagnosis of cardiomyopathy induced by chemotherapy or peripartum within the 12 months prior to Visit 1 Symptomatic bradycardia or second or third degree heart block without a pacemaker after adjusting beta-blocker therapy, if appropriate Systolic blood pressure (SBP) ≥ 180 mmHg at Visit 2. If SBP >150mmHg and <180mmHg at Visit 2, the patient should be receiving at least 3 antihypertensive drugs Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 or Visit 2 Chronic pulmonary disease requiring home oxygen, oral steroid therapy or hospitalisation for exacerbation within 12 months, or significant chronic pulmonary disease in the opinion of the investigator, or primary pulmonary arterial hypertension

	Indication of liver disease, defined by serum levels of either ALT (SGPT),AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at Visit 1
	Impaired renal function, defined as eGFR < 20 mL/min/1.73 m2 (CKD-EPI) or requiring dialysis, as determined at Visit 1
	Haemoglobin (HgB) <9 g/dl at Visit 1
	History of ketoacidosis
	Major surgery (major according to the investigator's assessment) performed within 90 days prior to Visit 1, or scheduled major elective surgery (e.g. hip replacement) within 90 days after Visit 1
	Gastrointestinal surgery or gastrointestinal disorder that could interfere with trial medication absorption in the investigator's opinion
	Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or low risk prostate cancer (patients with pre-treatment PSA < 10 ng/mL, and biopsy Gleason score of ≤ 6 and clinical stage T1c or T2a)
	Presence of any other disease than heart failure with a life expectancy of <1 years in the opinion of the investigator
	Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
	Current use or prior use of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 12 weeks prior to Visit 1 or during screening period until Visit 2 (Randomisation). Discontinuation of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor for the purposes of study enrolment is not permitted.
	Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded
	Known allergy or hypersensitivity to empagliflozin or other SGLT-2 inhibitors
	Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial

	Women who are pregnant, nursing, or who plan to become pregnant while in the trial Any other clinical condition that would jeopardise patients safety while participating in this trial, or may prevent the subject from adhering to the trial protocol Implanted cardioverter defibrillator (ICD) or a cardiac resynchronization therapy (CRT) within 3 months prior to Visit 1, or if there is an intent to implant ICD or CRT within 3 months of visit 1
Recruitment / selection of participants	NR
Intervention(s)	SGLT2i (Empagliflozin) Patients received 10 mg empagliflozin for a median of 16 months in addition to recommended therapy
Comparator	Placebo Patients received daily placebo for a median of 16 months in addition to recommended therapy
Population subgroups	Patients with eGFR <30 ml/min/1.72 (see Zannad 2021) Patients with and without T2DM (see Anker 2020)
Number of participants	n=3730
Duration of follow-up	median of 16 months
Indirectness	NA

Method of analysis	ITT analysis
Additional comments	Intention to treat

Study arms

SGLT2i (empagliflozin) (N = 1863)

Patients received a daily dose of 10 mg empagliflozin in addition to recommended therapy Patients also received Beta-blocker (94.7%), ACEI / ARB without neprilysin inhibitor (70.5%), ACEI / ARB with neprilysin inhibitor (18.3%), MRA (70.1%)

Placebo (N = 1867)

Patients received daily placebo in addition to recommended therapy Patients also received Beta-blocker (94.7%), ACEI / ARB without neprilysin inhibitor (68.9%), ACEI / ARB with neprilysin inhibitor (20.7%), MRA (72.6%)

Characteristics

Arm-level characteristics

Characteristic	SGLT2i (empagliflozin) (N = 1863)	Placebo (N = 1867)
% Female Sample size	n = 437 ; % = 23.5	n = 456 ; % = 24.4
Age (Years (mean, SD)) Mean (SD)	67.2 (10.8)	66.5 (11.2)

Characteristic	SGLT2i (empagliflozin) (N = 1863)	Placebo (N = 1867)
Ethnicity Sample size	n = NA	n = NA
White Sample size	n = 1325 ; % = 71.1	n = 1304 ; % = 69.8
Black Sample size	n = 123 ; % = 6.6	n = 134 ; % = 7.2
Asian Sample size	n = 337 ; % = 18.1	n = 335 ; % = 17.9
Other or Missing Sample size	n = 78 ; % = 4.2	n = 94 ; % = 5
NYHA class Sample size	n = NA	n = NA
Class II Sample size	n = 1399 ; % = 75.1	n = 1401 ; % = 75
Class III Sample size	n = 455 ; % = 24.4	n = 455 ; % = 24.4
Class IV	n = 9 ; % = 0.5	n = 11 ; % = 0.6

Characteristic	SGLT2i (empagliflozin) (N = 1863)	Placebo (N = 1867)
Sample size		
Heart failure aetiology Sample size	n = NA	n = NA
Ischaemic Sample size	n = 983 ; % = 52.8	n = 946 ; % = 50.7
Non-ischaemic Sample size	n = 880 ; % = 47.2	n = 921 ; % = 49.3
LVEF (%) Mean (SD)	27.7 (6)	27.2 (6.1)
Type 2 diabetes Sample size	n = 927 ; % = 49.8	n = 929 ; % = 49.8
Atrial fibrillation Sample size	n = 664 ; % = 35.6	n = 705 ; % = 37.8
Previous heart failure hospitalisation In the last 12 months Sample size	n = 577 ; % = 31	n = 574 ; % = 30.7
Renal function (eGFR; mL/min/1.73m2)	61.8 (21.7)	62.2 (21.5)

Characteristic	SGLT2i (empagliflozin) (N = 1863)	Placebo (N = 1867)
Mean (SD)		
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACEI / ARB without neprilysin inhibitor Sample size	n = 1314 ; % = 70.5	n = 1286 ; % = 68.9
ACEI / ARB with neprilysin inhibitor Sample size	n = 340 ; % = 18.3	n = 384 ; % = 20.7
MRA Sample size	n = 1306 ; % = 70.1	n = 1355 ; % = 72.6
Beta-blocker Sample size	n = 1765 ; % = 94.7	n = 1768 ; % = 94.7
Device therapy Sample size	n = NA	n = NA
ICD Sample size	n = 578 ; % = 31	n = 593 ; % = 31.8
CRT Sample size	n = 220 ; % = 11.8	n = 222 ; % = 11.9

Outcomes

Study timepoints

Baseline

16 month

12 month

Dichotomous outcomes

Outcome	SGLT2i (empagliflozin), Baseline, N = 1863	SGLT2i (empagliflozin), 16 month, N = 1863	SGLT2i (empagliflozin), 12 month, N = 1863	Placebo, Baseline, N = 1867	Placebo, 16 month, N = 1867	Placebo, 12 month, N = 1867
All-cause mortality No of events	n = NA	n = 249 ; % = 13.4	n = NA	n = NA	n = 266 ; % = 14.2	n = NA
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) No of events	n = NA	n = 246 ; % = 13.2	n = NA	n = NA	n = 342 ; % = 18.3	n = NA
CV mortality No of events	n = NA	n = 187 ; % = 10	n = NA	n = NA	n = 202 ; % = 10.8	n = NA

All-cause mortality - Polarity - Lower values are better

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

CV mortality - Polarity - Lower values are better

Hazard Ratio data

Outcome	SGLT2i (empagliflozin) vs Placebo, 16 month, N2 = 1863, N1 = 1867	SGLT2i (empagliflozin) vs Placebo, 12 month, N2 = 1863, N1 = 1867
All-cause mortality HR Hazard ratio/95% CI	0.92 (0.77 to 0.98)	NA
CV mortality Hazard ratio/95% CI	0.92 (0.75 to 1.12)	NA
Health-related quality of life (KCCQ clinical summary score) Hazard ratio/95% CI	NA	1.7 (0.5 to 3)
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) Hazard ratio/95% CI	0.69 (0.59 to 0.81)	NA

All-cause mortality HR - Polarity - Lower values are better

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

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

Continuous outcomes

Outcome	SGLT2i (empagliflozin), Baseline, N = 1863	SGLT2i (empagliflozin), 16 month, N = NA	SGLT2i (empagliflozin), 12 month, N = 1863	Placebo, Baseline, N = 1863	Placebo, 16 month, N = NA	Placebo, 12 month, N = 1863
Health-related quality of life (KCCQ clinical summary score) range 0-100, change score Mean (SD)	NR	NA (NA)	5.8 (0.4)	NR	NA (NA)	4.1 (0.4)

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

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

All-cause mortality; no. of events. SLGT2i (empagliflozin) v Placebo at 16 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits HF-related (hospitalisation for HF); no of events. SLGT2i (empagliflozin) v Placebo at 16 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Health-related quality of life (KCCQ clinical summary score); SLGT2i (empagliflozin) v Placebo at 12 months

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

CV mortality; no of events. SGLT2i (empagliflozin) v Placebo at 16 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

All cause mortality; TTE event data. SGLT2i (empagliflozin) v Placebo at 16 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

CV mortality; TTE data. SGLT2i (empagliflozin) v Placebo at 16 months

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

Health-related quality of life (KCCQ clinical summary score); TTE data. SGLT2i (empagliflozin) v Placebo at 12 months

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

Unplanned hospitalisation or visits HF-related (hospitalisation for HF); TTE SGLT2i (empagliflozin) v Placebo at 16 months

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

Packer, 2019

Bibliographic Reference	Packer, Milton; Butler, Javed; Filippatos, Gerasimos S; Jamal, Waheed; Salsali, Afshin; Schnee, Janet; Kimura, Karen; Zeller, Cordula; George, Jyothis; Brueckmann, Martina; Anker, Stefan D; Zannad, Faiez; 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; 2019; vol. 21 (no. 10); 1270-1278

Study details

Secondary publication of another included study – see primary study for details	Rationale for and design of the EMPEROR-Reduced trial See main trial paper for details: Packer 2020. PMID: 32865377.

Pagnesi, 2023

Bibliographic Reference	Pagnesi, Matteo; Metra, Marco; Cohen-Solal, Alain; Edwards, Christopher; Adamo, Marianna; Tomasoni, Daniela; Lam, Carolyn S P; Chioncel, Ovidiu; Diaz, Rafael; Filippatos, Gerasimos; Ponikowski, Piotr; Sliwa, Karen; Voors, Adriaan A; Kimmoun, Antoine; Novosadova, Maria; Takagi, Koji; Barros, Marianela; Damasceno, Albertino; Saidu, Hadiza; Gayat, Etienne; Pang, Peter S; Celutkiene, Jelena; Cotter, Gad; Mebazaa, Alexandre; Davison, Beth; Uptitrating Treatment After Heart Failure Hospitalization Across the Spectrum of Left Ventricular Ejection Fraction.; Journal of the American College of Cardiology; 2023; vol. 81 (no. 22); 2131-2144

Study details

Secondary publication of another included study – see primary study for details	STRONG-HF (LVEF ≤40% subgroup). These data were prioritised for analysis in this review due to matching the protocol population. See Mebazaa 2022 for full details
Other publications associated with this study included in review	Mebazaa 2022 - main trial report Kimmoun 2019 - study design and rationale Cotter 2001 - amended study design
Trial name / registration number	STRONG-HF: NCT03412201.
Study type	Randomised controlled trial (RCT)
Additional comments	The treatment benefit of high-intensity care vs usual care on the primary endpoint was consistent across the whole LVEF spectrum

Study arms

High intensity care (N = 365)

The first dose adjustment occurred just after randomisation (within 2 days before anticipated hospital discharge), when patients were prescribed medical therapy with β blockers, renin-angiotensin blockers (ie, ACE inhibitors [or ARBs if intolerant to ACE inhibitors] or ARN inhibitors), and mineralocorticoid receptor antagonists adjusted to at least half the optimal doses. Doses were optimised at visit 4 (week 2)

Usual care (N = 366)

Follow up and therapy adjustments after discharge were according to the local practice.

Characteristics

Arm-level characteristics

Characteristic	High intensity care (N = 365)	Usual care (N = 366)
% Female LVEF ≤40% subgroup Sample size	n = 126 ; % = 34.5	n = 124 ; % = 33.9
Age LVEF ≤40% subgroup Mean (SD)	59.9 (13.68)	60.3 (14.34)
Black Sample size	n = 99 ; % = 27.1	n = 100 ; % = 27.3
White Sample size	n = 261 ; % = 71.5	n = 262 ; % = 71.6
Native American Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Other Sample size	n = 5 ; % = 1.4	n = 4 ; % = 1.1

Characteristic	High intensity care (N = 365)	Usual care (N = 366)
Pacific Islander Sample size	n = 0 ; % = 0	n = 0 ; % = 0
NYHA Class I Sample size	n = 23 ; % = 6.8	n = 28 ; % = 8.4
NYHA Class II Sample size	n = 88 ; % = 26.2	n = 112 ; % = 33.5
NYHA Class III Sample size	n = 144 ; % = 42.9	n = 130 ; % = 38.9
NYHA class IV Sample size	n = 81 ; % = 24.1	n = 64 ; % = 19.2
Ischaemic Sample size	n = 165 ; % = 45.3	n = 159 ; % = 43.4
Non-ischaemic Sample size	n = 199 ; % = 54.7	n = 207 ; % = 56.6
Type 2 diabetes 'Diabetes' Sample size	n = 96 ; % = 26.3	n = 101 ; % = 27.7

Characteristic	High intensity care (N = 365)	Usual care (N = 366)
Atrial fibrillation History of atrial fibrillation or atrial flutter Sample size	n = 141 ; % = 38.6	n = 160 ; % = 43.7
Previous heart failure hospitalisation in past year Sample size	n = 101 ; % = 27.7	n = 95 ; % = 26
ACE inhibitors/ARB/ARNI Sample size	n = 246 ; % = 67.6	n = 236 ; % = 64.5
Beta-blocker Sample size	n = 110 ; % = 30.2	n = 133 ; % = 36.3
MRA Sample size	n = 347 ; % = 95.3	n = 353 ; % = 96.4
Cardiac resynchronisation therapy Sample size	n = 3 ; % = 0.8	n = 3 ; % = 0.8
Automatic internal cardiac defibrillator Sample size	n = 3 ; % = 0.8	n = 5 ; % = 1.4

Outcomes

Study timepoints

90 day

180 day

Dichotomous and continuous outcomes

Outcome	High intensity care, 90 day, N = 365	High intensity care, 180 day, N = 346	Usual care, 90 day, N = 366	Usual care, 180 day, N = 346
All-cause mortality Kaplan-Meier estimates No of events	-	n = 33 ; % = 11	-	n = 31 ; % = 9.6
CV mortality Kaplan-Meier estimates No of events	-	n = 28 ; % = 9.2	-	n = 29 ; % = 9.2
Unplanned hospitalisation or visits (HF-related) (HF re-admission) Kaplan-Meier estimates No of events	-	n = 35 ; % = 10.1	-	n = 51 ; % = 17.9
Health-related quality of life EQ-5D VAS) range 0-100, change score; baseline values not reported Mean (SD)	10.77 (0.97)	-	8.29 (0.98)	-
Acute kidney injury (undefined)	n = 3 ; % = 0.8	-	n = 0 ; % = 0	-

Outcome	High intensity care, 90 day, N = 365	High intensity care, 180 day, N = 346	Usual care, 90 day, N = 366	Usual care, 180 day, N = 346
No of events				
Hyperkalaemia (undefined) No of events	n = 13 ; % = 3.6	-	n = 5 ; % = 2.8	-
Falls (undefined) No of events	n = 1 ; % = 0.3	-	n = 0 ; % = 0	-

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (HF re-admission) - Polarity - Lower values are better

Health-related quality of life EQ-5D VAS) - Polarity - Higher values are better

Acute kidney injury (undefined) - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

Falls (undefined) - Polarity - Lower values are better

Hazard ratio

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

All-cause mortality - 180 days - dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality - 180 days - dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (HF re-admission) - 180 days - dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

EQ-5D VAS change from baseline to 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unblinded and subjective outcome; plus possible selection of outcome data from multiple scales)*
Overall bias and Directness	Overall Directness	Directly applicable

Acute kidney injury (undefined) - 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome not defined)*

Hyperkalaemia (undefined) - 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome not defined)*

Falls (undefined) - 90 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome not defined)*

Palau, 2022

Bibliographic Reference	Palau, Patricia; Amiguet, Martina; Dominguez, Eloy; Sastre, Clara; Mollar, Anna; Seller, Julia; Garcia Pinilla, Jose Manuel; Larumbe, Ainoha; Valle, Alfonso; Gomez Doblas, Juan Jose; de la Espriella, Rafael; Minana, Gema; Mezcua, Ainhoa Robles; Santas, Enrique; Bodi, Vicent; Sanchis, Juan; Pascual-Figal, Domingo; Gorriz, Jose Luis; Bayes-Genis, Antonio; Nunez, Julio; 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; 2022; vol. 24 (no. 10); 1816-1826

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with this study included in review	NA

Trial name / registration number	DAPA-VO2 / NCT04197635
Study location	Spain
Study setting	Not stated
Study dates	May 2019 - October 2021
Sources of funding	AstraZeneca, Unidad de Investigación Clínica y Ensayos Clínicos INCLIVA Health Research Institute, Spanish Clinical Research Network and CIBER Cardiovascular
Inclusion criteria	Stable chronic HF; adult patients >18 years old with stable symptomatic HF in NYHA class II–III during the last 2 months; LVEF ≤40% documented in the last 3 months by echocardiography or cardiac magnetic resonance; N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥600 pg/ml; estimated eGFR ≥30 ml/min/1.73 m2; Modification of Diet in Renal Disease formula at enrolment; optimal and stable background standard of care for HFrEF
Exclusion criteria	Inability to perform a valid (respiratory exchange ratio [RER] ≥1.05) baseline cardiopulmonary exercise test (CPET); HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, or uncorrected severe primary cardiac valve disease; myocardial infarction, unstable angina, stroke, or transient ischemic attack within 12 weeks prior to enrolment; patients receiving therapy with an SGLT2i within 8 weeks prior to enrolment, or previous intolerance of an SGLT2i; type 1 diabetes; coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or cardiac valve repair/replacement within 12 weeks prior to enrolment, or planned to undergo any of these operations after randomization; implantation of a cardiac resynchronization therapy (CRT) device within 12 weeks prior to enrolment or intent to implant a CRT device; previous cardiac transplantation or implantation of a ventricular assist device, or implantation expected after randomization; symptomatic bradycardia or second or third-degree heart block without a pacemaker; renal dysfunction (eGFR <30 ml/min/1.73 m2) or prior admission for acute renal failure in the last 4 weeks; pregnant or lactating women; woman of childbearing age, unless they are using highly effective contraceptive methods; patients with severe hepatic impairment (Child–Pugh class C)

Recruitment / selection of participants	Not stated
Intervention(s)	Dapagliflozin 10 mg; bottle contained 100 tablets and patients received their assigned bottles and were instructed to begin the treatment on the first day. The intervention was given for 3 months. Loop diuretics was stopped in one patient in the intervention arm
Comparator	Matching placebo treatment was given to the randomized patients taken orally. Later in the investigation, loop diuretics were up-titrated in two of the patients in control arm
Population subgroups	No subgroups identified
Number of participants	77
Duration of follow-up	3 months follow-up period post intervention and randomization
Indirectness	NA
Method of analysis	Modified ITT analysis
Additional comments	

Study arms

SGLT2 (Dapagliflozin 10 mg) (N = 45)

Loop diuretics 86.7%; ACEI or ARB or sacubitril/valsartan 97.8%; Sacubitril/valsartan 88.9%; MRA 77.8%; Beta-blockers 91.1%

Placebo (N = 45)

Loop diuretics 84.4%; ACEI or ARB or sacubitril/valsartan 95.6%; Sacubitril/valsartan 88.9%; MRA 71.1%; Beta-blockers 91.1%

Characteristics

Arm-level characteristics

Characteristic	SGLT2 (Dapagliflozin 10 mg) (N = 45)	Placebo (N = 45)
% Female Sample size	n = 10 ; % = 22.2	n = 11 ; % = 24.4
Age (Years (median, IQR)) Median (IQR)	69.8 (62.4 to 74)	67.3 (60.8 to 75.1)
NYHA class (II/IV) Sample size	n = 41 ; % = 91.1	n = 39 ; % = 86.7
Prior history of Ischemic heard disease Sample size	n = 27 ; % = 60	n = 22 ; % = 48.9
Prior history of atrial fibrillation Sample size	n = 26 ; % = 57.8	n = 23 ; % = 51.1
Left bundle branch block Sample size	n = 5 ; % = 11.1	n = 10 ; % = 22.2

Characteristic	SGLT2 (Dapagliflozin 10 mg) (N = 45)	Placebo (N = 45)
Hypertension Sample size	n = 33 ; % = 73.3	n = 37 ; % = 82.2
Type 2 diabetes (%) Sample size	n = 16 ; % = 35.6	n = 13 ; % = 28.9
Atrial fibrillation Sample size	n = 26 ; % = 57.8	n = 23 ; % = 51.1
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	64.1 (20.7)	69.4 (23)
Loop diuretics Sample size	n = 39 ; % = 86.7	n = 38 ; % = 84.4
ACEI or ARB or sacubitril/valsartan Sample size	n = 44 ; % = 97.8	n = 43 ; % = 95.6
Sacubitril-valsartan Sample size	n = 40 ; % = 88.9	n = 40 ; % = 88.9
MRA Sample size	n = 35 ; % = 77.8	n = 32 ; % = 71.1
Beta-blockers	n = 41 ; % = 91.1	n = 41 ; % = 91.1

Characteristic	SGLT2 (Dapagliflozin 10 mg) (N = 45)	Placebo (N = 45)
Sample size		
Device therapy Sample size	n = 23 ; % = 51.1	n = 21 ; % = 46.7
Implantable cardioverter-defibrillator Sample size	n = 15 ; % = 33.3	n = 15 ; % = 33.3
Cardiac resynchronization therapy Sample size	n = 8 ; % = 17.8	n = 6 ; % = 13.3

Outcomes

Study timepoints

3 month

Continuous outcomes

Outcome	SGLT2 (Dapagliflozin 10 mg), 3 month, N = 45	Placebo, 3 month, N = 45
Health-related quality of life (MLWHFQ overall score) range 0-105, final score Mean (95% CI)	24 (18.7 to 29.3)	21.4 (16.1 to 26.8)

Health-related quality of life (MLWHFQ overall score) - Polarity - Lower values are better

Dichotomous outcomes

Outcome	SGLT2 (Dapagliflozin 10 mg), 3 month, N = 45	Placebo, 3 month, N = 45
All-cause mortality No of events	n = 1 ; % = 2.2	n = 1 ; % = 2.2
Unplanned hospitalisation or visits (HF-related) (hospitalization for acute HF) No of events	n = 0 ; % = 0	n = 1 ; % = 2.2

All-cause mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (hospitalization for acute HF) - Polarity - Lower values are better

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

Health-related Quality of Life (MLWHF)- Overall score from baseline to 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Strudy lacks information about randomization process)*
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality at the end of follow-up (3 months)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Strudy lacks information about randomization process)*
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits (HF-related) (hospitalization for acute HF) at the end of follow-up (3 months)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Strudy lacks information about randomization process)*
Overall bias and Directness	Overall Directness	Directly applicable

Petrie, 2020

Bibliographic Reference Petrie, Mark C; Verma, Subodh; Docherty, Kieran F; Inzucchi, Silvio E; Anand, Inder; Belohlavek, Jan; Bohm, Michael; Chiang, Chern-En; Chopra, Vijay K; de Boer, Rudolf A; Desai, Akshay S; Diez, Mirta; Drozdz, Jaroslaw; Dukat, Andre; Ge, Junbo; Howlett, Jonathan; Katova, Tzvetana; Kitakaze, Masafumi; Ljungman, Charlotta E A; Merkely, Bela; Nicolau, Jose C; O'Meara, Eileen; Vinh, Pham Nguyen; Schou, Morten; Tereshchenko, Sergey; Kober, Lars; Kosiborod, Mikhail N; Langkilde, Anna Maria; Martinez, Felipe A; Ponikowski, Piotr; Sabatine, Marc S; Sjostrand, Mikaela; Solomon, Scott D; Johanson, Per; Greasley, Peter J; Boulton, David; Bengtsson, Olof; Jhund, Pardeep S; McMurray, John J V; Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes.; JAMA; 2020; vol. 323 (no. 14); 1353-1368

Study details

Secondary publication of another included study – see primary study for details	Secondary publication of DAPA-HF. See parent study for details: McMurray (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England journal of medicine; 2019; vol. 381 (no. 21); 1995-2008
Trial name / registration number	DAPA-HF
Study type	Randomised controlled trial (RCT)
Number of participants	4744
Duration of follow-up	median 18.2 months

Study arms

SGLT2i (dapagliflozin) (N = 2373)

Patients received 10 mg dapagliflozin daily in addition to recommended therapy. Patients also received Beta-blocker (96.0%), ACEI (56.1%), ARB (28.4%), Sacubitril-valsartan (10.5%), MRA (71.5%)

Placebo (N = 2371)

Patients received daily placebo in addition to recommended therapy Patients also received Beta-blocker (96.2%), ACEI (56.1%), ARB (26.7%), Sacubitril-valsartan (10.9%), MRA (70.6%)

Outcomes

Study timepoints

Baseline

18.2 month

8 month (For QoL only)

Hazard ratios

Outcome	SGLT2i (dapagliflozin) vs Placebo, 18.2 month, N2 = 2373, N1 = 2371
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Hazard ratio/95% CI	0.88 (0.7 to 1.12)
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Hazard ratio/95% CI	0.78 (0.63 to 0.97)
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Hazard ratio/95% CI	0.85 (0.66 to 1.1)
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Hazard ratio/95% CI	0.79 (0.63 to 1.01)

Outcome	SGLT2i (dapagliflozin) vs Placebo, 18.2 month, N2 = 2373, N1 = 2371
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Hazard ratio/95% CI	0.62 (0.48 to 0.8)
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Hazard ratio/95% CI	0.77 (0.61 to 0.95)
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Hazard ratio/95% CI	0.63 (0.48 to 0.81)
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Hazard ratio/95% CI	0.76 (0.61 to 0.95)
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Hazard ratio/95% CI	0.67 (0.3 to 1.49)
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Hazard ratio/95% CI	0.73 (0.39 to 1.34)

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits HF related (Hospitalisation for HF or an urgent HF visit) - Polarity - Lower values are better

Unplanned hospitalisation or visits HF related (Hospitalisation for HF or an urgent HF visit) - Polarity - Lower values are better

AKI (worsening kidney function) - Polarity - Lower values are better

Dichotomous outcomes

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = 2373	Placebo, 18.2 month, N = 2371
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo No of events	n = 133 ; % = 10.2	n = 151 ; % = 11.6
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Participants per 100 patient-years	6.9	7.8
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo No of events	n = 143 ; % = 13.3	n = 178 ; % = 16.7
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Participants per 100 patient-years	9.1	11.7
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo No of events	n = 106 ; % = 8.2	n = 125 ; % = 9.6

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = 2373	Placebo, 18.2 month, N = 2371
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Participants per 100 patient-years	5.5	6.5
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo No of events	n = 121 ; % = 11.3	n = 148 ; % = 13.9
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Participants per 100 patient-years	7.7	9.7
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo No of events	n = 95 ; % = 7.3	n = 150 ; % = 11.5
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Participants per 100 patient-years	5.1	8.2
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo No of events	n = 142 ; % = 13.2	n = 176 ; % = 16.5
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo	9.6	12.6

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = 2373	Placebo, 18.2 month, N = 2371
Participants per 100 patient-years		
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo No of events	n = 93 ; % = 7.2	n = 146 ; % = 11.2
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Participants per 100 patient-years	5.0	8.0
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo No of events	n = 138 ; % = 12.8	n = 172 ; % = 16.2
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Participants per 100 patient-years	9.3	12.2
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo No of events	n = 10 ; % = 0.8	n = 15 ; % = 1.1
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Participants per 100 patient-years	0.5	0.8

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = 2373	Placebo, 18.2 month, N = 2371
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo No of events	n = 18 ; % = 1.7	n = 24 ; % = 2.3
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Participants per 100 patient-years	1.2	1.6
No diabetes At baseline, n= 1295 for intervention, n= 1305 for placebo No of events	n = 68 ; % = 5.3	n = 59 ; % = 4.5
Diabetes At baseline, n= 1073 for intervention, n= 1063 for placebo No of events	n = 43 ; % = 4	n = 57 ; % = 5.4

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits HF related (Hospitalisation for HF or an urgent HF visit) - Polarity - Lower values are better

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

Acute kidney injury (worsening kidney function) - Polarity - Lower values are better

- Withdrawal due to drug-related adverse events (discontinuation of study drug due to adverse event) - Polarity - Lower values are better

Continuous variables

Outcome	SGLT2i (dapagliflozin), Baseline, N = 2373	SGLT2i (dapagliflozin), 8 month, N = 2373	Placebo, Baseline, N = 2371	Placebo, 8 month, N = 2371
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Median (IQR)	79.2 (60.4 to 92.7)	NR	79.2 (62.5 to 91.7)	NR
No diabetes At baseline, n= 1298 for intervention, n= 1307 for placebo Mean (95% CI)	NR	5.4 (4.3 to 6.4)	NR	3.1 (2.1 to 4.2)
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Median (IQR)	75 (55.2 to 91.7)	NR	75 (57.3 to 91.7)	NR
Diabetes At baseline, n= 1075 for intervention, n= 1064 for placebo Mean (95% CI)	NR	7 (5.7 to 8.3)	NR	3.5 (2.1 to 4.9)

Health-related quality of life (KCQL TSS) - Polarity - Higher values are better

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

All-cause mortality - Subgroup No diabetes-Hazard Ratio-FUP 18.2 months

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

All-cause mortality - Subgroup Diabetes-Hazard Ratio -FUP 18.2 months

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

CV mortality - Subgroup No diabetes-Hazard Ratio-FUP 18.2 months

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

CV mortality - Subgroup Diabetes-Hazard Ratio-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits HF related (hospitalisation for HF or an urgent HF visit)-Subgroup No diabetes-Hazard Ratio-FUP 18.2 months

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

Unplanned hospitalisation or visits HF related (Hospitalisation for HF or an urgent HF visit)-Subgroup Diabetes-Hazard Ratio- FUP 18.2 months

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

Unplanned hospitalisation or visits HF related (hospitalisation for HF)-Subgroup No diabetes-Hazard Ratio-FUP 18.2 months

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

Unplanned hospitalisation or visits HF related (hospitalisation for HF)-Subgroup Diabetes-Hazard Ratio- FUP 18.2 months

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

Acute kidney injury (worsening kidney function)- Subgroup No diabetes-Hazard Ratio-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not specifically AKI as defined in protocol)*

Acute kidney injury (worsening kidney function)-Subgroup Diabetes-Hazard Ratio-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not specifically AKI as defined in protocol)*

All-cause mortality - Subgroup No diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

All-cause mortality - Subgroup No diabetes-Participants per 100 patient-years-FUP 18.2 months

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

All-cause mortality - Subgroup Diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

All-cause mortality - Subgroup Diabetes-Participants per 100 patient-years-FUP 18.2 months

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

CV mortality - Subgroup No diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

CV mortality - Subgroup No diabetes-Participants per 100 patient years-FUP 18.2 months

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

CV mortality - Subgroup Diabetes-Events-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

CV mortality - Subgroup Diabetes-Participants per 100 patient-years-FUP 18.2 months

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

Unplanned hospitalisation or visits HF related (hospitalisation for HF or an urgent HF visit)-Subgroup No diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits HF related (hospitalisation for HF or an urgent HF visit)-Subgroup No diabetes-Participants per 100 patient years-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits HF related (hospitalisation for HF or an urgent HF visit)-Subgroup Diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits HF related (hospitalisation for HF or an urgent HF visit)-Subgroup Diabetes-Participants per 100 patient years-FUP 18.2 months

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

Unplanned hospitalisation or visits HF related (hospitalisation for HF)-Subgroup No diabetes-Events-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits HF related (hospitalisation for HF)-Subgroup No diabetes-Participants per 100 patient years-FUP 18.2 months

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

Unplanned hospitalisation or visits HF related (hospitalisation for HF)-Subgroup Diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: not TTE outcome as specified in the protocol)*

Unplanned hospitalisation or visits HF related (hospitalisation for HF)-Subgroup Diabetes-Participants per 100 patient years-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Acute kidney injury (worsening kidney function)-Subgroup No diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not specifically AKI as defined in protocol)*

Acute kidney injury (worsening kidney function)-Subgroup No diabetes-Participants per 100 patient years-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not specifically AKI as defined in protocol)*

Acute kidney injury (worsening kidney function)-Subgroup Diabetes-Events-FUP 18.2 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not specifically AKI as defined in protocol)*

Acute kidney injury (worsening kidney function)-Subgroup Diabetes-Participants per 100 patient years-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not specifically AKI as defined in protocol)*

Withdrawal due to drug-related adverse events (discontinuation of study drug due to adverse event)-Subgroup No diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome definition different from the protocol)*

Withdrawal due to drug-related adverse events (discontinuation of study drug due to adverse event)-Subgroup Diabetes-Events-FUP 18.2 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome definition different from the protocol)*

Health-related quality of life (KCQL overall summary score)-Subgroup No diabetes-change score at 8 months

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

Health-related quality of life (KCQL overall summary score)-Subgroup Diabetes-change score at 8 months

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

Piepoli, 2021

Bibliographic Reference	Piepoli, Massimo F; Hussain, Rizwan I; Comin-Colet, Josep; Dosantos, Ramon; Ferber, Philippe; Jaarsma, Tiny; Edelmann, Frank; 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; 2021; vol. 23 (no. 1); 127-135

Study details

Secondary publication of another included study – see primary study for details	N/A
Other publications associated with this study included in review	Rationale and study design for OUTSTEP-HF: Edelmann 2020 (EPPI ID: 15338166)
Trial name / registration number	NCT02900378
Study type	Randomised controlled trial (RCT)
Study location	19 European counties
Study setting	120 sites
Study dates	Not reported
Sources of funding	Novartis Pharma AG

Inclusion criteria	Ambulatory patients aged ≥18 years with a diagnosis of symptomatic heart failure (New York Heart Association [NYHA] class ≥II) with reduced ejection fraction, defined as LVEF ≤40% Plasma NT-proBNP level of >300 pg/mL or BNP ≥100 pg/mL or confirmation of hospitalisation for heart failure in the last 12 months Patients on stable medication for heart failure (i.e., ACEI/ARB, beta-blockers, MRA) for at least 4 weeks prior to visit 1, where the minimal daily dose of ACEI/ARB was equivalent to at least 2.5 mg/d enalapril Willingness to wear accelerometer wrist band Living in a setting that allows free movement and self-responsibility for scheduling sleep and daily activities.
Exclusion criteria	Use of other investigational drugs within 5 half-lives or 30 days of enrolment, whichever is longer History of hypersensitivity to study drugs Prior use of sacubitril/valsartan Known history of any type of angioedema Patients with significantly impaired or limited mobility, or bed bound and 'or fatigue due to medical conditions other than heart failure Patients with COPD contributing to dyspnoea, or whose COPD medication has been altered within 4 weeks prior to screening Patients with palsy, tremor or rigor affecting the non-dominant arm Patients with any skin condition affecting the non-dominant arm that would limit their ability to wear the actigraphy device Patients fully dependent on mobility support Patients requiring a dual RAAS blockade (i.e., treatment with both ACEIs and ARBs or concomitant treatment with aliskiren)

	Patients with decompensated heart failure within 4 weeks of screening
	Symptomatic hypotension and/or SBP <100 mmHg at screening or randomisation
	Serum potassium >5.4 mmol/L at screening or randomisation
	Acute coronary syndrome, stroke, transient ischaemic attack, major vascular surgery, PCI or carotid angioplasty within 3 months prior to screening
	Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 14 week study duration
	Implantation of pacemaker (CRT-P) or defibrillator (CRT-D) or upgrading of an existing conventional pacemaker or ICD to a CRT device within 3 months prior to screening or such procedure planned within the 14-week study duration; patients with an implantation of conventional pacemaker or an ICD or with a revision of a pacemaker or other device electrodes within 1 month prior to screening.
	Patients with existing or planned/intended heart transplant or VAD
	Diagnosis of peripartum or chemotherapy induced cardiomyopathy within 12 months prior to screening
	Documented untreated ventricular arrhythmia with syncopal episodes within 3 months prior to screening
	Symptomatic bradycardia or second or third degree of cardiac electrical conduction without a pacemaker
	Haemodynamically significant mitral and/or aortic disease (except mitral regurgitation due to ventricular dilatation)
	Other haemodynamically significant obstructive lesions of left ventricular outflow, including aortic and sub-aortic stenosis
	Any surgical or medical condition that could affect absorption, distribution, metabolism or excretion of study drugs
	Evidence of hepatic disease
	Current or planned active treatment with bile sequestering agents
	Patients with bilateral renal artery stenosis
	Patients with thyroid dysfunction who have not been on a stable dose of L-thyroxin within 3 months prior to screening
	Patients with Grave's disease or severe adipositas

	Patients with ongoing alcohol or drug use or dependence Documented long QT syndrome or QTc >450 msec for males and 470 msec for males within 3 months prior to screening History of malignancy of any organ system (except for localised basal cell carcinoma pf the skin or in situ cervical cancer) treated or untreated within the past 5 years regardless of local recurrence or metastases Pregnant and breastfeeding women, women of child-bearing potential
Recruitment / selection of participants	No further information
Intervention(s)	ARNI (Sacubitril/valsartan) titrated up to a maximum of 97 mg / 103 mg twice daily, oral administration, for 12 weeks. A 2 week screening period took place prior to the 12 week treatment period. Patients continued background therapies for heart failure and cardiovascular disease and symptomatic treatment while receiving randomised treatment, with the exception of ACEIs/ARBs, which were replaced by study drug after a washout period of 36 hours at the end of the screening period. Sacubitril/valsartan initiated at 24/26 mg twice daily and up-titrated to target dose of 97/103 mg twice daily by week 4. At baseline, 97.7% were taking ACEI/ARBs, 90.6% were taking beta-blockers and 64.4% were taking MRAs.
Comparator	ACEI (Enalapril) titrated up to a maximum of 10 mg twice daily, oral administration, for 12 weeks. A 2 week screening period took place prior to the 12 week treatment period. Patients continued background therapies for heart failure and cardiovascular disease and symptomatic treatment while receiving randomised treatment, with the exception of ACEIs/ARBs, which were replaced by study drug after a washout period of 36 hours at the end of the 2 week screening period. Enalapril initiated at 2.5 mg twice daily and up-titrated to target dose of 10 mg twice daily by week 4. At baseline, 97.1% were taking ACEI/ARBs, 92.6% were taking beta-blockers, and 69.4% were taking MRAs.
Population subgroups	N/A

Number of participants	621 patients randomised
Duration of follow-up	12 weeks
Indirectness	
Method of analysis	Other Type of analysis unclear

Study arms

ARNI (sacubitril/valsartan) (N = 310)

Patients continued background therapies for heart failure and cardiovascular disease and symptomatic treatment while receiving randomised treatment, with the exception of ACEIs/ARBs, which were replaced by study drug after a washout period of 36 hours. Sacubitril/valsartan initiated at 24/26 mg twice daily and up-titrated to target dose of 97/103 mg twice daily by week 4. At baseline, 97.7% were taking ACEI/ARBs, 90.6% were taking beta-blockers and 64.4% were taking MRAs.

ACEI (enalapril) (N = 311)

Patients continued background therapies for heart failure and cardiovascular disease and symptomatic treatment while receiving randomised treatment, with the exception of ACEIs/ARBs, which were replaced by study drug after a washout period of 36 hours. Enalapril initiated at 2.5 mg twice daily and up-titrated to target dose of 10 mg twice daily by week 4. At baseline, 97.1% were taking ACEI/ARBs, 92.6% were taking beta-blockers, and 69.4% were taking MRAs.

Characteristics

Arm-level characteristics

Characteristic	ARNI (sacubitril/valsartan) (N = 310)	ACEI (enalapril) (N = 311)
% Female Sample size	n = 71 ; % = 22.98	n = 61 ; % = 19.68
Age (years) Mean (SD)	67.16 (11.04)	66.62 (10.45)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
NYHA class Sample size	n = NA	n = NA
NYHA Class II Sample size	n = 161 ; % = 52.1	n = 162 ; % = 52.26
NYHA Class III Sample size	n = 146 ; % = 47.25	n = 146 ; % = 47.1
NYHA class IV Sample size	n = 2 ; % = 0.65	n = 2 ; % = 0.65
Heart failure aetiology Sample size	n = NA	n = NA

Characteristic	ARNI (sacubitril/valsartan) (N = 310)	ACEI (enalapril) (N = 311)
Ischaemic Sample size	n = 177 ; % = 57.28	n = 174 ; % = 56.13
Non-ischaemic Sample size	n = 132 ; % = 42.72	n = 136 ; % = 43.87
LVEF Mean (SD)	NR	NR
Type 2 diabetes Sample size	n = NR ; % = NR	n = NR ; % = NR
Uncomplicated diabetes Type of diabetes not specified Sample size	n = 73 ; % = 23.62	n = 93 ; % = 30
Complicated diabetes Type of diabetes not specified Sample size	n = 23 ; % = 7.44	n = 24 ; % = 7.74
Atrial fibrillation Sample size	n = 147 ; % = 47.57	n = 122 ; % = 39.35
Previous heart failure hospitalisation Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	ARNI (sacubitril/valsartan) (N = 310)	ACEI (enalapril) (N = 311)
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	NR	NR
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACEI/ARB Sample size	n = 302 ; % = 97.7	n = 301 ; % = 97.1
Beta-blockers Sample size	n = 280 ; % = 90.6	n = 287 ; % = 92.6
Diuretics Sample size	n = 240 ; % = 77.7	n = 234 ; % = 75.5
MRAs Sample size	n = 199 ; % = 64.4	n = 215 ; % = 69.4
Device therapy Mean (SD)	NR	NR

Outcomes

Study timepoints

12 week

Dichotomous outcomes

Outcome	ARNI (sacubitril/valsartan), 12 week, N = 309	ACEI (enalapril), 12 week, N = 310
All-cause mortality No of events	n = 1 ; % = 0.3	n = 4 ; % = 1.3
Unplanned hospitalisation or visits (HF-related) (reported as 'cardiac failure'; hospitalisation not specified) No of events	n = 11 ; % = 3.56	n = 17 ; % = 5.48
Hyperkalaemia (undefined) No of events	n = 22 ; % = 7.12	n = 11 ; % = 3.55

All-cause mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF-related) (reported as 'cardiac failure'; hospitalisation not specified) - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

Continuous outcomes

Outcome	ARNI (sacubitril/valsartan), 12 week, N = 302	ACEI (enalapril), 12 week, N = 302
Health-related quality of life (SF-12) range 0-100, change score Mean (SD)	NA (NA)	NA (NA)

Outcome	ARNI (sacubitril/valsartan), 12 week, N = 302	ACEI (enalapril), 12 week, N = 302
Health-related quality of life (PCS-12 physical component summary) range 0-100, change score Mean (SD)	2.58 (7.11)	1.65 (6.74)
Health-related quality of life (MCS-12 mental component summary) range 0-100, change score Mean (SD)	1.45 (8.37)	1.79 (8.55)
Health-related quality of life (EQ-VAS) range 0-100, change score Mean (SD)	4.5 (17.31)	4.01 (14.77)
Health-related quality of life (EQ-5D) range -0.59 to 1, change score Mean (SD)	0.03 (0.14)	0.02 (0.12)

Health-related quality of life (SF-12) - Polarity - Higher values are better

Health-related quality of life (EQ-VAS) - Polarity - Higher values are better

Health-related quality of life (EQ-5D) - Polarity - Higher values are better

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

All-cause mortality - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Hyperkalaemia (undefined) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: outcome not defined)*

Health-related quality of life (SF-12) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

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

Health-related quality of life (EQ-VAS) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

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

Health-related quality of life (EQ-5D) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 12 weeks

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

Rogers, 2012

Bibliographic Reference	Rogers JK; McMurray JJ; Pocock SJ; Zannad F; Krum H; van Veldhuisen DJ; Swedberg K; Shi H; Vincent J; Pitt B; Eplerenone in patients with systolic heart failure and mild symptoms: analysis of repeat hospitalizations.; Circulation; 2012; vol. 126 (no. 19)

Study details

Secondary publication of another included study – see primary study for details	Secondary publication of Zannad, 2011

Other publications associated with this study included in review	Zannad, 2011; Zannad, 2010; Eschalier, 2013
Trial name / registration number	EMPAHSIS-HF/ NCT00232180.
Study type	Randomised controlled trial (RCT)
Study location	Not specified
Study setting	study hospitals
Study dates	See primary study
Sources of funding	Supported by Pfizer
Inclusion criteria	See primary study
Exclusion criteria	See primary study
Recruitment / selection of participants	See primary study
Intervention(s)	See primary study
Comparator	See primary study

Population subgroups	Not specified
Number of participants	2737 participants
Duration of follow-up	4.5 months (median)
Indirectness	None
Method of analysis	ITT analysis
Additional comments	No TTE data

Study arms

Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)

Up to 50 mg daily of eplerenone

Placebo (N = 1373)

Placebo

Characteristics

Study-level characteristics

Characteristic	Study (N = 2737)
% Female Sample size	n = NR ; % = NR
0 Hospitalisations Sample size	n = 516 ; % = 22.7
1 Hospitalisation Sample size	n = 60 ; % = 21
2 or more Hospitalisations Sample size	n = 34 ; % = 19.2
Age Mean (SD)	NR (NR)
0 Hospitalisations Mean (SD)	68.3 (7.6)
1 Hospitalisation Mean (SD)	69.9 (7.8)
2 or more Hospitalisations Mean (SD)	70.6 (7.6)
LVEF	NR (NR)

Characteristic	Study (N = 2737)
Mean (SD)	
0 Hospitalisations Mean (SD)	26.1 (4.7)
1 Hospitalisation Mean (SD)	25.5 (4.8)
2 or more Hospitalisations Mean (SD)	25.6 (4.6)
Type 2 diabetes Sample size	n = NR ; % = NR
0 Hospitalisations Sample size	n = 665
1 Hospitalisation Sample size	n = 122 ; % = 42.7
2 or more Hospitalisations Sample size	n = 72 ; % = 40.7
Atrial fibrillation Sample size	n = NR ; % = NR

Characteristic	Study (N = 2737)
0 Hospitalisation Sample size	n = 678 ; % = 29.8
1 Hospitalisation Sample size	n = 107 ; % = 37.4
2 or more Hospitalisations Sample size	n = 59 ; % = 33.3
Previous heart failure hospitalisation Sample size	n = NR ; % = NR
0 Hospitalisations Sample size	n = 1127 ; % = 49.6
1 Hospitalisation Sample size	n = 190 ; % = 66.4
2 or more Hospitalisations Sample size	n = 123 ; % = 69.5
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	NR (NR)
0 Hospitalisations	72.2 (21.8)

Characteristic	Study (N = 2737)
Mean (SD)	
1 Hospitalisation Mean (SD)	62.9 (17.6)
2 or more Hospitalisations Mean (SD)	65 (23.4)

Outcomes

Mortality

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1364	Placebo, , N = 1373
All-cause mortality No of events	n = 205 ; % = NR	n = 253 ; % = NR
CV mortality No of events	n = 178 ; % = NR	n = 215 ; % = NR

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Hospitalisations

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1364	Placebo, , N = 1373
Unplanned hospitalisation or visits (HF-related) (HF hospitalisations) (total admissions) No of events	n = 312 ; % = NR	n = 481 ; % = NR

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

Hospitalisations

Rate ratio

Outcome	Mineralocorticoid receptor antagonist (eplerenone) vs Placebo, , N2 = 1364, N1 = 1373
Unplanned hospitalisation or visits (HF-related) (HF hospitalisations) Custom value	Rate ratio: 0.53 (0.43-0.66)

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

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

Unplanned hospitalisation or visits (HF-related) (HF hospitalisations)

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

CV mortality

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

All-cause mortality

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

Unplanned hospitalisation or visits (HF-related) (HF hospitalisations) - Rate ratio - Mineralocorticoid receptor antagonist (eplerenone)-Placebo

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

Shen, 2021

Bibliographic Reference	Shen, Li; Kristensen, Soren Lund; Bengtsson, Olof; Bohm, Michael; de Boer, Rudolf A; Docherty, Kieran F; Inzucchi, Silvio E; Katova, Tzvetana; Kober, Lars; Kosiborod, Mikhail N; Langkilde, Anna Maria; Lindholm, Daniel; Martinez, M Felipe A; O'Meara, Eileen; Nicolau, Jose C; Petrie, Mark C; Ponikowski, Piotr; Sabatine, Marc S; Schou, Morten; Sjostrand, Mikaela; Solomon, Scott D; Jhund, Pardeep S; McMurray, John J V; Dapagliflozin in HFrEF Patients Treated With Mineralocorticoid Receptor Antagonists: An Analysis of DAPA-HF.; JACC. Heart failure; 2021; vol. 9 (no. 4); 254-264

Study details

Secondary publication of another included study – see primary study for details	Secondary publication of DAPA-HF. See parent study for details: McMurray (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England journal of medicine; 2019; vol. 381 (no. 21); 1995-2008
Trial name / registration number	DAPA-HF
Study type	Randomised controlled trial (RCT)
Number of participants	4744 randomisation Hyperkalaemia data on 4599 (hyperkalaemia at BL excluded from analysis)
Duration of follow-up	median 18.2 months

Study arms

SGLT2i (dapagliflozin) (N = 2373)

Patients received 10 mg dapagliflozin daily in addition to recommended therapy. Patients also received Beta-blocker (96.0%), ACEI (56.1%), ARB (28.4%), Sacubitril-valsartan (10.5%), MRA (71.5%)

Placebo (N = 2371)

Patients received daily placebo in addition to recommended therapy Patients also received Beta-blocker (96.2%), ACEI (56.1%), ARB (26.7%), Sacubitril-valsartan (10.9%), MRA (70.6%)

Outcomes

Study timepoints

18.2 month

Dichotomous outcomes

Outcome	SGLT2i (dapagliflozin), 18.2 month, N = 2307	Placebo , 18.2 month, N = 2292
Hyperkalaemia (serum potassium concentration >5.5 mmol/l) excluded patients with baseline serum potassium >5.5 mmol/l (n=145). Calculated by adding MRA subgroups together No of events	n = 243 ; % = 10.5	n = 263 ; % = 11.5

Hyperkalaemia (serum potassium concentration >5.5 mmol/l) - Polarity - Lower values are better

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

Hyperkalaemia (serum potassium concentration >5.5 mmol/l) - Events at FUP 18.2 months

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

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

Secondary publication of another included study – see primary study for details	CHARM rationale and design. See McMurray 2003 for full details

Tsutsui, 2017

Bibliographic Reference	Tsutsui H; Ito H; Kitakaze M; Komuro I; Murohara T; Izumi T; Sunagawa K; Yasumura Y; Yano M; Yamamoto K; Yoshikawa T; Tsutamoto T; Zhang J; Okayama A; Ichikawa Y; Kanmuri K; Matsuzaki M; ; 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; 2017; vol. 82 (no. 1)

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with this study included in review	Zannad, 2011; Rogers, 2012; Eschalier, 2013
Trial name / registration number	J-EMPHASIS-HF NCT01115855
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Study centres
Study dates	Not specified

Sources of funding	Pfizer
Inclusion criteria	Japanese patients ≥55 years of age who had chronic HF of ischemic or non-ischemic aetiology (duration of ≥4 weeks) symptoms of NYHA functional class II or higher left ventricular ejection fraction (LVEF) ≤30% (or ≤35% in addition to QRS duration >130ms on ECG) treatment with an ACE inhibitor, ARB, beta-blocker, or diuretic
Exclusion criteria	Acute myocardial infarction or stroke within 30 days prior to randomisation serum potassium level >5.0mEq/L estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 within 24 h prior to randomization need for a potassium-sparing diuretic such as spironolactone any other clinically significant coexisting conditions
Recruitment / selection of participants	Not specified
Intervention(s)	Eplerenone was initiated at a dose of 25mg once daily provided that the serum potassium level was <5.0mEq/L when dosage was initiated, and increased after 4 weeks to 50mg once daily (or initiated at 25mg on alternate days and increased to 25mg daily, if eGFR was 30 to <50mL/min/1.73 m2). Thereafter, serum potassium level was measured at each visit except for months 2, 3, and 4. Investigators were instructed to decrease the dose of study drug if the serum potassium level was 5.5–5.9mEq/L and to withhold the study drug if the serum potassium level was ≥6.0mEq/L. Potassium was to be re-measured within 72h after withholding the study drug, and the study drug was to be restarted only if the level was <5.0mEq/L.
Comparator	Placebo

Population subgroups	Sex, age, systolic blood pressure, pulse pressure, heart rate, estimated GFR, baseline NYHA cohort, primary diagnosis, baseline BNP, baseline UACR, Beta-blocker, ACE-inhibitor and ARB use, LVEF, atrial fibrillation, diabetes, heart disease, hypertension, CRT or ICD, QRS, left bundle-branch block present, and prior CV hospitalisation within 180 days.
Number of participants	221 participants
Duration of follow-up	30 months
Indirectness	None
Method of analysis	ITT analysis
Additional comments	No time to event data reported. The results are reported as number of participants who experienced the event.

Study arms

Mineralocorticoid receptor antagonist (eplerenone) (N = 111)

Eplerenone was initiated at a dose of 25mg once daily provided that the serum potassium level was <5.0mEq/L when dosage was initiated, and increased after 4 weeks to 50mg once daily (or initiated at 25mg on alternate days and increased to 25mg daily, if eGFR was 30 to <50mL/min/1.73 m2). Thereafter, serum potassium level was measured at each visit except for months 2, 3, and 4. Investigators were instructed to decrease the dose of study drug if the serum potassium level was 5.5–5.9mEq/L and to withhold the study drug if the serum potassium level was ≥6.0mEq/L. Potassium was to be re-measured within 72h after withholding the study drug, and the study drug was to be restarted only if the level was <5.0mEq/L.

Placebo (N = 110)

Placebo

Characteristics

Arm-level characteristics

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 111)	Placebo (N = 110)
% Female Sample size	n = 26 ; % = 23.4	n = 19 ; % = 17.3
Age Mean (SD)	69 (8.7)	68.4 (7.7)
NYHA class Sample size	n = NR ; % = NR	n = NR ; % = NR
NYHA Class II Sample size	n = 91 ; % = 82	n = 92 ; % = 83.6
NYHA class III/IV Sample size	n = 20 ; % = 18.6	n = 18 ; % = 16.4
Heart failure aetiology Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 111)	Placebo (N = 110)
Ischemic heart disease Sample size	n = 31 ; % = 27.9	n = 43 ; % = 39.1
Idiopathic dilated cardiomyopathy Sample size	n = 52 ; % = 46.8	n = 48 ; % = 43.6
Hypertension Sample size	n = 9 ; % = 8.1	n = 6 ; % = 5.5
Other causes Sample size	n = 19 ; % = 17.1	n = 13 ; % = 11.8
LVEF Mean (SD)	25.6 (5)	26.6 (4)
Type 2 diabetes Sample size	n = 37 ; % = 33.3	n = 51 ; % = 46.4
Atrial fibrillation Sample size	n = 37 ; % = 33.3	n = 39 ; % = 35.5
Previous heart failure hospitalisation Sample size	n = 90 ; % = 81.1	n = 79 ; % = 71.8

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 111)	Placebo (N = 110)
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	57.1 (15.8)	56.1 (14.6)
Diuretic Sample size	n = 95 ; % = 85.6	n = 93 ; % = 84.5
ACE-inhibitor Sample size	n = 56 ; % = 50.5	n = 54 ; % = 49.1
ARB Sample size	n = 41 ; % = 36.9	n = 40 ; % = 36.4
ACE inhibitor, ARB, or both Sample size	n = 92 ; % = 82.9	n = 90 ; % = 81.8
Beta-blockers Sample size	n = 98 ; % = 88.3	n = 92 ; % = 83.6
Digitalis Sample size	n = 12 ; % = 10.8	n = 19 ; % = 17.3
Antiarrhythmic drug Sample size	n = 23 ; % = 20.7	n = 26 ; % = 23.6

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 111)	Placebo (N = 110)
Antiplatelet Sample size	n = 48 ; % = 43.2	n = 57 ; % = 51.8
Oral anti-coagulant Sample size	n = 50 ; % = 45	n = 66 ; % = 60
Statin Sample size	n = 50 ; % = 45	n = 62 ; % = 56.4
Cardiac resynchronization therapy/ implantable cardioverter-defibrillator with cardiac resynchronization (CRT/CRT-D) Sample size	n = 8 ; % = 7.2	n = 7 ; % = 6.4
Implantable cardioverter-defibrilator (ICD) Sample size	n = 16 ; % = 14.4	n = 10 ; % = 9.1

Outcomes

Study timepoints

30 month (Median)

Mortality

Outcome	Mineralocorticoid receptor antagonist (eplerenone), 30 month, N = 111	Placebo, 30 month, N = 110
All-cause mortality No of events	n = 17 ; % = 15.3	n = 10 ; % = 9.1
CV mortality No of events	n = 14 ; % = 12.6	n = 6 ; % = 5.5
All-cause mortality Hazard ratio (95%CI) Custom value	1.77 (0.81, 3.87)	NR
CV mortality Hazard ratio (95%CI) Custom value	2.40 (0.92, 6.24)	NR

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Number of deaths

Hospitalisation

Outcome	Mineralocorticoid receptor antagonist (eplerenone), 30 month, N = 111	Placebo, 30 month, N = 110
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) No of events	n = 27 ; % = 24.3	n = 33 ; % = 30
Unplanned hospitalisation or visits HF-related (hospitalisation for HF) Hazard ratio (95%CI) Custom value	0.75 (0.45, 1.25)	NR

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

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

Hospitalisation

Adverse events

Outcome	Mineralocorticoid receptor antagonist (eplerenone), 30 month, N = 111	Placebo, 30 month, N = 110
Hyperkalaemia (undefined) No of events	n = 8 ; % = 7.2	n = 6 ; % = 5.5

Hyperkalaemia (undefined) - Polarity - Lower values are better

Adverse events

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

Hyperkalaemia (undefined)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: definition for hyperkalaemia not provided)*

CV mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to the outcome assessment process being unblinded)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

All-cause mortality (HR)

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

CV mortality (HR)

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

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF) (HR)

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Tsutsui, 2017

Bibliographic Reference	Tsutsui, Hiroyuki; Momomura, Shinichi; Saito, Yoshihiko; Ito, Hiroshi; Yamamoto, Kazuhiro; Ohishi, Tomomi; Okino, Naoko; Guo, Weinong; 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; 2017; vol. 70 (no. 3); 225-231

Study details

Secondary publication of another included study – see primary study for details	Rationale and design of PARALLEL-HF See primary study Tsutsui 2021, EPPI ID = 15338370
Other publications associated with this study included in review	Tsutsui 2018, EPPI ID = 15338623
Trial name / registration number	PARALLEL-HF / NCT02468232

Tsutsui, 2018

Bibliographic Reference	Tsutsui, Hiroyuki; Momomura, Shin-Ichi; Saito, Yoshihiko; Ito, Hiroshi; Yamamoto, Kazuhiro; Ohishi, Tomomi; Okino, Naoko; Kitamura, Toshihito; Guo, Weinong; 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; 2018; vol. 82 (no. 10); 2575-2583

Study details

Secondary publication of another included study – see primary study for details	Baseline characteristics for PARALLEL-HF See Tsutsui 2021, EPPI ID: 15338370 for trial details
Other publications associated with this study included in review	Trial design and rationale: Tsutsui 2017, EPPI ID: 15339935
Trial name / registration number	PARALLEL-HF / NCT02468232

Tsutsui, 2021

Bibliographic Reference	Tsutsui, Hiroyuki; Momomura, Shin-Ichi; Saito, Yoshihiko; Ito, Hiroshi; Yamamoto, Kazuhiro; Sakata, Yasushi; Desai, Akshay Suvas; Ohishi, Tomomi; Iimori, Takayuki; Kitamura, Toshihito; Guo, Weinong; 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; 2021; vol. 85 (no. 5); 584-594

Study details

Secondary publication of another included study – see primary study for details	N/A
Other publications associated with this study included in review	Tsutsui 2017 (EPPI ID: 15339935) Tsutsui 2018 (EPPI ID: 15338623)
Trial name / registration number	PARALLEL-HF NCT02468232
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Approximately 50 study sites in Japan
Study dates	Patients were screened between June 2015 and December 2016

Sources of funding	Novartis Pharma AG
Inclusion criteria	Male/female patients aged 20 years or older Diagnosis of chronic heart failure (NYHA class II - IV) and a reduced ejection fraction (LVEF ≤35%) NT-proBNP ≥600 pg/mL at the screening visit, or NT-proBNP ≥400 pg/mL for those hospitalised for heart failure within the past 12 months Treatment with a stable dose of ACEI or ARB for at last 4 weeks prior to study entry Treatment with a beta-blocker, unless contra-indicated or not tolerated, at a stable dose for at least 4 weeks prior to screening Treatment with a MRA should be considered, taking account of renal function, serum potassium, and tolerability. If given, dose of MRA should be stable for at least 4 weeks prior to screening
Exclusion criteria	Hypersensitivity to study drugs or drugs o similar chemical classes Documented history of intolerance to ACEIs or ARBs Known history of angioedema Current acute decompensated heart failure (exacerbation of chronic heart failure manifested by signs and symptoms that may require intravenous therapy) Symptomatic hypotension and/or a SBP <100 mgHg at the screening visit or <95 mmHg at the end of the run-in eGFR <30 mL/min/1.73 m2 at screening or end of run-in, or >35% decline in eGFR between screening and end of run-in Serum potassium >5.2 mmol/L at screening or >5.4 mmol/L at the end of run-in Acute coronary syndrome, stroke, transient ischaemic attack, cardiac, carotid or other major cardiovascular surgery, percutaneous coronary intervention or carotid angioplasty within 3 months prior to screening Implants including a cardiac resynchronisation therapy pacemaker (CRT-P) or a cardiac resynchronisation therapy defibrillator (CRT-D), upgrade of existing conventional pacemaker or an implantable cardioverter defibrillator (ICD) to a CRT

	device within 3 months prior to screening visit, or the intent to implant such a device. patients who had a conventional pacemaker or an ICD implanted or had revisions to a pacemaker or other device leads within 1 month before the screening visit were excluded. History of heart transplant or ventricular assist device (VAD), or the intent to transplant or implant a VAD History of severe pulmonary disease
Recruitment / selection of participants	No further information
Intervention(s)	ARNI (Sacubitril/valsartan) 200 mg twice daily Two week single blind run-in with sacubitril/valsartan 50 mg twice daily. There was a 36 hour washout period for the discontinuation of ACEI and ARBS before sacubitril/valsartan treatment was started. Other background medications for chronic heart failure were continued. At the end of the run-in, only patients who could tolerate sacubitril/valsartan proceeded to randomised treatment. Sacubitril/valsartan was initiated at 100 mg twice daily for 4 weeks and up-titrated to the target dose of 200 mg twice daily, if tolerated. Patients were allowed to continue background heart failure medications, such as beta-blockers and MRAs, but not ACEIs and ARBs. 36 hour washout period of sacubitril/valsartan at the beginning of the double blind treatment period, to prevent overlap of sacubitril/valsartan administered during the run in period and reduce risk of angioedema.
Comparator	Enalapril 10 mg twice daily Two week single blind run-in with sacubitril/valsartan 50 mg twice daily. There was a 36 hour washout period for the discontinuation of ACEI and ARBS before sacubitril/valsartan treatment was started. Other background medications for chronic heart failure were continued. At the end of the run-in, only patients who could tolerate sacubitril/valsartan proceeded to randomised treatment.

	Enalapril was initiated at 5 mg twice daily for 4 weeks and up-titrated t target dose of 10 mg twice daily, if tolerated. Patients were allowed to continue background heart failure medications, such as beta-blockers and MRAs, but not ACEIs and ARBs. 36 hour washout period of sacubitril/valsartan at the beginning of the double blind treatment period, to prevent overlap of sacubitril/valsartan administered during the run in period and reduce risk of angioedema.
Population subgroups	Subgroup analysis reported for primary composite outcome (CV death or HF hospitalisation) for age (<65 years/≥65 years), diabetes at baseline, baseline eGFR (<60 mL/min/1.73m2/≥60 mL/min1.73m2)
Number of participants	225 randomised participants
Duration of follow-up	median follow up 33.6 months
Method of analysis	Other Type of analysis unclear
Additional comments	Not specified

Study arms

ARNI (sacubitril/valsartan) (N = 112)

Sacubitril/valsartan 200 mg twice daily

ACEI (enalapril) (N = 113)

Enalapril 10 mg twice daily

Characteristics

Arm-level characteristics

Characteristic	ARNI (sacubitril/valsartan) (N = 112)	ACEI (enalapril) (N = 113)
% Female Sample size	n = 15 ; % = 13.5	n = 16 ; % = 14.3
Age Mean (SD)	69 (9.7)	66.7 (10.9)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
NYHA class Sample size	n = NA	n = NA
Class I Sample size	n = 4 ; % = 3.6	n = 4 ; % = 3.6
Class II Sample size	n = 101 ; % = 91	n = 104 ; % = 92.9
Class III Sample size	n = 6 ; % = 5.4	n = 4 ; % = 3.6

Characteristic	ARNI (sacubitril/valsartan) (N = 112)	ACEI (enalapril) (N = 113)
Class IV Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Heart failure aetiology Primary heart failure aetiology Sample size	n = NA	n = NA
Ischaemic Sample size	n = 57 ; % = 51.4	n = 49 ; % = 43.8
Non-ischaemic Sample size	n = 54 ; % = 48.6	n = 63 ; % = 56.2
LVEF Mean (SD)	28.6 (5.1)	27.7 (5.5)
Type 2 diabetes Diabetes mellitus (type not specified) Sample size	n = 52 ; % = 46.8	n = 52 ; % = 46.4
Atrial fibrillation Sample size	n = 36 ; % = 32.4	n = 40 ; % = 35.7
Previous heart failure hospitalisation Sample size	n = 80 ; % = 72.1	n = 82 ; % = 73.2

Characteristic	ARNI (sacubitril/valsartan) (N = 112)	ACEI (enalapril) (N = 113)
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	58.3 (17.6)	57.6 (14.7)
Background (non-randomised) heart failure medications Sample size	n = NA	n = NA
ACEI Sample size	n = 71 ; % = 64	n = 69 ; % = 61.6
ARB Sample size	n = 40 ; % = 36	n = 43 ; % = 38.4
MRA Sample size	n = 64 ; % = 57.7	n = 69 ; % = 61.6
Diuretic Sample size	n = 91 ; % = 82	n = 95 ; % = 84.8
Beta-blocker Sample size	n = 105 ; % = 94.6	n = 108 ; % = 96.4
Device therapy Cardiac resynchronisation therapy / implantable cardioverter-defibrillator Sample size	n = 16 ; % = 14.4	n = 26 ; % = 23.2

Outcomes

Study timepoints

33.9 month

6 month

Dichotomous outcomes

Outcome	ARNI (sacubitril/valsartan), 33.9 month, N = 111	ACEI (enalapril), 33.9 month, N = 112
All-cause mortality No of events	n = 2 ; % = 1.8	n = 1 ; % = 0.9
CV mortality No of events	n = 13 ; % = 11.7	n = 11 ; % = 9.8
Unplanned hospitalisation or visits (HF-related) (first HF hospitalisation) No of events	n = 25 ; % = 22.5	n = 20 ; % = 17.9
Withdrawal due to drug-related adverse events (permanent discontinuation of treatment due to AEs) No of events	n = 11 ; % = 9.9	n = 13 ; % = 11.6
Hyperkalaemia (undefined)	n = 13 ; % = 11.7	n = 17 ; % = 15.2

Outcome	ARNI (sacubitril/valsartan), 33.9 month, N = 111	ACEI (enalapril), 33.9 month, N = 112
No of events		

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

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

Withdrawal due to drug-related adverse events (permanent discontinuation of treatment due to AEs) - Polarity - Lower values are better

Hyperkalaemia (undefined) - Polarity - Lower values are better

Contrast outcomes

Outcome	ARNI (sacubitril/valsartan) vs ACEI (enalapril), 33.9 month, N2 = 111, N1 = 112	ARNI (sacubitril/valsartan) vs ACEI (enalapril), 6 month, N2 = 111, N1 = 112
CV mortality Hazard ratio/95% CI	1.17 (0.52 to 2.61)	NA
Unplanned hospitalisation or visits (HF-related) (first HF hospitalisation) Hazard ratio/95% CI	1.27 (0.7 to 2.28)	NA
Health-related quality of life (KCCQ clinical summary score) range 0-100, change score (LSM change from baseline -2.22 for ARNI (sacubitril/valsartan) and -3.49 for ACEI (enalapril)	NA (NA)	1.27 (0.57)

Outcome	ARNI (sacubitril/valsartan) vs ACEI (enalapril), 33.9 month, N2 = 111, N1 = 112	ARNI (sacubitril/valsartan) vs ACEI (enalapril), 6 month, N2 = 111, N1 = 112
Mean (p value)		

CV mortality - Polarity - Lower values are better

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

Health-related quality of life (KCCQ clinical summary score) - Polarity - Higher values are better

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

All-cause mortality - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 months

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

CV mortality (Hazard Ratio) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 months

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

Unplanned hospitalisation or visits (HF-related) (first HF hospitalisation) -ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: reported as number of events)*

Unplanned hospitalisation or visits (HF-related) (first HF hospitalisation) (Hazard Ratio) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 moths

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

Withdrawal due to drug-related adverse events (permanent discontinuation of treatment due to AEs) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 months

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

Hyperkalaemia (undefined) - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 months

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

Health-related quality of life (KCCQ clinical summary score) mean treatment difference - ARNI (sacubitril/valsartan) vs ACEI (enalapril) at 33.9 months

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

Udelson, 2010

Bibliographic Reference	Udelson JE; Feldman AM; Greenberg B; Pitt B; Mukherjee R; Solomon HA; Konstam MA; 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; 2010; vol. 3 (no. 3)

Study details

Secondary publication of another included study – see primary study for details	N/A
Trial name / registration number	Unique identifier: NCT00082589
Study location	US

Study setting	Unclear
Study dates	Not reported
Sources of funding	Trial funded by Pfizer Inc, all investigators and/or their institutions received research funding from Pfizer Inc.
Inclusion criteria	Age ≥21 years w NYHA functional class II and III LVEF of ≤35% by equilibrium-gated RVG at screening On stable therapy with an ACEI and/or ARB and BB (unless documented intolerance)
Exclusion criteria	Current decompensated HF HF hospitalization or severe HF (NYHA functional class IV) within 6 months of screening Serum potassium >5.5 mEq/L, History of hyperkalemia (K >6.0 mEq/L) with eplerenone or spironolactone, Creatinine clearance of <30 mL/min Biventricular pacemaker placed within 6 months of screening, Requiring potassium-sparing diuretics or spironolactone.
Intervention(s)	Initially 25 mg of eplerenone daily. After 4 weeks the dose was increased to the target dose of 50 mg (two 25 mg tablets daily) . Serum potassium was monitored throughout the study, and if necessary, doses were titrated down.
Comparator	Matching placebo

Number of participants	226
Duration of follow-up	Study drug treatment duration was 36 weeks
Method of analysis	ITT analysis
Additional comments	

Study arms

MRA (eplerenone) (N = 117)

96.6% background BB; 86% background ACEI

Placebo (N = 109)

93.6% background BB; 86% background ACEI

Characteristics

Arm-level characteristics

Characteristic	MRA (eplerenone) (N = 117)	Placebo (N = 109)
% Female	n = 19 ; % = 16.2	n = 18 ; % = 16.5
Sample size		

Characteristic	MRA (eplerenone) (N = 117)	Placebo (N = 109)
Age Mean (SD)	63.3 (12.2)	62 (12.9)
Ethnicity - Caucasian Sample size	% = 81.2	% = 85.3
NYHA class - NYHA II or III Sample size	n = 116 ; % = 99	n = 109 ; % = 100
Heart failure aetiology - Ischaemic Sample size	% = 60	% = 61
LVEF Mean (SE)	26.2 (0.6)	27 (0.6)
Type 2 diabetes Diabetes Sample size	n = 47 ; % = 40.2	n = 40 ; % = 36.7
Background (non-randomised) heart failure medications - ACEI Sample size	% = 86	% = 86
Background (non-randomised) heart failure medications - ARB Sample size	% = 25	% = 21

Characteristic	MRA (eplerenone) (N = 117)	Placebo (N = 109)
Background (non-randomised) heart failure medications - BB Sample size	% = 96.6	% = 93.6

Outcomes

Study timepoints

36 week

Dichotomous

Outcome	MRA (eplerenone), 36 week, N = 117	Placebo, 36 week, N = 109
Hyperkalaemia (undefined) No of events	n = 14 ; % = 12	n = 6 ; % = 5.5

Hyperkalaemia (undefined) - Polarity - Lower values are better

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

Hyperkalaemia (undefined)

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Unclear potassium threshold for hyperkalaemia definition)*

Vizzardi, 2014

Bibliographic Reference	Vizzardi, Enrico; Nodari, Savina; Caretta, Giorgio; D'Aloia, Antonio; Pezzali, Natalia; Faden, Giacomo; Lombardi, Carlo; Raddino, Riccardo; Metra, Marco; Dei Cas, Livio; 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; 2014; vol. 347 (no. 4); 271-6

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR

Study location	Italy
Study setting	study institute
Study dates	February 2001 to September 2004
Sources of funding	Not specified
Inclusion criteria	Had a diagnosis of CHF. Had a left ventricular ejection fraction (LVEF) <40% of either ischemic or non-ischemic causative factor. NYHA class I or II symptoms No history of acute decompensation (NYHA class III or IV) in the previous year Treated with an ACE inhibitor (or an ARB if not tolerated and a beta-blocker unless contraindicated, in addition to a loop diuretic if clinically indicated)
Exclusion criteria	Cockroft-Gault formula estimated glomerular filtration rate (eGFR) , 30 mL/min/ 1.73 m2 Serum K . 5.0 mEq/L Valvular heart disease amenable to surgical treatment Unstable angina or acute MI or coronary revascularization procedure within 3 months before enrolment Intravenous therapy with inotropic drugs within 3 months before enrolment Congenital heart disease, primary hepatic failure, active cancer or any life-threatening disease (other than HF) K+-sparing diuretics History of resuscitated ventricular arrhythmias (unless this occurred within 24 hours of a previous acute MI or in subjects with an implantable cardioverter defibrillator); and other clinical or general conditions contraindicating participation in a clinical trial.

Recruitment / selection of participants	Not specified
Intervention(s)	25 mg of spironolactone once per day. At 4 weeks, provided that serum potassium was ≤5.0 mmol/L, the dose of study drug could be increased to 50 mg once daily if eGFR was ≥50 mL/min/1.73 m2 and remained 25 mg once daily if eGFR was in the range of 30 to 49 mL/min/1.73 m2. At 8 weeks, if study drug was well tolerated, the dose could be increased to 100 mg 4 times a day. Potassium and renal function were tested every week during the up-titration and then every 2 to 4 weeks as clinically indicated. If hyperkalemia developed at any time or eGFR ranged below 30/mL/ min/1.73 m2, the dose could be decreased to 25 mg every other day. Study medication could be withheld in the event of serious hyperkalemia (.6.0 mEq/L), an eGFR of less than 30 mL/min/ 1.72 m2 after minimal dosage achieved, intercurrent illness or any condition in which such a course was deemed medically necessary to protect the patient's best interest.
Comparator	Placebo
Population subgroups	Ischemic and non-ischemic cardiomyopathy
Number of participants	130
Duration of follow-up	44 (±16) months
Indirectness	None
Method of analysis	Other Intergroup comparison between continuous variables.
Additional comments	Time to event data not reported. Number of events reported.

Study arms

Mineralocorticoid receptor antagonist (spironolactone) (N = 65)

25 mg of spironolactone once per day.

Placebo (N = 65)

Placebo

Characteristics

Arm-level characteristics

Characteristic	Mineralocorticoid receptor antagonist (spironolactone) (N = 65)	Placebo (N = 65)
Age Mean (SD)	61 (14.7)	65 (17.4)
NYHA class Sample size	n = NR ; % = NR	n = NR ; % = NR
Class I Sample size	n = 18 ; % = 27	n = 6 ; % = 9
Class II Sample size	n = 47 ; % = 73	n = 59 ; % = 91

Characteristic	Mineralocorticoid receptor antagonist (spironolactone) (N = 65)	Placebo (N = 65)
Heart failure aetiology Sample size	n = 29 ; % = 44.6	n = 39 ; % = 60
Type 2 diabetes Sample size	n = 10 ; % = 15.3	n = 8 ; % = 12.3
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	82.5 (27.9)	71.3 (18.09)
Background (non-randomised) heart failure medications Sample size	n = NR ; % = NR	n = NR ; % = NR
ACE-i/ ARBs Sample size	n = NR ; % = 100	n = NR ; % = 98.5
Beta-blockers Sample size	n = NR ; % = 97	n = NR ; % = 98.4
Diuretics Sample size	n = NR ; % = 75	n = NR ; % = 86
Amiodarone Sample size	n = NR ; % = 34	n = NR ; % = 32.8

Characteristic	Mineralocorticoid receptor antagonist (spironolactone) (N = 65)	Placebo (N = 65)
Device therapy Sample size	n = NR ; % = NR	n = NR ; % = NR
CRT Sample size	n = 46 ; % = 35	n = 44 ; % = 34
AICD Sample size	n = 26 ; % = 20	n = 29 ; % = 22

Outcomes

Mortality

Outcome	Mineralocorticoid receptor antagonist (spironolactone), , N = 65	Placebo, , N = 65
All-cause mortality No of events	n = 8 ; % = 12.3	n = 8 ; % = 12.3
CV mortality No of events	n = 3 ; % = 4.6	n = 8 ; % = 12.3

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Hyperkalaemia

Outcome	Mineralocorticoid receptor antagonist (spironolactone), , N = 65	Placebo, , N = 65
Hyperkalaemia (undefined) No of events	n = 2 ; % = 3	n = 0 ; % = 0

Hyperkalaemia (undefined) - Polarity - Lower values are better

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

Hyperkalaemia (undefined)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to participants and people delivering the intervention being aware of the intervention and the allocation sequence was unlikely to be randomised)*
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to participants and people delivering the intervention being aware of the intervention and the allocation sequence was unlikely to be randomised)*
Overall bias and Directness	Overall Directness	Directly applicable

CV mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to participants and people delivering the intervention being aware of the intervention and the allocation sequence was unlikely to be randomised)*
Overall bias and Directness	Overall Directness	Directly applicable

White, 2007

Bibliographic Reference	White, Michel; Lepage, Serge; Lavoie, Joel; De Denus, Simon; Leblanc, Marie-Helene; Gossard, Denis; Whittom, Lucette; Racine, Normand; Ducharme, Anique; Dabouz, Farida; Rouleau, Jean-Lucien; Touyz, Rhian; 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; 2007; vol. 13 (no. 2); 86-94

Study details

Secondary publication of another included study – see primary study for details	NA
Other publications associated with	NA

this study included in review	
Trial name / registration number	NA
Study location	Montreal, Quebec, Canada
Study setting	Hospital care
Study dates	NA
Sources of funding	NA
Inclusion criteria	Symptomatic Heart failure; LVEF <40%; on stable and optimal dose of ACE inhibitors for at least 3 months;
Exclusion criteria	NA
Recruitment / selection of participants	NA
Intervention(s)	ARB (Candesartan). The patients were randomized to receive candesartan at an initial dose of either 4 or 8 mg once daily followed by 8 weeks of titration phase and 16 weeks of observation period. The goal was to achieve 32 mg per day. The dose of candesartan was doubled every 2 weeks until the target dose of candesartan was achieved. Down titration was allowed at all times.
Comparator	Placebo. Patients in the control arm continued on the stable optimal dose of ACE inhibitors
Population subgroups	NA

Number of participants	68
Duration of follow-up	24 weeks
Indirectness	NA
Method of analysis	Available case analysis

Study arms

ARB (Candesartan) + ACE inhibitor (N = 41)

The patients were randomized to receive candesartan at an initial dose of either 4 or 8 mg once daily followed by 8 weeks of titration phase and 16 weeks of observation period. The goal was to achieve 32 mg per day

ACE inhibitor (N = 39)

Placebo arm

Characteristics

Arm-level characteristics

Characteristic	ARB (Candesartan) + ACE inhibitor (N = 41)	ACE inhibitor (N = 39)
% Female	n = 3 ; % = 7	n = 5 ; % = 13
Sample size		

Characteristic	ARB (Candesartan) + ACE inhibitor (N = 41)	ACE inhibitor (N = 39)
Age (Years (mean, SD)) Mean (SD)	62.7 (8.9)	62.5 (8.1)
II Sample size	n = 22 ; % = 53.7	n = 24 ; % = 61.5
III Sample size	n = 18 ; % = 43.9	n = 15 ; % = 38.5
IV Sample size	n = 1 ; % = 2.4	n = 0 ; % = 0
Coronary artery disease Sample size	n = 36 ; % = 88	n = 30 ; % = 77
Atrial fibrillation (%) Sample size	n = 7 ; % = 17	n = 13 ; % = 33
ACE-inhibitor Sample size	n = 41 ; % = 100	n = 39 ; % = 100
Diuretics (total) Sample size	n = 33 ; % = 80.5	n = 32 ; % = 82.1
Spironolactone	n = 13 ; % = 40	n = 14 ; % = 44

Characteristic	ARB (Candesartan) + ACE inhibitor (N = 41)	ACE inhibitor (N = 39)
Sample size		
Beta-blocker Sample size	n = 39 ; % = 95.1	n = 36 ; % = 92.3
Digitalis glycoside Sample size	n = 25 ; % = 61	n = 25 ; % = 64.1
Calcium-channel blocker Sample size	n = 3 ; % = 7.3	n = 3 ; % = 7.7
Statin Sample size	n = 28 ; % = 68.3	n = 34 ; % = 87.2

Outcomes

Study timepoints

24 week

Dichotomous Outcomes

Outcome	ARB (Candesartan) + ACE inhibitor, 24 week, N = 35	ACE inhibitor, 24 week, N = 33
All-cause mortality No of events	n = 0 ; % = 0	n = 1 ; % = 3
Withdrawal due to drug-related adverse events No of events	n = 4 ; % = 11.4	n = 4 ; % = 12.12
Hyperkalaemia (serum potassium concentration ≥ 5.5 mmol/L) No of events	n = 3 ; % = 8.6	n = 0 ; % = 0
Falls (symptomatic hypotension as a surrogate) No of events	n = 2 ; % = 5.7	n = 0 ; % = 0

All-cause mortality - Polarity - Lower values are better

Withdrawal due to drug-related adverse events - Polarity - Lower values are better

Hyperkalaemia (serum potassium concentration ≥ 5.5 mmol/L) - Polarity - Lower values are better

Falls (symptomatic hypotension as a surrogate) - Polarity - Lower values are better

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

All-cause mortality at the end of 24 weeks

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

Falls (symptomatic hypotension as a surrogate)-Events-24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness: symptomatic hypotension used as a surrogate for falls)*

Withdrawal due to drug-related adverse events - No of events-ARB (Candesartan) + ACE inhibitor-ACE inhibitor-t24

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

Hyperkalaemia (serumpotassiumconcentration≥5.5mmol/L) - No of events-ARB (Candesartan) + ACE inhibitor-ACE inhibitor-t24

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Zannad, 2010

Bibliographic Reference	Zannad F; McMurray JJ; Drexler H; Krum H; van Veldhuisen DJ; Swedberg K; Shi H; Vincent J; Pitt B; Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF).; European journal of heart failure; 2010; vol. 12 (no. 6)

Study details

Secondary publication of another included study – see primary study for details	Design and rationale for EMPHASIS-HF: see Zannad 2011 for full details
Trial name / registration number	EMPHASIS-HF
Study location	308 study locations including USA, Argentina, Australia, Belgium, Canada, Czechia, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Italy, Korea, Mexico, the Netherlands, Poland, Portugal, Russian Federation, Singapore, Slovakia, South Africa, Spain, Sweden, Ukraine, United Arab Emirates, United Kingdom, and Venezuela (information retrieved from NCT registration page)
Study setting	Study centres

Study dates	March 2006 to October 2011
Sources of funding	Pfizer

Zannad, 2011

Bibliographic Reference	Zannad F; McMurray JJ; Krum H; van Veldhuisen DJ; Swedberg K; Shi H; Vincent J; Pocock SJ; Pitt B; ; Eplerenone in patients with systolic heart failure and mild symptoms.; The New England journal of medicine; 2011; vol. 364 (no. 1)

Study details

Secondary publication of another included study – see primary study for details	N/A
Other publications associated with this study included in review	Zannad, 2010; Rogers, 2012; Eschalier, 2013
Trial name / registration number	EMPHASIS-HF NCT00232180
Study type	Randomised controlled trial (RCT)

Study location	278 study centres across 29 countries
Study setting	Specified study centres
Study dates	March 30, 2006 to May 25, 2010
Sources of funding	Pfizer
Inclusion criteria	Aged at least 55 years NYHA functional class II symptoms An ejection fraction no more than 30% (or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography). Treatment with an angiotensin-converting-enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or both, and a beta-blocker (unless contraindicated) at the recommended dose or maximum tolerated dose.
Exclusion criteria	Acute myocardial infarction NYHA class III or IV heart failure A serum potassium level exceeding 5.0 mmol per litre, an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m2 of body-surface area. A need for potassium-sparing diuretic Any other clinically significant coexisting condition
Recruitment / selection of participants	Recruited stated but not specified
Intervention(s)	Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated GFR was 30 to 49 ml per minute per 1.73 m2), provided the serum potassium level was no more than 5.0 mmol per litre.

Comparator	Placebo
Population subgroups	Subgroups are based on baseline demographic and clinical characteristics (20 prespecified subgroups).
Number of participants	2737 participants
Duration of follow-up	21 months (median)
Indirectness	None
Method of analysis	ITT analysis
Additional comments	

Study arms

Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)

Placebo (N = 1373)

Characteristics

Arm-level characteristics

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)	Placebo (N = 1373)
% Female Sample size	n = 309 ; % = 22.7	n = 301 ; % = 21.9
Age Mean (SD)	68.7 (7.7)	68.6 (7.6)
Ethnicity Sample size	n = NR ; % = NR	n = NR ; % = NR
White Sample size	n = 1127 ; % = 82.6	n = 1141 ; % = 83.1
Black Sample size	n = 37 ; % = 2.7	n = 30 ; % = 2.2
Asian Sample size	n = 158 ; % = 11.6	n = 158 ; % = 11.5
Other Sample size	n = 42 ; % = 3.1	n = 44 ; % = 3.2
NYHA class Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)	Placebo (N = 1373)
Heart failure aetiology Sample size	n = NR ; % = NR	n = NR ; % = NR
Ischemic heart disease Sample size	n = 951 ; % = 69.7	n = 935 ; % = 68.1
Nonischaemic heart disease Sample size	n = 410 ; % = 30.1	n = 436 ; % = 31.8
Unknown Sample size	n = 3 ; % = 0.2	n = 2 ; % = 0.1
LVEF Mean (SD)	26.2 (4.6)	26.1 (4.7)
Type 2 diabetes Sample size	n = 459 ; % = 33.7	n = 400 ; % = 29.1
Atrial fibrillation Sample size	n = 409 ; % = 30	n = 435 ; % = 31.7
Previous heart failure hospitalisation Sample size	n = 714 ; % = 52.3	n = 726 ; % = 52.9

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)	Placebo (N = 1373)
Renal function (eGFR; mL/min/1.73m2) Mean (SD)	71.2 (21.9)	70.4 (21.7)
Background (non-randomised) heart failure medications Sample size	n = NR ; % = NR	n = NR ; % = NR
Diuretic Sample size	n = 1150 ; % = 84.3	n = 1176 ; % = 85.7
ACE-inhibitor Sample size	n = 1068 ; % = 78.3	n = 1055 ; % = 76.8
ARB Sample size	n = 261 ; % = 19.1	n = 266 ; % = 19.4
ACE inhibitor, ARB or both Sample size	n = 1282 ; % = 94	n = 1275 ; % = 92.9
Beta-blocker Sample size	n = 1181 ; % = 86.6	n = 1193 ; % = 86.9
Digitalis glycosides Sample size	n = 363 ; % = 26.6	n = 377 ; % = 27.5

Characteristic	Mineralocorticoid receptor antagonist (eplerenone) (N = 1364)	Placebo (N = 1373)
Antiarrhythmic drug Sample size	n = 196 ; % = 14.4	n = 192 ; % = 14
Antithrombotic drug Sample size	n = 1205 ; % = 88.3	n = 1214 ; % = 88.4
Lipid-lowering agent Sample size	n = 857 ; % = 62.8	n = 856 ; % = 62.3
Device therapy Sample size	n = NR ; % = NR	n = NR ; % = NR
Implantable cardioverter-defibrillator Sample size	n = 178 ; % = 13	n = 184 ; % = 13.4
Cardiac-resynchronization therapy Sample size	n = 38 ; % = 2.8	n = 22 ; % = 1.6
Implantable cardioverter-defibrillator with cardiac resynchronization Sample size	n = 74 ; % = 5.4	n = 99 ; % = 7.2

Outcomes

Mortality

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1364	Placebo, , N = 1373
All-cause mortality No of events	n = 171 ; % = 12.5	n = 213 ; % = 15.5
CV mortality No of events	n = 147 ; % = 10.8	n = 185 ; % = 13.5
All-cause mortality (HR (95%CI)) Adjusted hazard ratio Custom value	0.76 (0.62-0.93)	NR
CV mortality (HR (95%CI)) Adjusted hazard ratio Custom value	0.76 (0.61 to 0.94)	NR

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Hospitalisation

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1364	Placebo, , N = 1373
Unplanned hospitalisation or visits HF-related (hospitalisation for HF)	n = 164 ; % = 12	n = 253 ; % = 18.4

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1364	Placebo, , N = 1373
No of events		
Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF) (HR (95%CI)) Adjusted hazard ratio Custom value	0.58 (0.47 to 0.70)	NR

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

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

Adverse events

Outcome	Mineralocorticoid receptor antagonist (eplerenone), , N = 1360	Placebo, , N = 1369
Hyperkalaemia (Number of participants with hyperkalemia) No of events	n = 109 ; % = 8	n = 50 ; % = 3.7
Withdrawal of study drug due to adverse events No of events	n = 188 ; % = 13.8	n = 222 ; % = 16.2

Hyperkalaemia - Polarity - Lower values are better

Withdrawal of study drug due to adverse events - Polarity - Lower values are better

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

All-cause mortality

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

CV mortality

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

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF)

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

Hyperkalaemia (undefined)

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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality HR

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

CV mortality HR

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

Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF) HR

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

Withdrawal of study drug due to adverse events

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

Appendix E Forest plots

E.1 Rapid optimisation versus usual care

Figure 2: All-cause mortality (dichotomous)

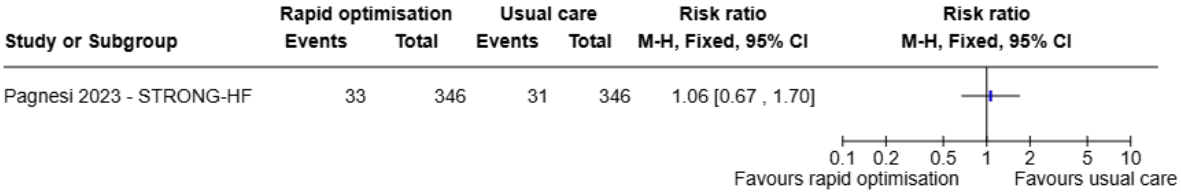


Figure 3: Cardiovascular mortality (dichotomous)

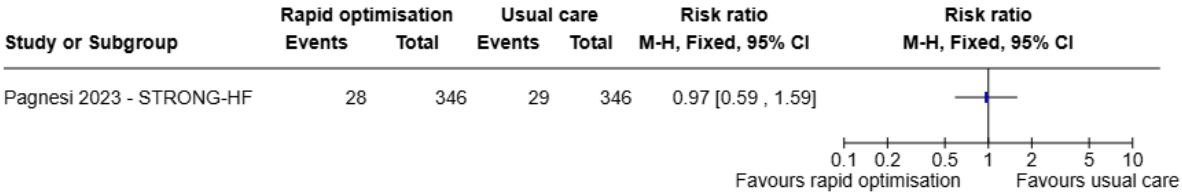


Figure 4: Health-related quality of life (EQ5D VAS, change from baseline (continuous, range 0-100, higher values are better)

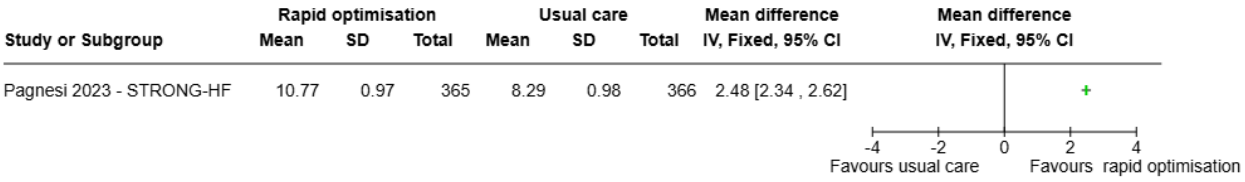


Figure 5: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, dichotomous)

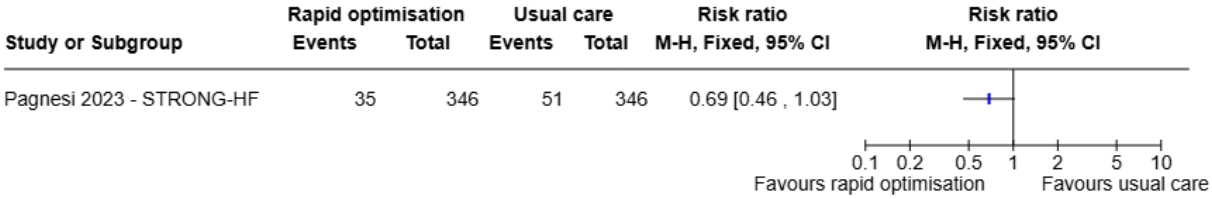


Figure 6: Acute kidney injury (dichotomous)

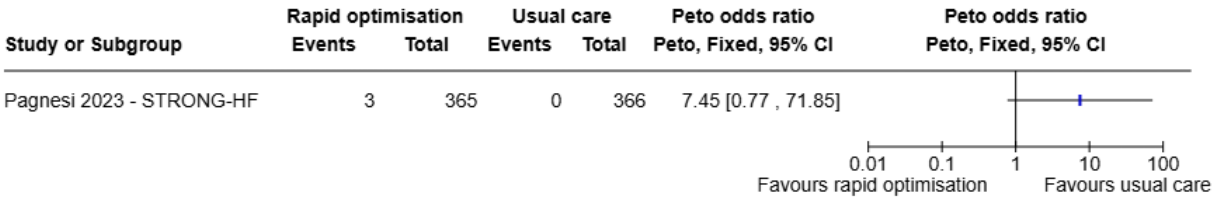


Figure 7: Hyperkalaemia (dichotomous)

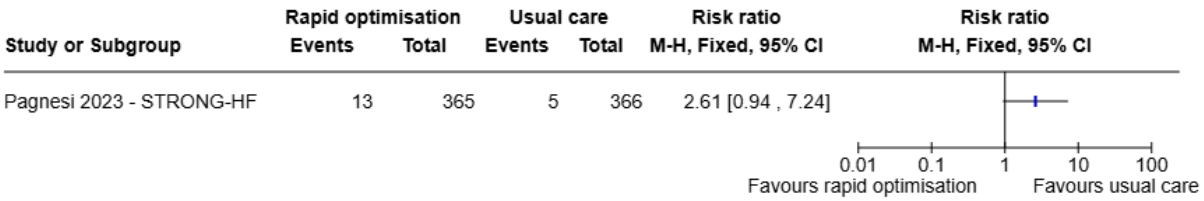
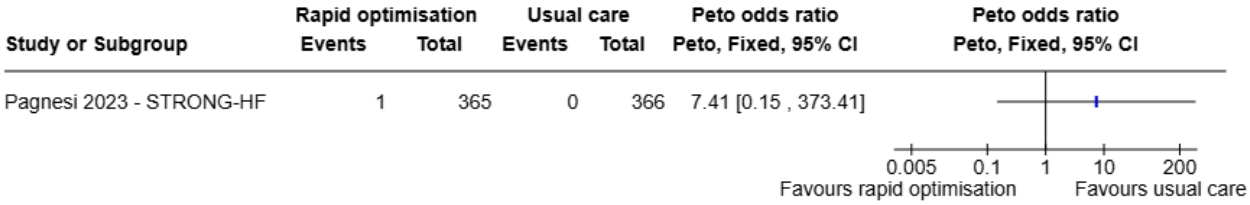


Figure 8: Falls (dichotomous)



E.2 SGLT2i + ACEI/ARB + BB + MRA versus ACEI/ARB + BB + MRA + placebo

Figure 9: All-cause mortality (time-to-event)

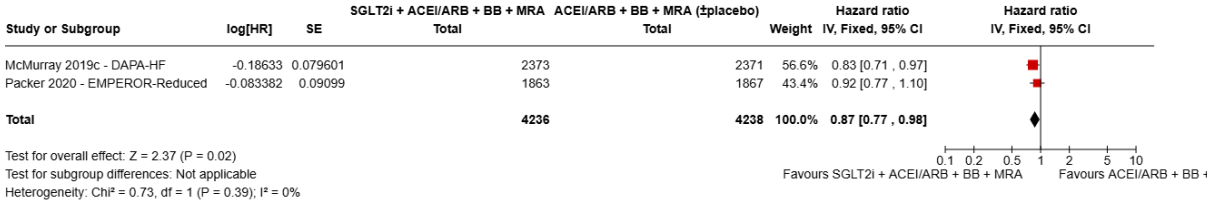


Figure 10: All-cause mortality (dichotomous)

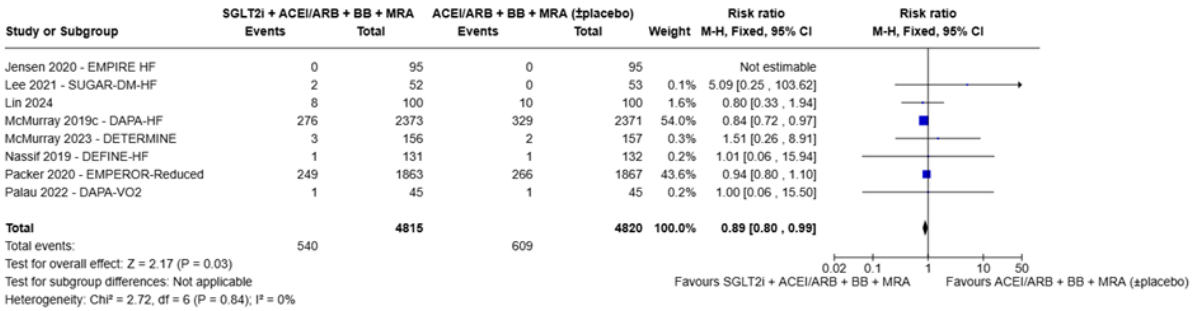


Figure 11: Cardiovascular mortality (time-to-event)

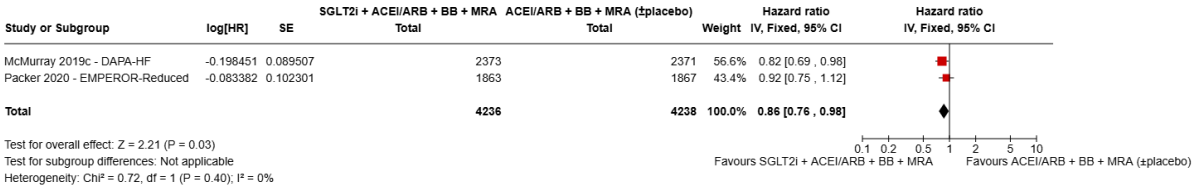


Figure 12: Cardiovascular mortality (dichotomous)

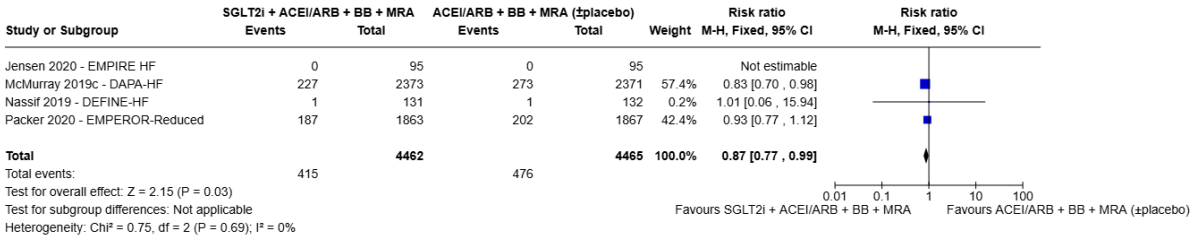


Figure 13: Health-related quality of life (KCCQ overall summary score, higher is better, range 0-100, change or final score)

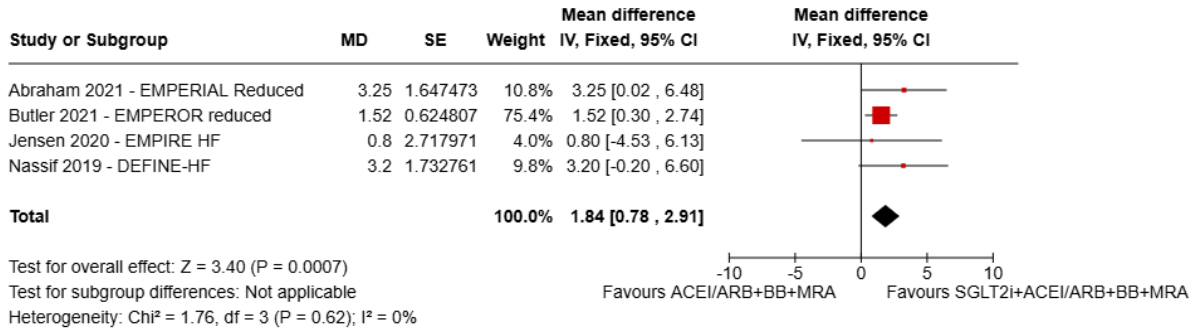


Figure 14: Health-related quality of life (KCCQ clinical summary score, higher is better, range 0-100, change or final score)

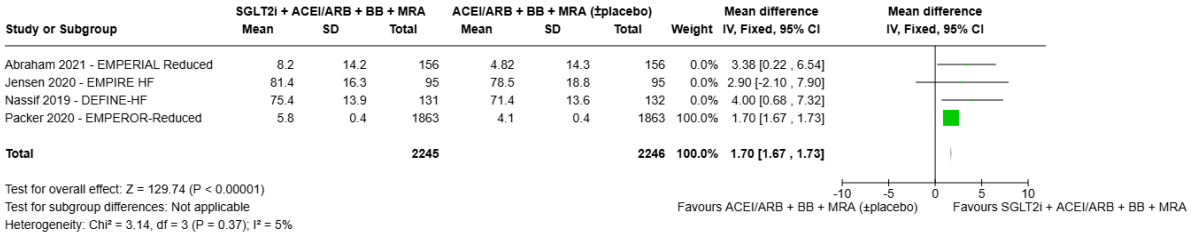
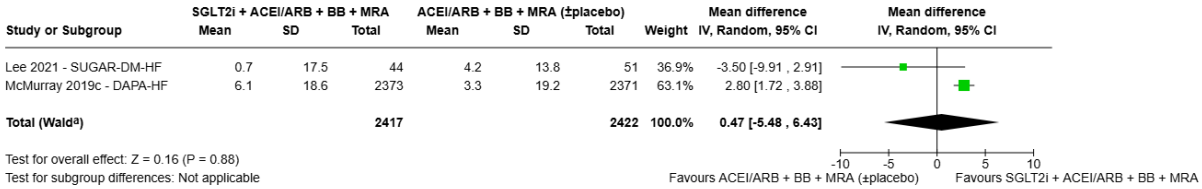


Figure 15: Health-related quality of life (KCCQ total symptom score, higher is better, range 0-100, change score)



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Figure 16: Unplanned hospitalisation or visits (HF-related) (first hospitalisation for HF, time-to-event)

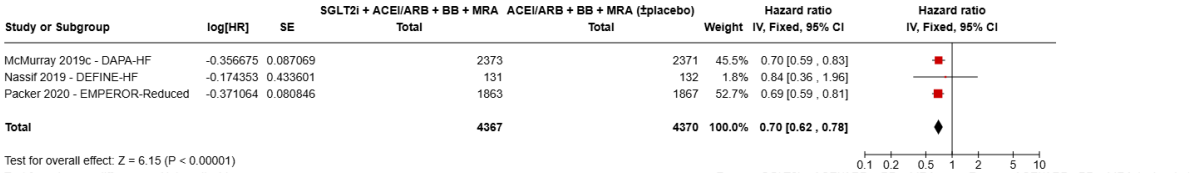


Figure 17: Unplanned hospitalisation or visits (HF-related) (total hospitalisations for HF, rate ratio)

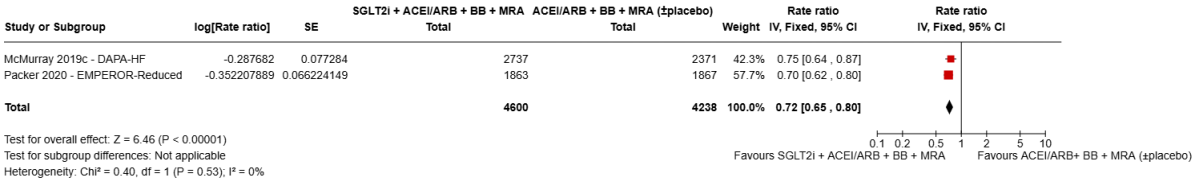


Figure 18: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, dichotomous)

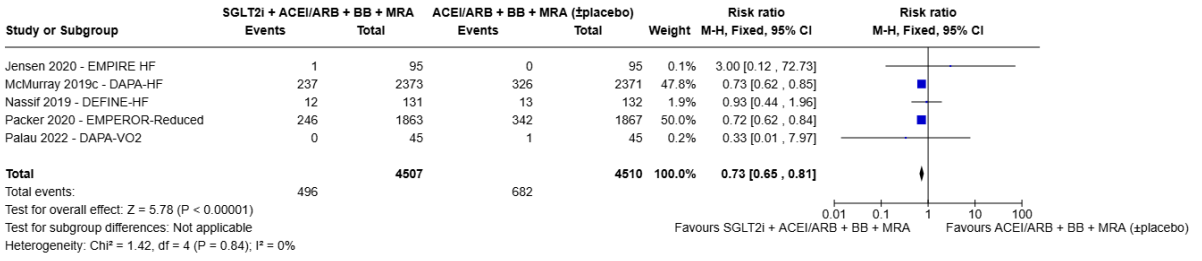


Figure 19: Withdrawal due to drug-related adverse events (dichotomous)

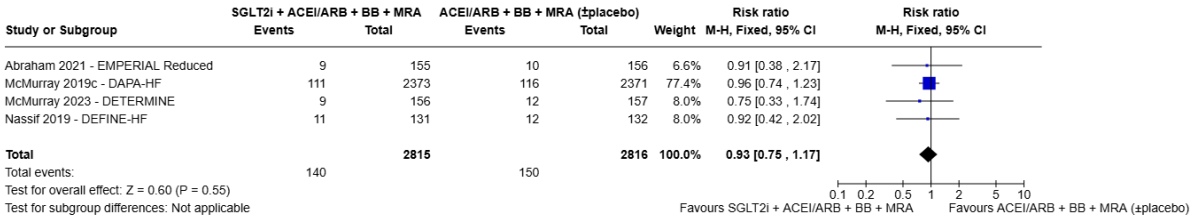


Figure 20: Acute kidney injury (dichotomous)

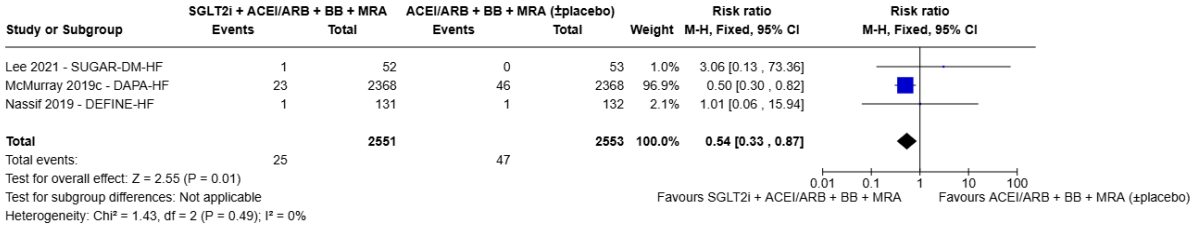


Figure 21: Hyperkalaemia (dichotomous)

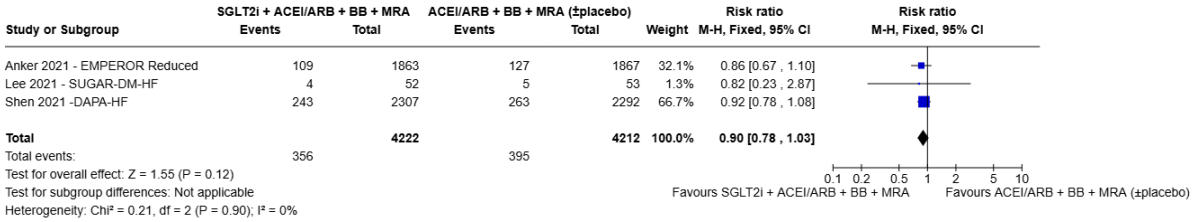
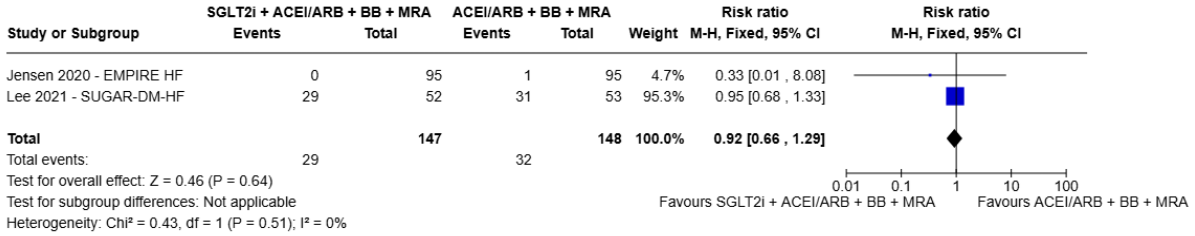


Figure 22: Falls (symptomatic hypotension as a surrogate)(dichotomous)



E.3 MRA + ACEI/ARB + BB versus ACEI/ARB + BB + placebo

Figure 23: All-cause mortality (time-to-event)

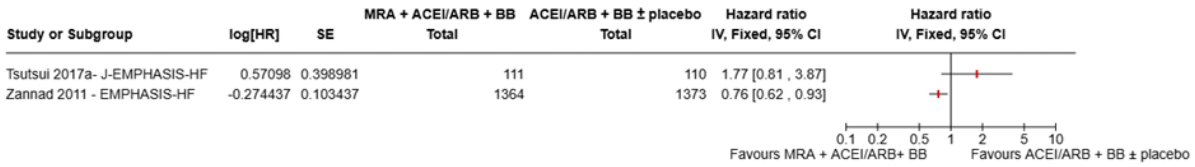


Figure 24: All-cause mortality (dichotomous)

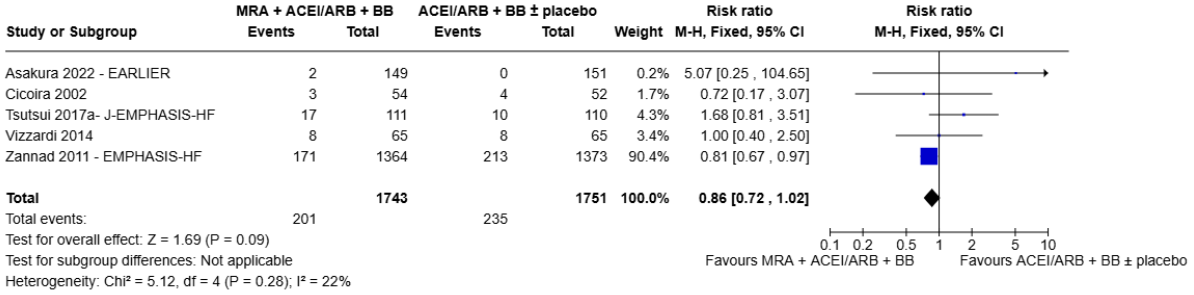


Figure 25: Cardiovascular mortality (time-to-event)

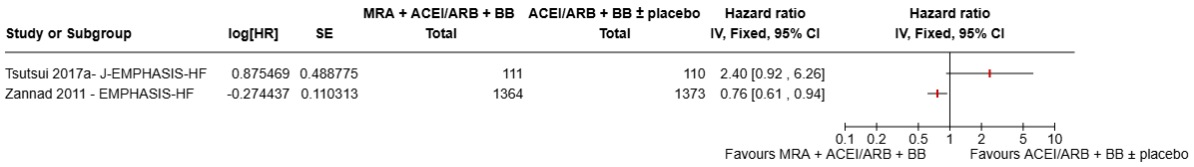


Figure 26: Cardiovascular mortality (dichotomous)

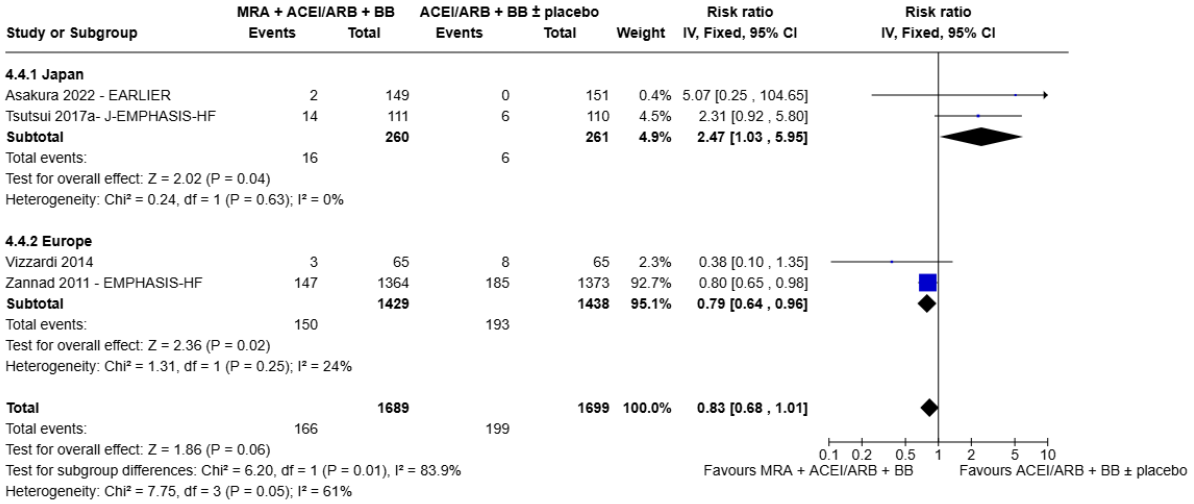


Figure 27: Health-related quality of life (EQ-VAS, range 0-100, higher values are better)

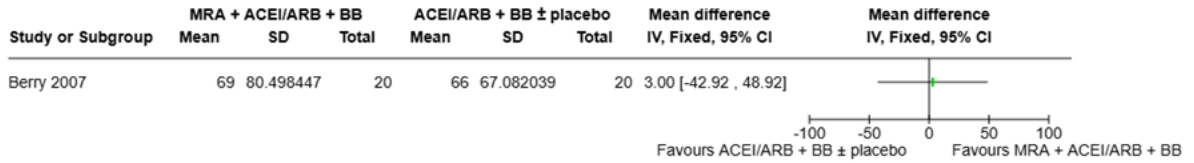


Figure 28: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, time-to-event)

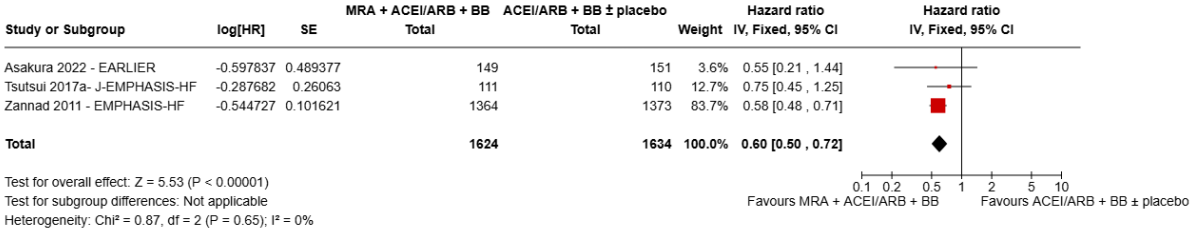


Figure 29: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, dichotomous)

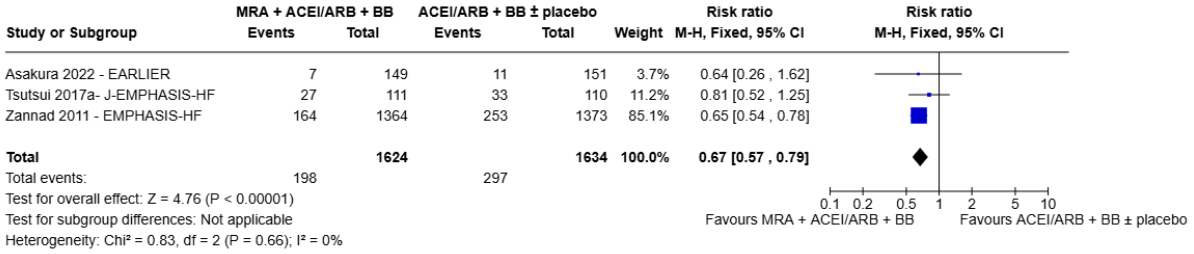


Figure 30: Unplanned hospitalisation or visits (HF-related) (hospitalisation for HF including repeat events)

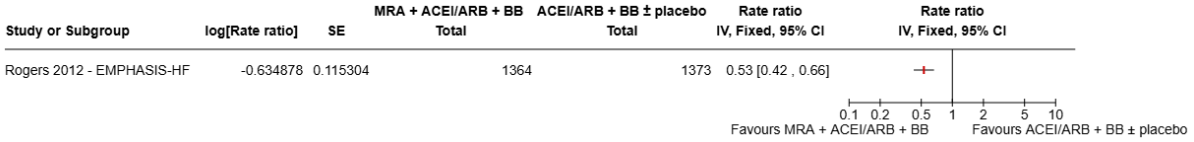


Figure 31: Withdrawal of study drug due to adverse events (dichotomous)

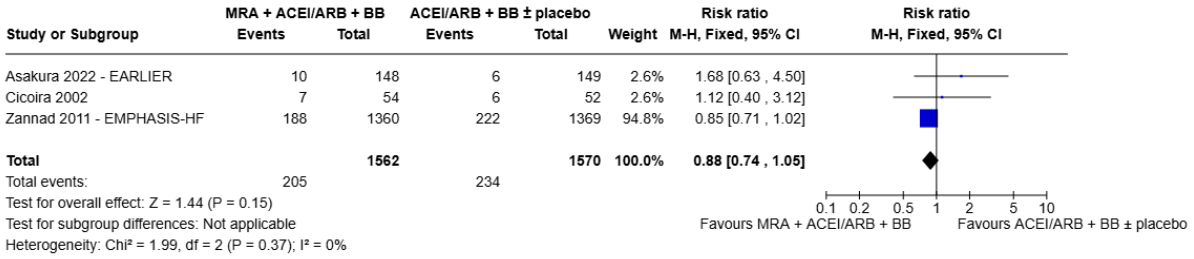


Figure 32: Acute kidney injury (dichotomous)

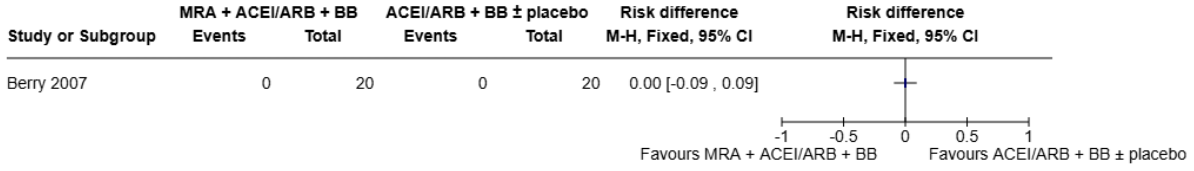
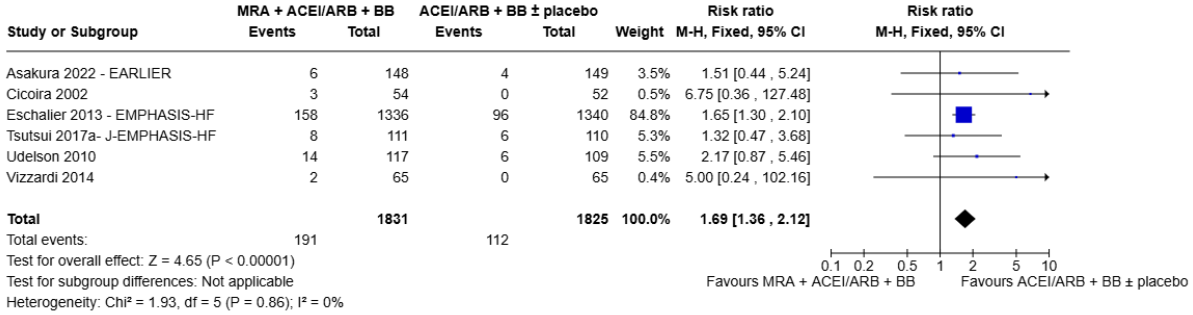


Figure 33: Hyperkalaemia (dichotomous)



E.4 MRA + ARB + BB versus ARB + BB + placebo

Figure 34: Withdrawal due to drug-related adverse events (dichotomous).

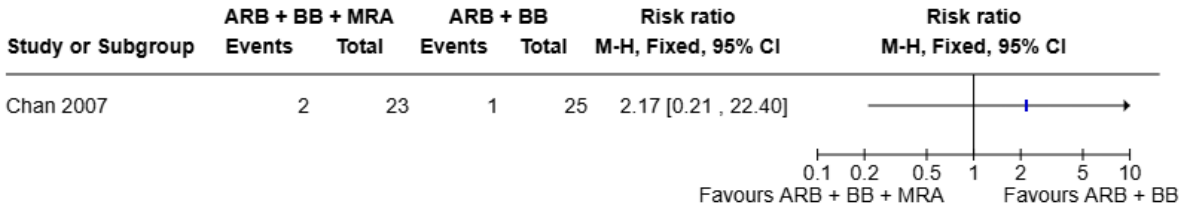
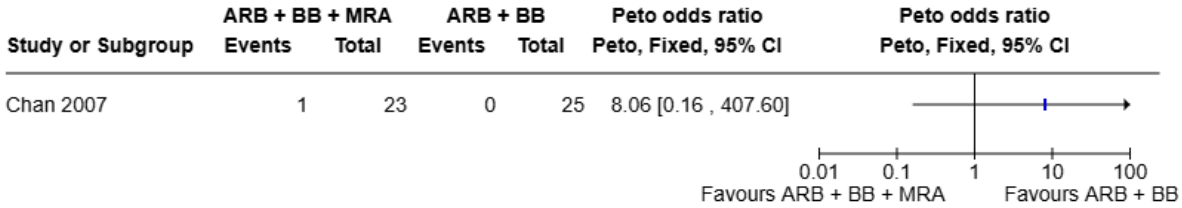


Figure 35: Hyperkalemia (dichotomous)



E.5 ARB + ACEI + BB versus ACEI + BB + placebo

Figure 36: All-cause mortality (time-to-event)

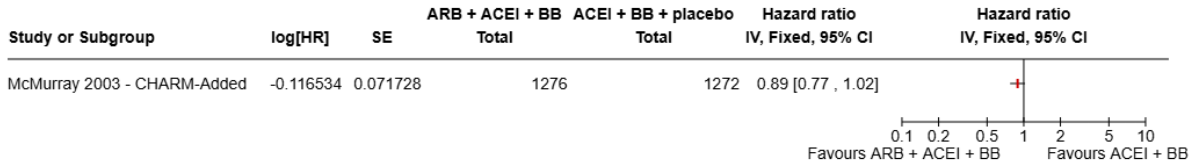


Figure 37: All-cause mortality (dichotomous)

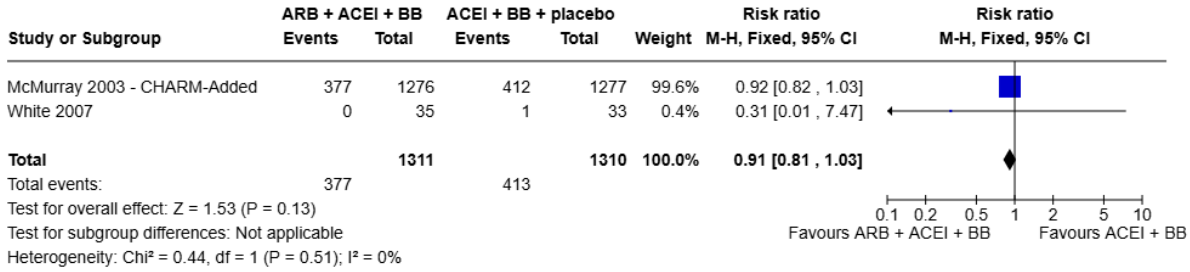


Figure 38: Cardiovascular mortality (time-to-event)

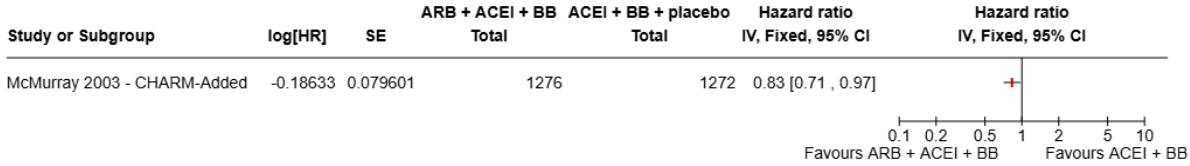


Figure 39: Cardiovascular mortality (dichotomous)

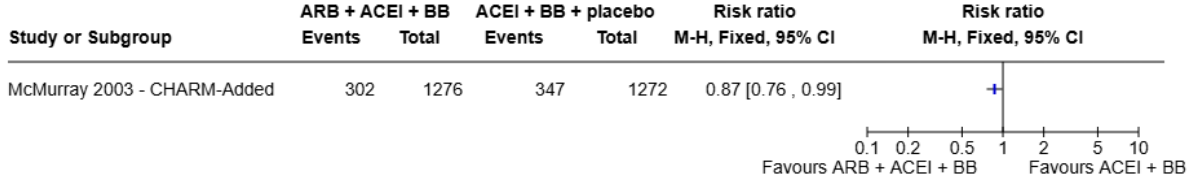


Figure 40: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, time-to-event)

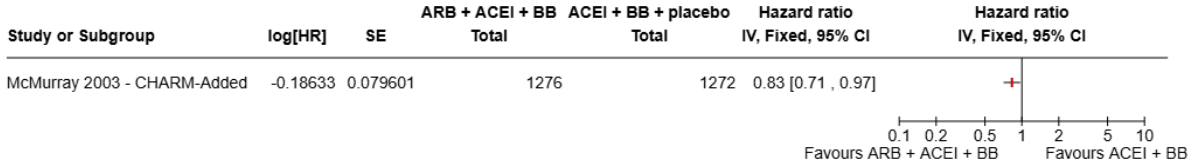


Figure 41: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, dichotomous)

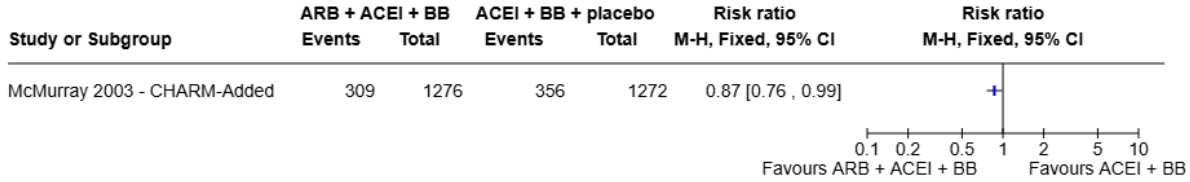


Figure 42: Withdrawal due to drug-related adverse events (dichotomous)

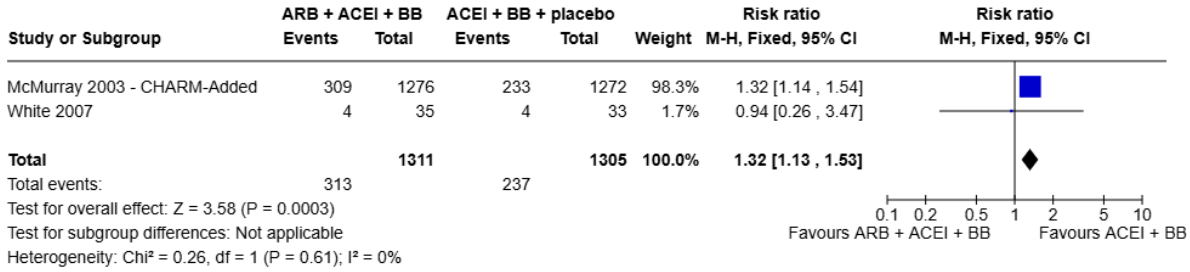


Figure 43: Hyperkalaemia (dichotomous)

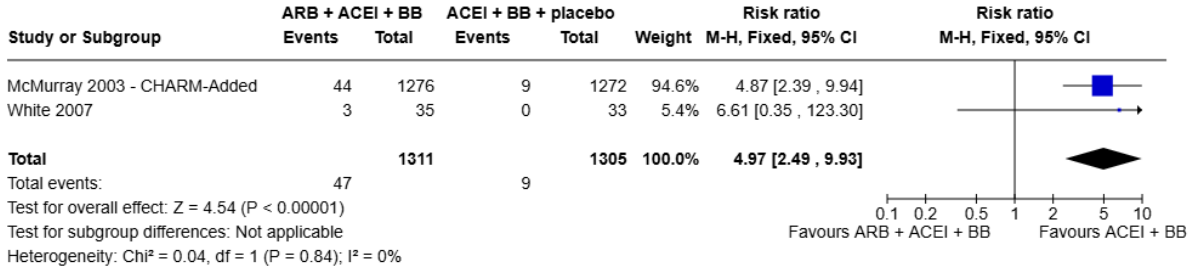
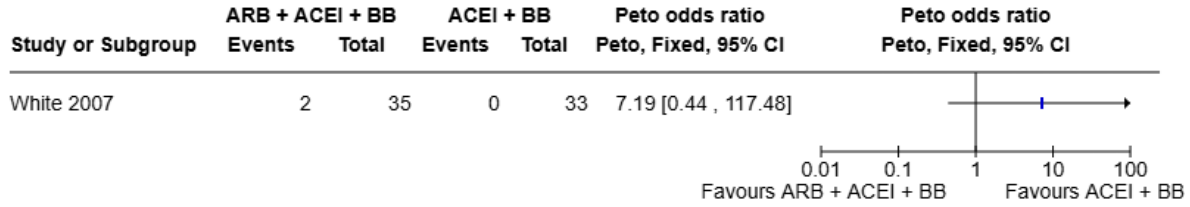


Figure 44: Falls (symptomatic hypotension as a surrogate, dichotomous)



E.6 ARNI + MRA + BB versus ARB + MRA + BB

Figure 45: All-cause mortality (time-to-event)

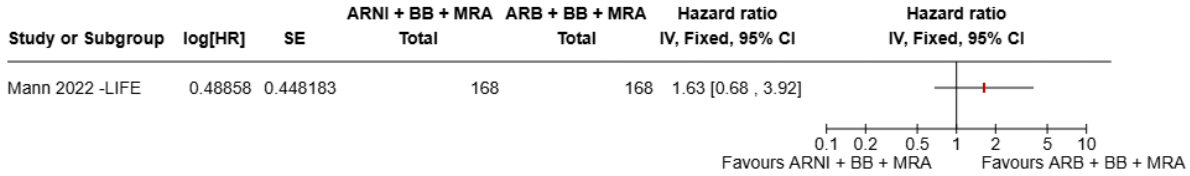


Figure 46: All-cause mortality (dichotomous)

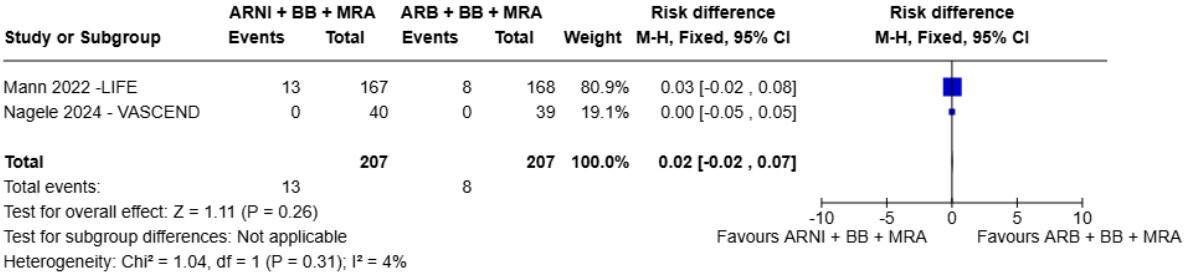


Figure 47: Cardiovascular mortality (time-to-event)

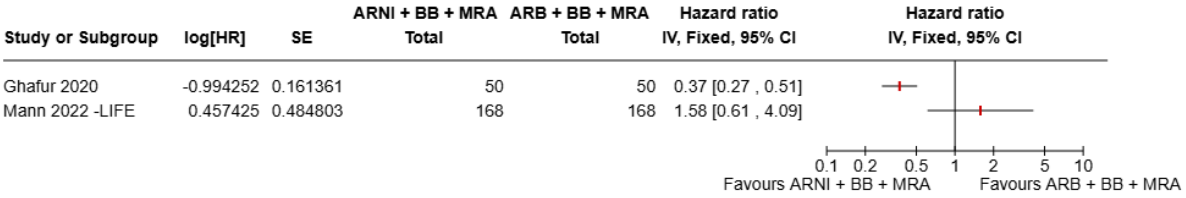


Figure 48: Cardiovascular mortality (dichotomous)

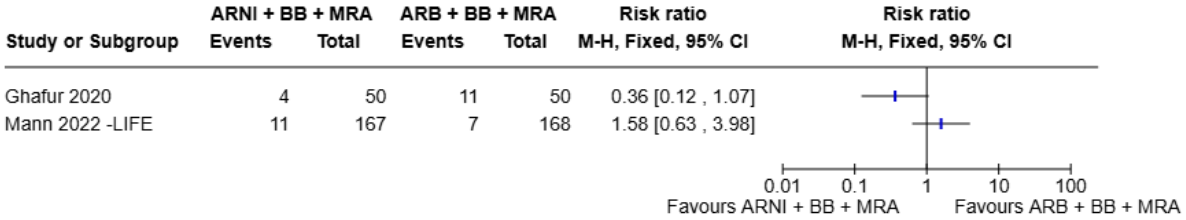


Figure 49: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, time-to-event)

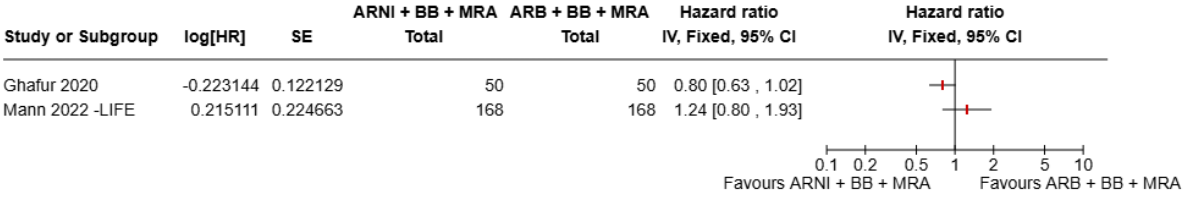


Figure 50: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, dichotomous)

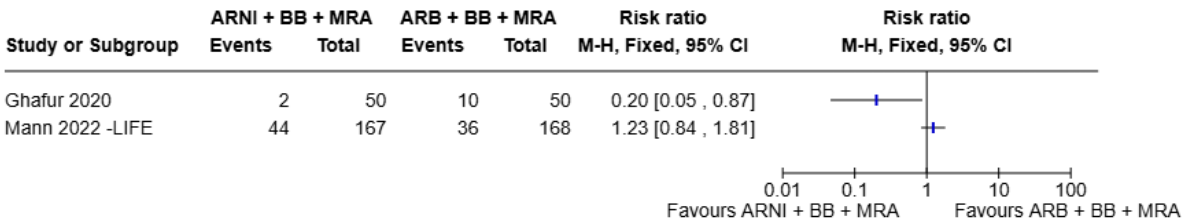


Figure 51: Withdrawal due to drug-related adverse events (dichotomous)

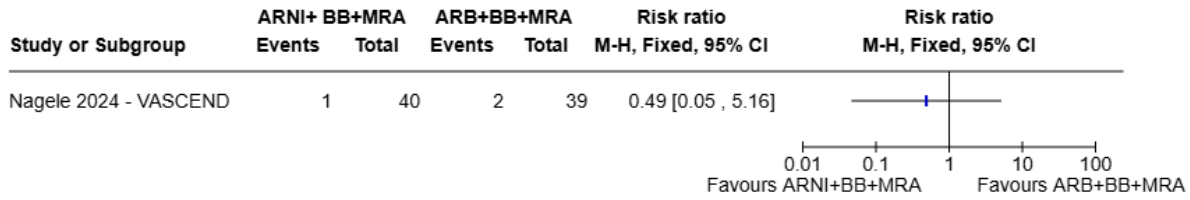


Figure 52: Hyperkalaemia (potassium ≥5.5 mEq/L)

E.7 ARNI + MRA + BB versus ACEI + MRA + BB

Figure 53: All-cause mortality (time-to-event)

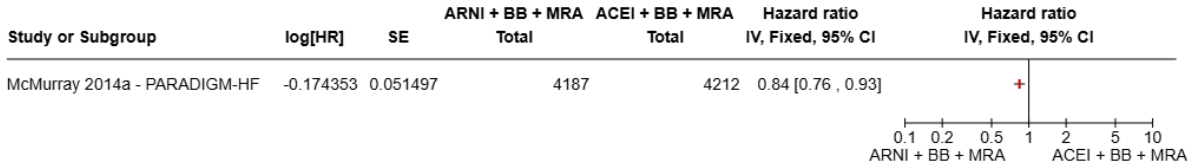


Figure 54: All-cause mortality (dichotomous)

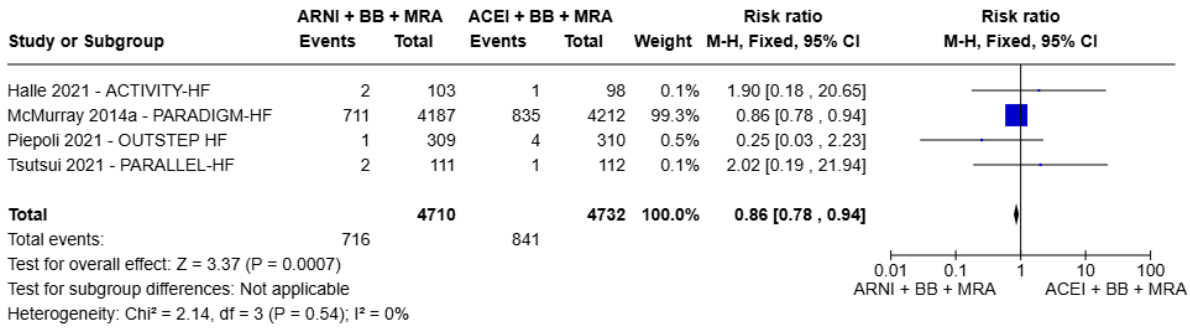


Figure 55: Cardiovascular mortality (time-to-event)

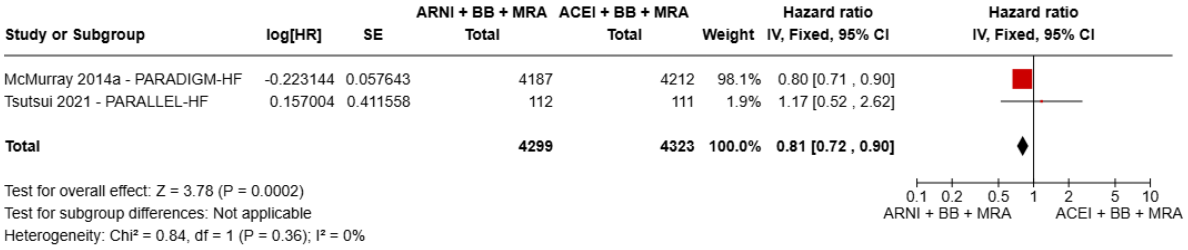


Figure 56: Cardiovascular mortality (dichotomous)

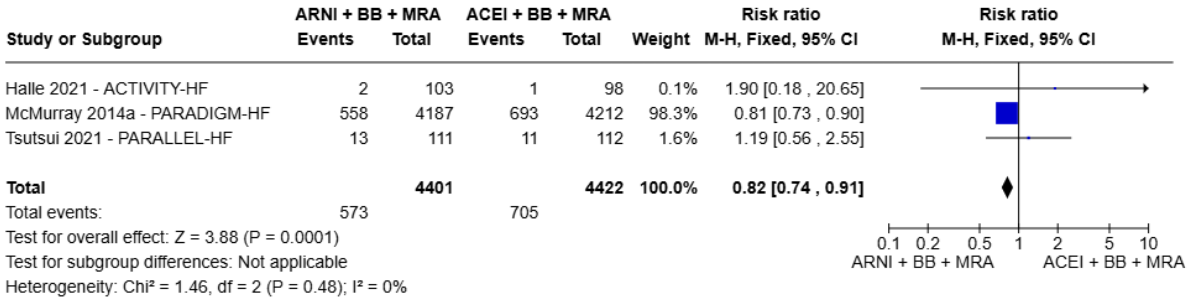


Figure 57: Health-related quality of life (KCCQ clinical summary score, range 0-100, higher values are better, change score)

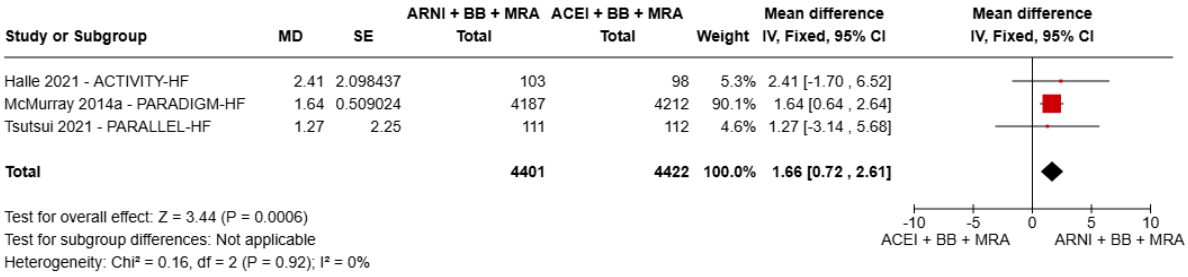


Figure 58: Health-related quality of life (KCCQ overall summary score, range 0-100, higher values are better, change score)

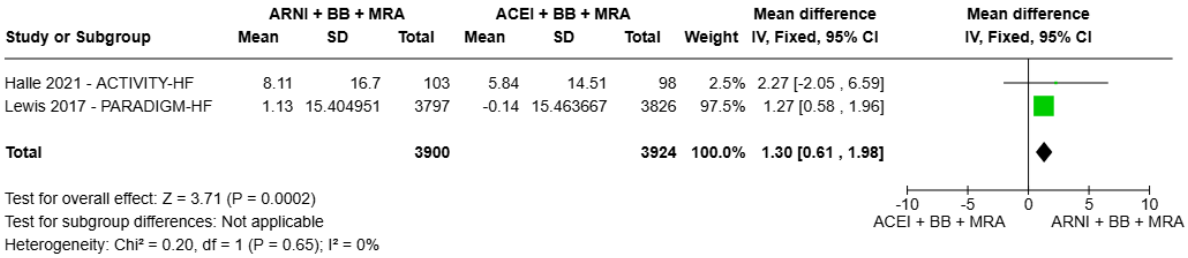


Figure 59: Health-related quality of life (EQ-5D, range 0-1, higher values are better, change score)

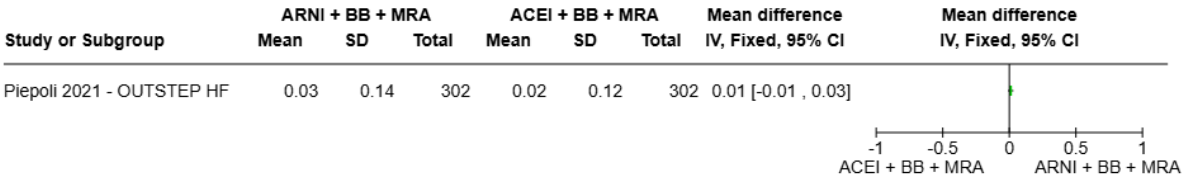


Figure 60: Health-related quality of life (EQ-VAS, range 0-100, higher values are better, change score)

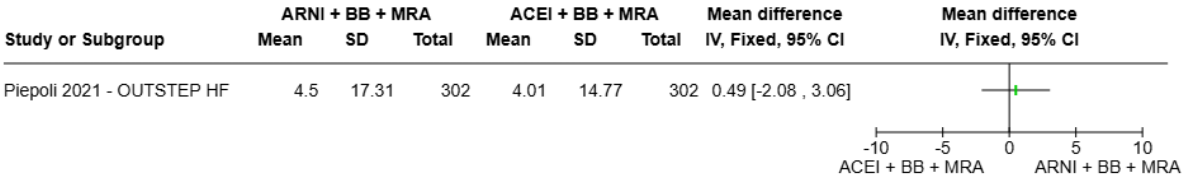


Figure 61: Health-related quality of life (SF-12, mental component score, range 0-100, higher values are better, change score)

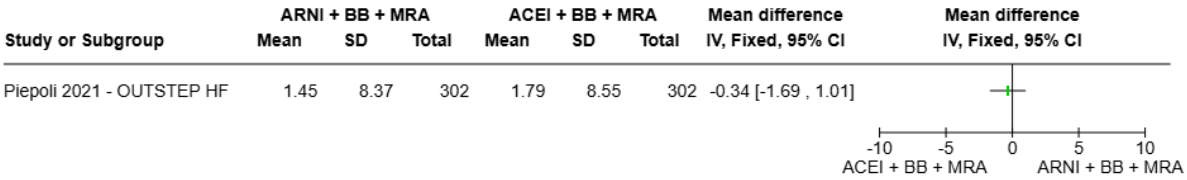


Figure 62: Health-related quality of life (SF-12, physical component score, range 0 to 100, higher values are better, change score)

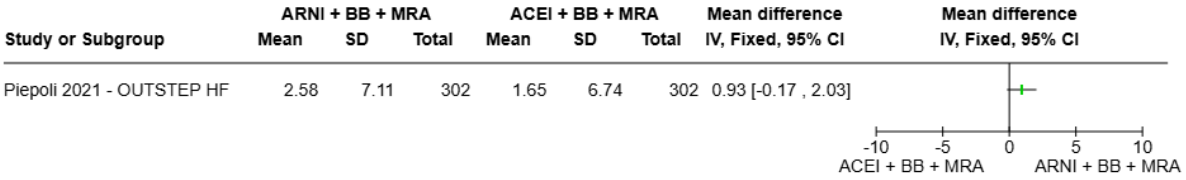


Figure 63: Health-related quality of life (SF-36 mental component score, range 0 to 100, higher values are better, change score)

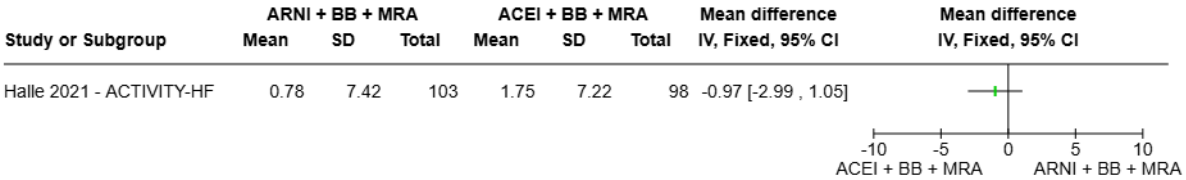


Figure 64: Health-related quality of life (SF-36 physical component score, range 0 to 100, higher values are better, change score)

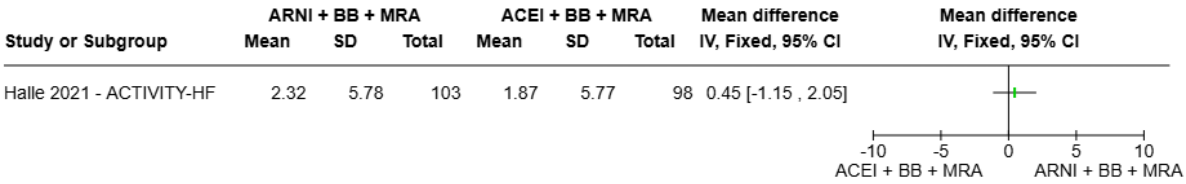


Figure 65: Unplanned hospitalisation or visits (HF-related) (first unplanned hospitalisation or visits HF-related, time-to-event)

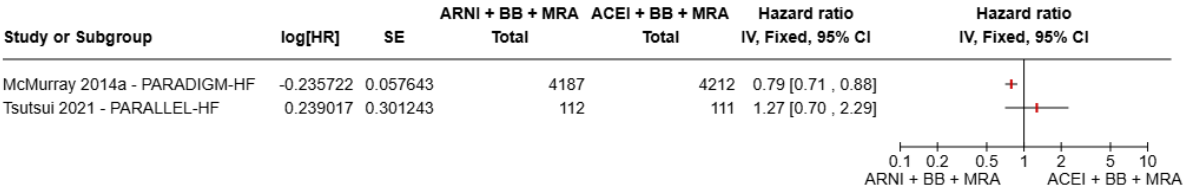


Figure 66: Unplanned hospitalisation or visits HF-related (dichotomous)

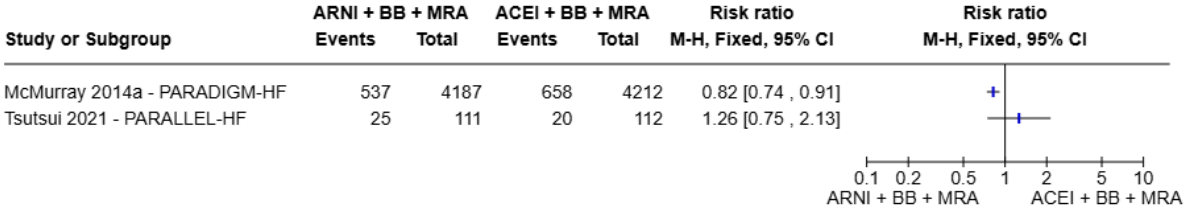


Figure 67: Withdrawal due to drug-related adverse events (dichotomous)

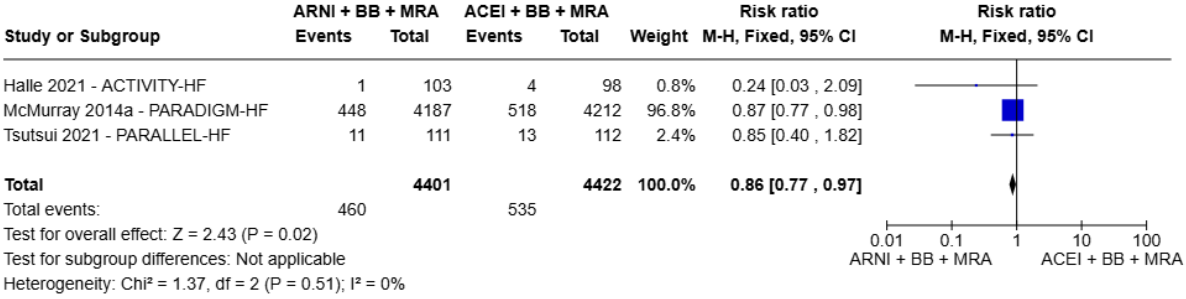


Figure 68: Acute kidney injury (dichotomous)

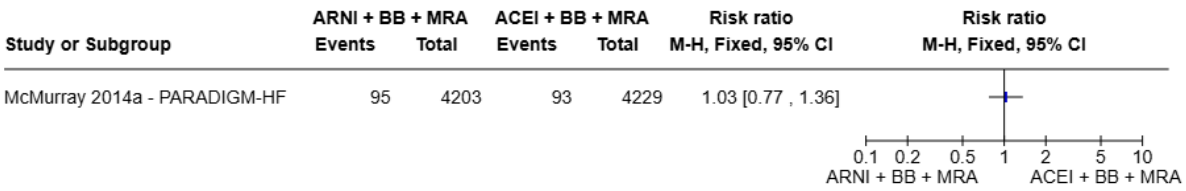
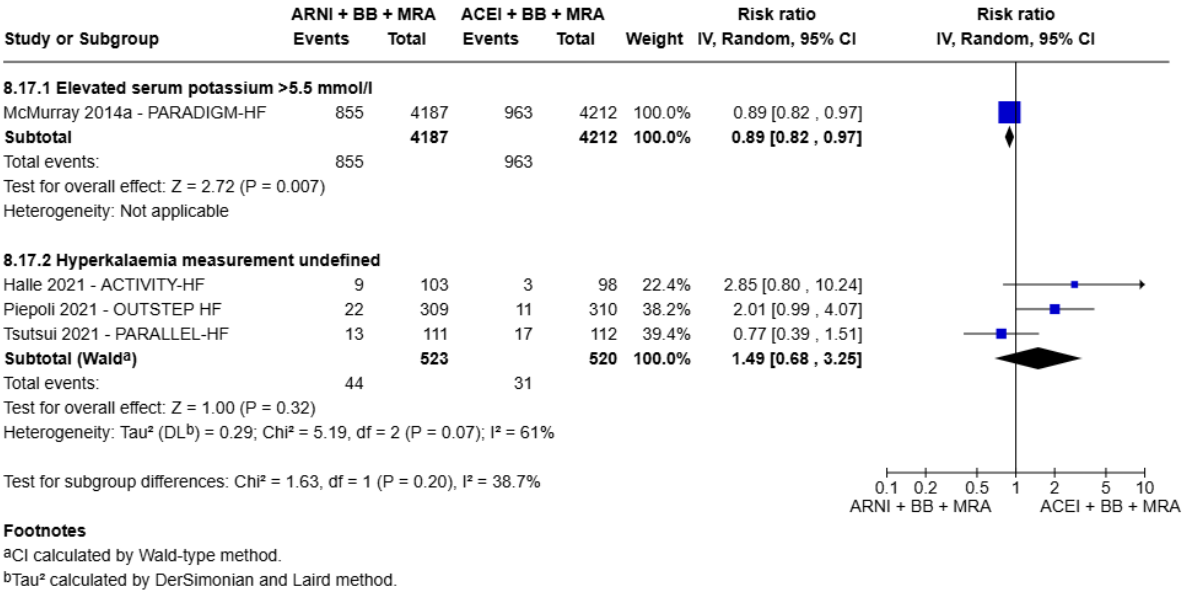


Figure 69: Hyperkalaemia (dichotomous)

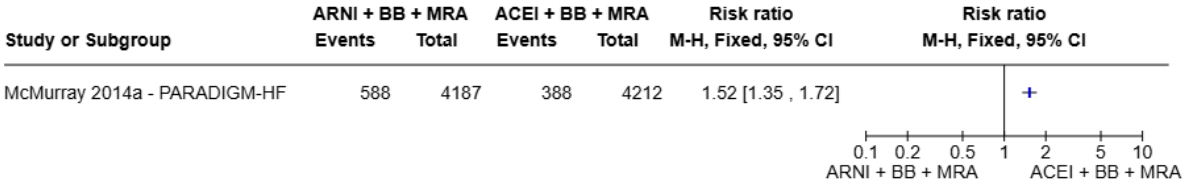


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 70: Falls (symptomatic hypotension as a surrogate)



E.8 ARNI + BB versus ACEI + BB

Figure 71: All-cause mortality (dichotomous)

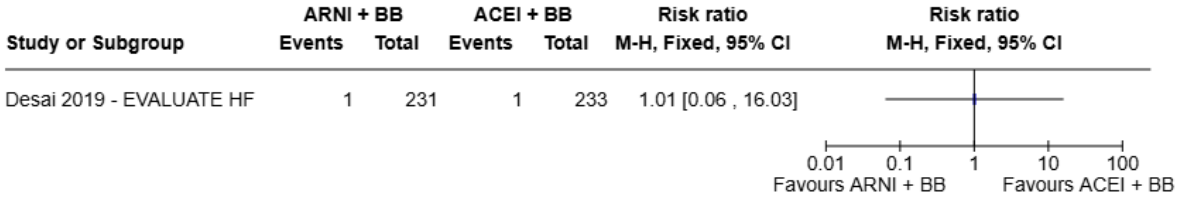


Figure 72: Health-related quality of life (KCCQ overall summary score, range 0-100, higher values are better, change score)

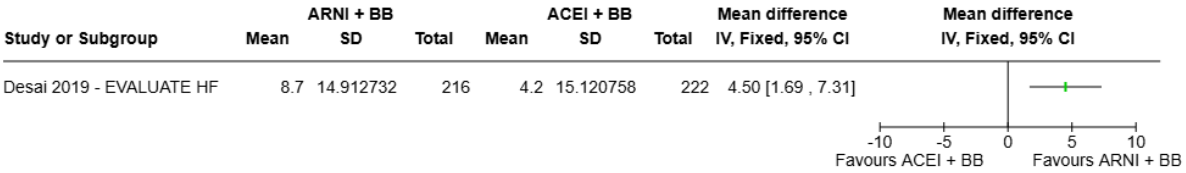
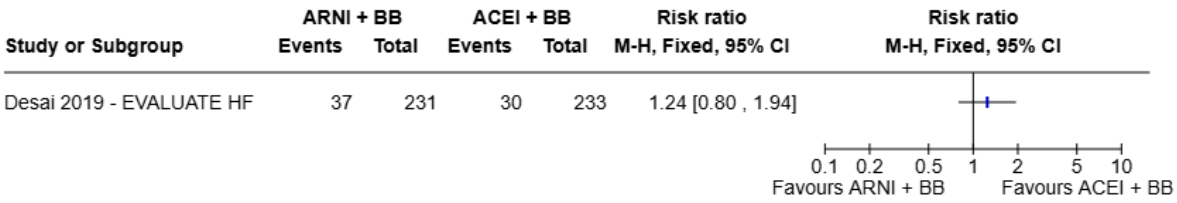


Figure 73: Hyperkalaemia (K>5.3 meq/L)



E.9 Subgroups with and without type 2 diabetes: SGLT2i + ACEI + BB + MRA versus ACEI + BB + MRA + placebo

Figure 74: All-cause mortality (time-to-event)

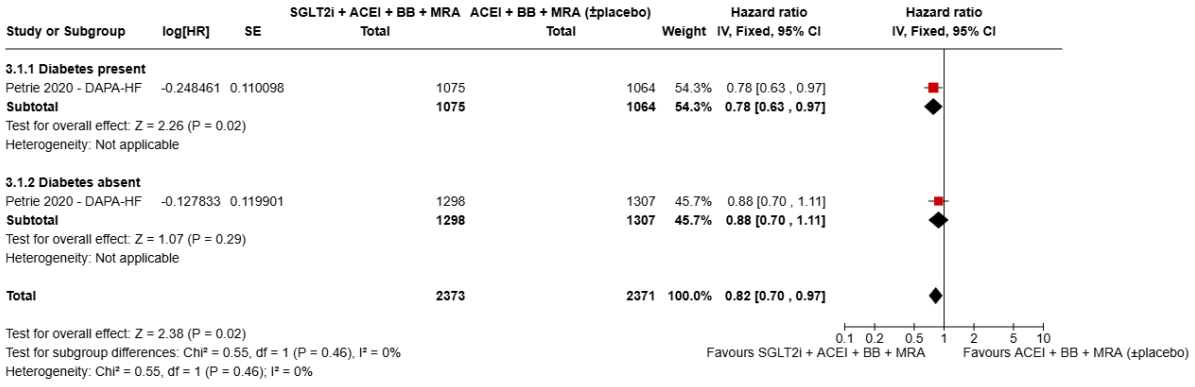


Figure 75: All-cause mortality (dichotomous)

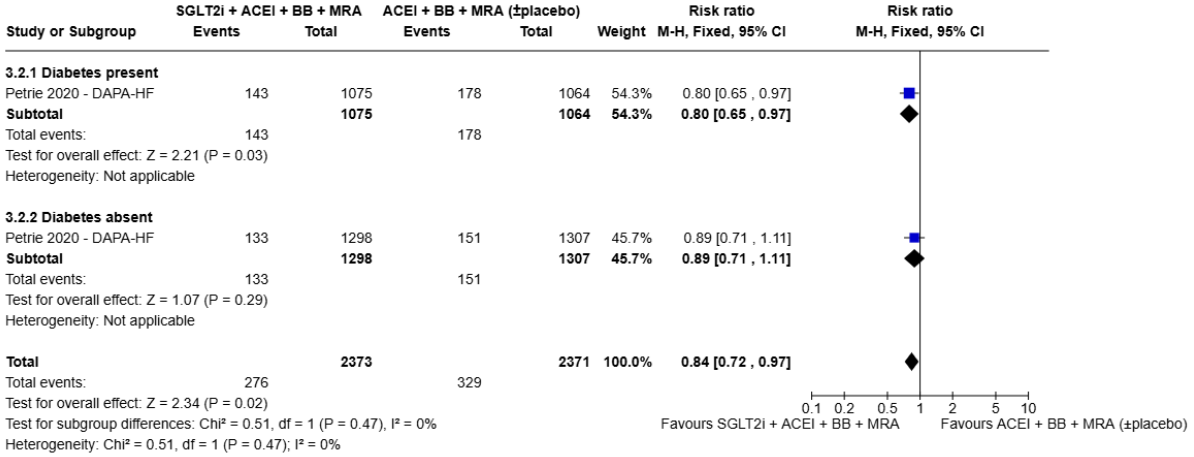


Figure 76: Cardiovascular mortality (time-to-event)

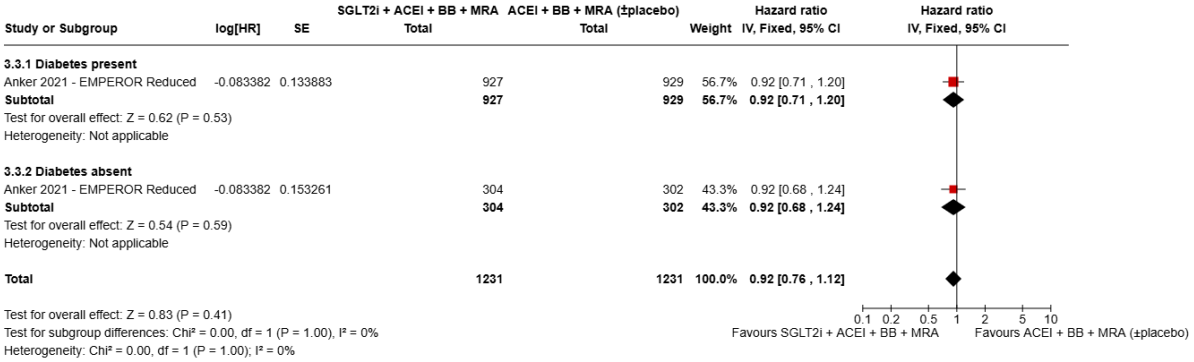


Figure 77: Cardiovascular mortality (dichotomous)

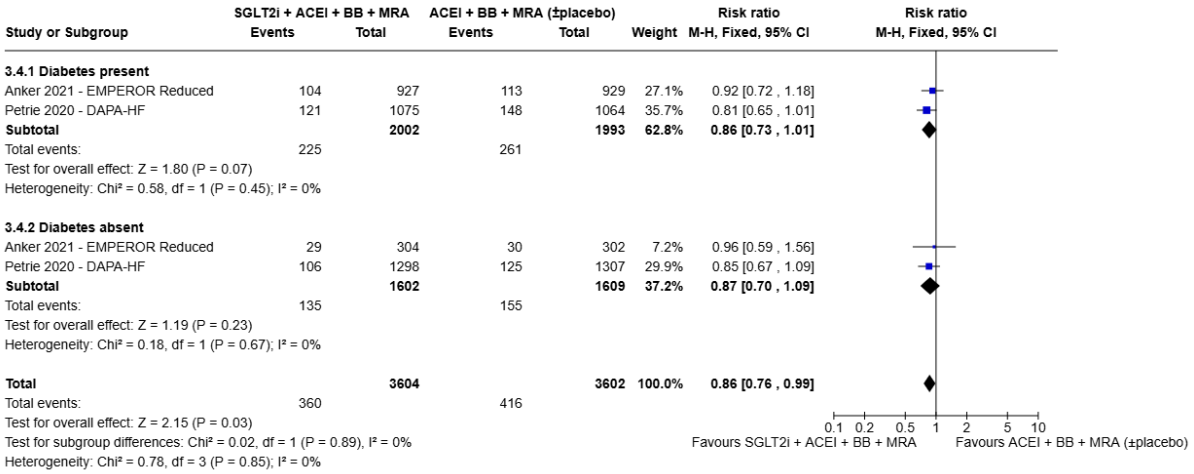


Figure 78: Health-related quality of life (KCCQ clinical summary score, range 0-100, higher values are better, change score)

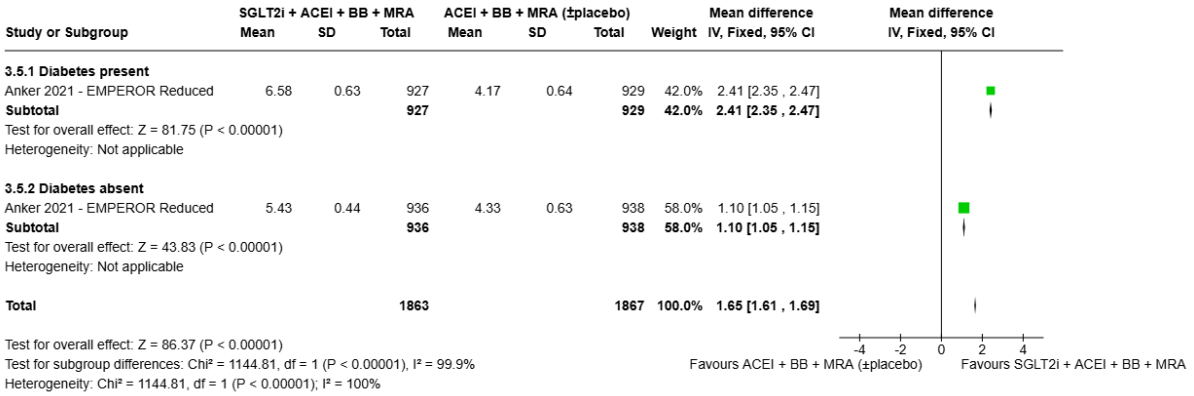


Figure 79: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, time-to-event)

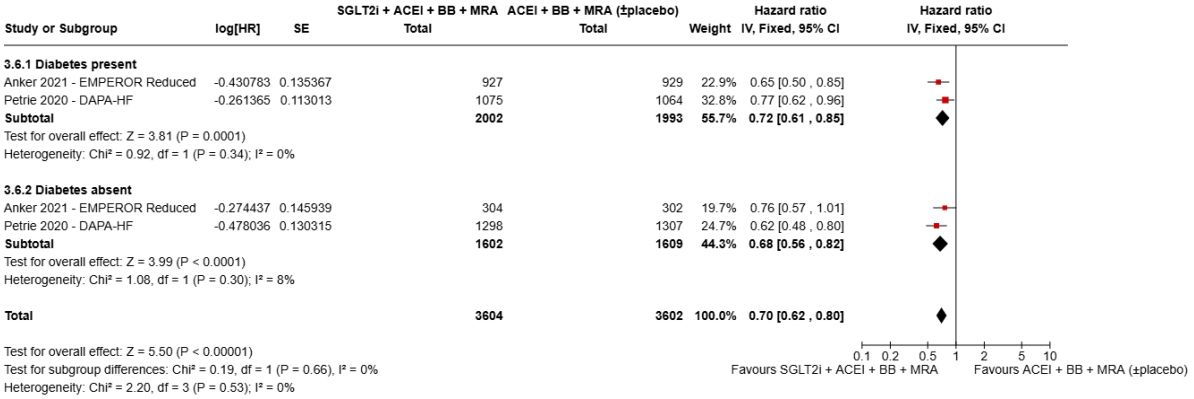
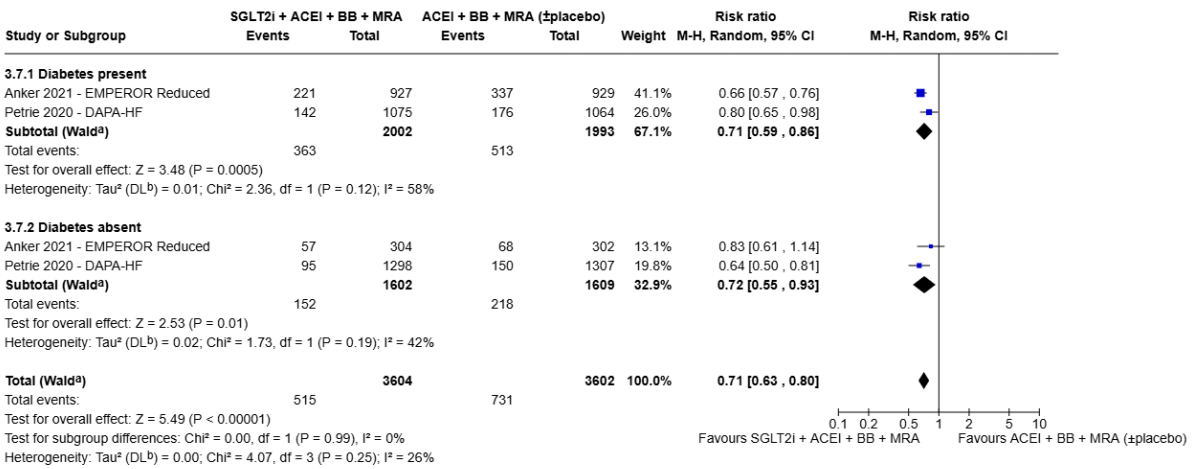


Figure 80: Unplanned hospitalisation or visits (HF-related) (HF hospitalisation, dichotomous)



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 81: Withdrawal due to drug-related adverse events (dichotomous)

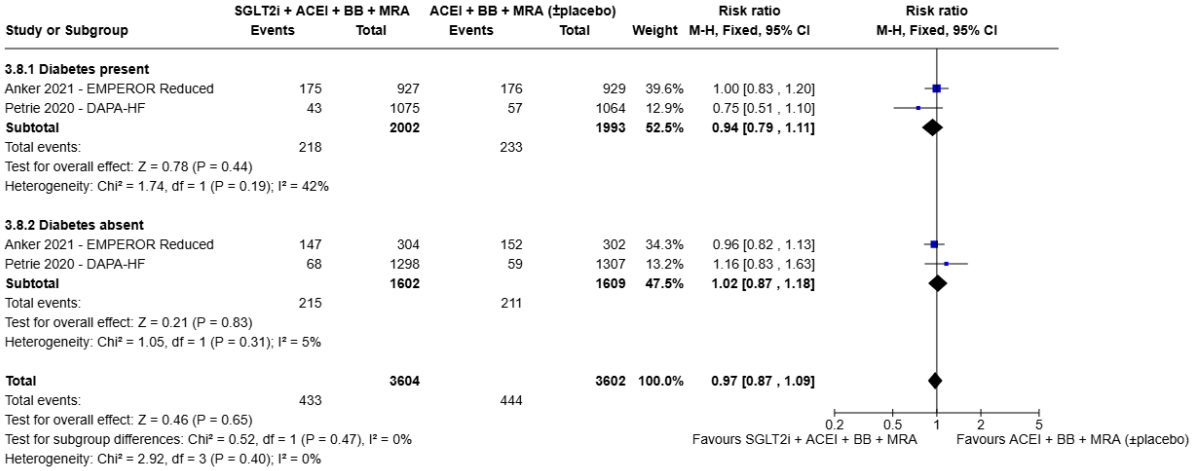
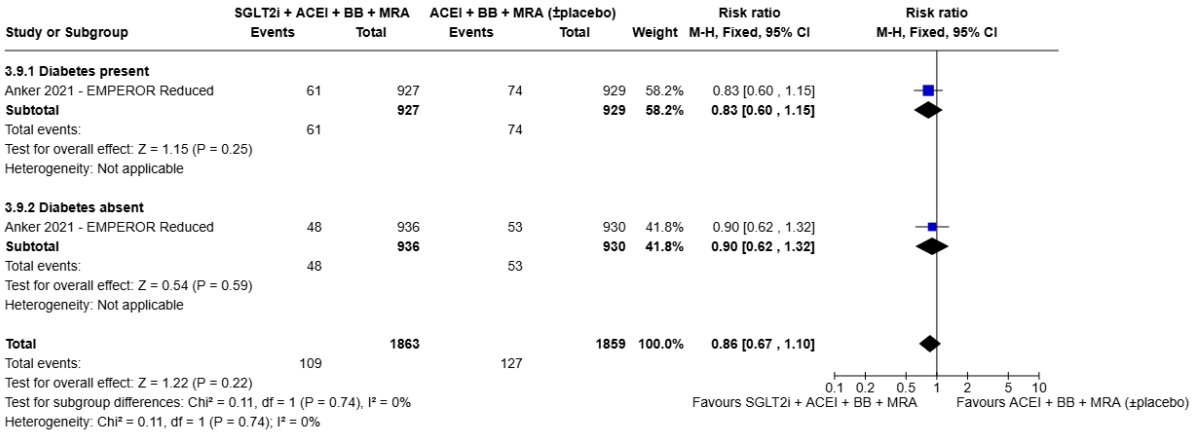


Figure 82: Hyperkalaemia (dichotomous)



Appendix F GRADE tables

Table 21: Clinical evidence profile: Rapid optimisation versus usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rapid optimisation	usual care	Relative (95% CI)	Absolute (95% CI)		
All cause mortality (follow-up: 180 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	33/346 (9.5%)	31/346 (9.0%)	**RR 1.06** (0.67 to 1.70)	**5 more per 1,000** (from 30 fewer to 63 more)	⨁◯◯◯ Very low[a,b]	CRITICAL
Cardiovascular mortality (follow-up: 180 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	28/346 (8.1%)	29/346 (8.4%)	**RR 0.97** (0.59 to 1.59)	**3 fewer per 1,000** (from 34 fewer to 49 more)	⨁◯◯◯ Very low[a,b]	CRITICAL
Health-related quality of life (EQ-5D VAS, higher is better, change from baseline) (follow-up: 90 days; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	365	366	-	MD **2.48 higher** (2.34 higher to 2.62 higher)	⨁⨁⨁⨁ High	CRITICAL
Unplanned hospitalisation or visits HF related (HFhospital re-admission) (follow-up: 180 days)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	35/346 (10.1%)	51/346 (14.7%)	**RR 0.69** (0.46 to 1.03)	**46 fewer per 1,000** (from 80 fewer to 4 more)	⨁⨁◯◯ Low[a,b]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rapid optimisation	usual care	Relative (95% CI)	Absolute (95% CI)		
Acute kidney injury (follow-up: 90 days)												
1	randomised trials	not serious	not serious	serious[c]	very serious[b]	none	3/365 (0.8%)	0/366 (0.0%)	**Peto OR 7.45** (0.77 to 71.85)	**10 more per 1,000** (from 0 fewer to 20 more)[d]	⨁◯◯◯ Very low[b,c]	CRITICAL
Hyperkalaemia (follow-up: 90 days)												
1	randomised trials	not serious	not serious	serious[c]	serious[b]	none	13/365 (3.6%)	5/366 (1.4%)	**RR 2.61** (0.94 to 7.24)	**22 more per 1,000** (from 1 fewer to 85 more)	⨁⨁◯◯ Low[b,c]	CRITICAL
Falls (follow-up: 90 days)												
1	randomised trials	not serious	not serious	serious[c]	very serious[b]	none	1/365 (0.3%)	0/366 (0.0%)	**Peto OR 7.41** (0.15 to 373.41)	**0 fewer per 1,000** (from 0 fewer to 10 more)[d]	⨁◯◯◯ Very low[b,c]	CRITICAL

CI: confidence interval; EQ-5D VAS: EuroQoL 5-dimensions questionnaire visual analogue scale; HF: Heart failure; MD: Mean difference; OR: Odds ratio; RCT: Randomised controlled trial; RR: Relative risk

a. Downgraded by 1 increment for outcome indirectness: time-to-event data not available for reduced EF subgroup

*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes); MID for EQ5D VAS = 9.37.*

c. Downgraded by 1 increment for outcome indirectness: Outcome not defined

d. Absolute effect calculated from risk difference

Table 22: Clinical evidence profile: SGLT2i + ACEI/ARB + BB+MRA versus ACEI/ARB +BB+MRA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI/ARB + BB + MRA	ACEI/ARB + BB + MRA + placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) (follow-up: range 16 to 18 months)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	-/4236	-/4238	**HR 0.87** (0.77 to 0.98)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
All-cause mortality (dichotomous) (follow-up: range 3 months to 24 months)												
8	randomised trials	not serious	not serious	serious[b]	not serious	none	540/4815 (11.2%)	609/4820 (12.6%)	**RR 0.89** (0.80 to 0.99)	**14 fewer per 1,000** (from 25 fewer to 1 fewer)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Cardiovascular mortality (HR) (follow-up: range 16 to 18 months)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	-/4236	-/4238	**HR 0.86** (0.76 to 0.98)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
Cardiovascular mortality (dichotomous) (follow-up: range 3 to 18 months)												
4	randomised trials	not serious	not serious	serious[b]	serious[a]	none	415/4462 (9.3%)	476/4465 (10.7%)	**RR 0.87** (0.77 to 0.99)	**14 fewer per 1,000** (from 25 fewer to 1 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
Health related quality of life (KCCQ clinical summary score); change or final score (follow-up: 3 months; Scale from: 0 to 100, higher is better)												
4	randomised trials	not serious	not serious	not serious	not serious	none	2245	2246	-	MD **1.7 higher** (1.67 higher to 1.73 higher)	⨁⨁⨁⨁ High	CRITICAL
Health-related quality of life (KCCQ - overal summary score, change or final scores) (follow-up: range 12 weeks to 52 weeks; Scale from: 0 to 100, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI/ARB + BB + MRA	ACEI/ARB + BB + MRA + placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	not serious	not serious	not serious	none	382	383	-	MD **1.84 higher** (0.78 higher to 2.91 higher)	⨁⨁⨁⨁ High	CRITICAL
Health-related quality of life (KCCQ total symptom score), change score (follow-up: 8 months; Scale from: 0 to 100, higher is better)												
1	randomised trials	not serious	very serious[c]	not serious	very serious[a]	none	2417	2422	-	MD **0.47 higher** (5.48 lower to 6.43 higher)	⨁⨁◯◯ Low[a,c]	CRITICAL
First hospitalisation for heart failure (HR) (follow-up: range 3 to 18 months)												
3	randomised trials	not serious	not serious	not serious	not serious	none	-/4367	-/4370	**HR 0.70** (0.62 to 0.78)	**Not estimable**	⨁⨁⨁⨁ High	CRITICAL
Total hospitalisations for heart failure (rate ratio) (follow-up: range 16 months to 18 months)												
2	randomised trials	not serious	not serious	not serious	not serious	none	-/4236	-/4238	**Rate ratio 0.72** (0.65 to 0.80)	**60 fewer per 1000 patient(s) per years** (from 75 fewer to 43 fewer)[e]	⨁⨁⨁⨁ High	CRITICAL
Hospitalisation for heart failure (dichotomous) (follow-up: range 3 months to 18 months)												
5	randomised trials	not serious	not serious	serious[b]	serious[a]	none	496/4507 (11.0%)	682/4510 (15.1%)	**RR 0.73** (0.65 to 0.81)	**41 fewer per 1,000** (from 53 fewer to 29 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
Withdrawal due to drug-related adverse events (follow-up: range 3 months to 18 months)												
4	randomised trials	not serious	not serious	not serious	serious[a]	none	140/2815 (5.0%)	150/2816 (5.3%)	**RR 0.93** (0.75 to 1.17)	**4 fewer per 1,000** (from 13 fewer to 9 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI/ARB + BB + MRA	ACEI/ARB + BB + MRA + placebo	Relative (95% CI)	Absolute (95% CI)		
Acute kidney injury (follow-up: range 3 months to 18 months)												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	25/2551 (1.0%)	47/2553 (1.8%)	**RR 0.54** (0.33 to 0.87)	**8 fewer per 1,000** (from 12 fewer to 2 fewer)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Hyperkalaemia (follow-up: range 3 to 18 months)												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	356/4222 (8.4%)	395/4212 (9.4%)	**RR 0.90** (0.78 to 1.03)	**9 fewer per 1,000** (from 21 fewer to 3 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Symptomatic hypotension (surrogate for falls) (follow-up: range 12 weeks to 40 weeks)												
2	randomised trials	very serious[d]	not serious	serious[f]	very serious[a]	none	29/147 (19.7%)	32/148 (21.6%)	**RR 0.92** (0.66 to 1.29)	**17 fewer per 1,000** (from 74 fewer to 63 more)	⨁◯◯◯ Very low[a,d,f]	CRITICAL

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; HF: Heart Failure; HR: Hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: Mean difference; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

a. Downgraded by 1 increment for imprecision if the 95% CI crosses one MID and two increments if the 95% CI crosses both MIDs (default MID=0.8 and 1.25 for dichotomous outcomes and 0.5 x median baseline SD of the intervention and control group for continuous outcomes, or 0.5 x control group SD if baseline values not reported; MID=5 for KCCQ)

b. Downgraded by 1 increment for outcome indirectness: dichotomous when time-to-event is the prespecified measure

c. Downgraded by 1 increment for inconsistency (unexplained heterogeneity was present that was too significant to permit pooling, resulting in single studies)

d. Downgraded by 2 increments for high risk of bias in >50% analysis weighting (missing data; no information about pre-specified analyses)

e. Absolute effect calculated using total event rates per 100 person years reported in the papers.

f. Downgraded by 1 increment for outcome indirectness (symptomatic hypotension used as a surrogate for falls in the protocol)

Table 23: Clinical evidence profile: MRA + ACEI/ARB + BB versus ACEI/ARB +BB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA +ACEI/ARB+ BB	ACEI/ARB + BB +placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality HR (Tsutsui, 2017) (follow-up: 30 months)												
1	randomised trials	not serious	serious[a]	not serious	very serious[b]	none	111	110	**HR 1.77** (0.81 to 3.87)	**Not estimable**	⨁◯◯◯ Very low[a,b]	CRITICAL
All-cause mortality HR (Zannad, 2011) (follow-up: median 21 months)												
1	randomised trials	not serious	serious[a]	not serious	serious[b]	none	1364	1373	**HR 0.76** (0.62 to 0.93)	**Not estimable**	⨁⨁◯◯ Low[a,b]	CRITICAL
All-cause mortality (dichotomous) (follow-up: range 6 months to 44 months)												
5	randomised trials	not serious	not serious	not serious	serious[b]	none	201/1743 (11.5%)	235/1751 (13.4%)	**RR 0.86** (0.72 to 1.02)	**19 fewer per 1,000** (from 38 fewer to 3 more)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Cardiovascular mortality HR (Tsutsui, 2017) (follow-up: 30 months)												
1	randomised trials	not serious	serious[a]	not serious	serious[b]	none	111	110	**HR 2.40** (0.92 to 6.26)	**Not estimable**	⨁⨁◯◯ Low[a,b]	CRITICAL
Cardiovascular mortality HR (Zannad, 2011) (follow-up: median 21 months)												
1	randomised trials	not serious	serious[a]	not serious	serious[b]	none	1364	1373	**HR 0.76** (0.61 to 0.94)	**Not estimable**	⨁⨁◯◯ Low[a,b]	CRITICAL
Cardiovascular mortality (dichotomous) - Japan (follow-up: range 6 months to 30 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA +ACEI/ARB+ BB	ACEI/ARB + BB +placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[c]	serious[d]	serious[e]	serious[b]	none	16/260 (6.2%)	6/261 (2.3%)	**RR 2.47** (1.03 to 5.95)	**34 more per 1,000** (from 1 more to 114 more)	⨁◯◯◯ Very low[b,c,d,e]	CRITICAL
Cardiovascular mortality (dichotomous) - Europe (follow-up: range 21 months to 44 months)												
2	randomised trials	not serious	serious[d]	serious[e]	serious[b]	none	150/1429 (10.5%)	193/1438 (13.4%)	**RR 0.79** (0.64 to 0.96)	**28 fewer per 1,000** (from 48 fewer to 5 fewer)	⨁◯◯◯ Very low[b,d,e]	CRITICAL
Cardiovascular mortality (dichotomous) - total (follow-up: range 6 months to 44 months)												
4	randomised trials	not serious	very serious[f]	serious[e]	serious[b]	none	166/1689 (9.8%)	199/1699 (11.7%)	**RR 0.83** (0.68 to 1.01)	**20 fewer per 1,000** (from 37 fewer to 1 more)	⨁◯◯◯ Very low[b,e,f]	CRITICAL
Health-related quality of life (EQ-VAS, higher is better) (follow-up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[g]	not serious	not serious	very serious[b]	none	20	20	-	MD **3 higher** (42.92 lower to 48.92 higher)	⨁◯◯◯ Very low[b,g]	CRITICAL
Unplanned hospitalisation or visits HF related (hospitalisation for HF, HR) (follow-up: range 6 months to 30 months)												
3	randomised trials	not serious	not serious	not serious	not serious	none	1624	1634	**HR 0.60** (0.50 to 0.72)	**Not estimable**	⨁⨁⨁⨁ High	CRITICAL
Unplanned hospitalisation or visits HF related (HF-related hospitalisation) (follow-up: range 6 months to 30 months)												
3	randomised trials	not serious	not serious	serious[e]	not serious	none	198/1624 (12.2%)	297/1634 (18.2%)	**RR 0.67** (0.57 to 0.79)	**60 fewer per 1,000** (from 78 fewer to 38 fewer)	⨁⨁⨁◯ Moderate[e]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA +ACEI/ARB+ BB	ACEI/ARB + BB +placebo	Relative (95% CI)	Absolute (95% CI)		
Unplanned hospitalisation or visits HF related (hospitalisation for HF including repeat events) (follow-up: median 25 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	1364 participants - -	1373 participants 35.0% -	**Rate ratio 0.53** (0.42 to 0.66)	**Not estimable**	⨁⨁⨁⨁ High	CRITICAL
Withdrawal due to adverse events (follow-up: range 6 months to 21 months)												
3	randomised trials	not serious	not serious	not serious	serious[b]	none	205/1562 (13.1%)	234/1570 (14.9%)	**RR 0.88** (0.74 to 1.05)	**18 fewer per 1,000** (from 39 fewer to 7 more)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Acute kidney injury (follow-up: 12 weeks)												
1	randomised trials	very serious[g]	not serious	not serious	very serious[h]	none	0/20 (0.0%)	0/20 (0.0%)	**Risk Difference 0.00** (-0.09 to 0.09)	**0 per 1,000** (from 90 lower to to 90 more)	⨁◯◯◯ Very low[g,h]	CRITICAL
Hyperkalaemia (follow-up: range 6 months to 44 months)												
6	randomised trials	not serious	not serious	not serious	not serious	none	191/1831 (10.4%)	112/1825 (6.1%)	**RR 1.69** (1.36 to 2.12)	**42 more per 1,000** (from 22 more to 69 more)	⨁⨁⨁⨁ High	CRITICAL

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; EQ-VAS: EuroQoL visual analogue scale; HF: Heart Failure; HHF: Hospitalisation for heart failure; HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk

a. Downgraded by 1 increment for inconsistency: Tsutsui and Zannad studies demonstrated opposite directions for the effect estimate so not appropriate to pool these trials.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes; MID for EQ5D VAS = 33.5.
c. Downgraded by 1 increment because of some concerns about risk of bias due to the outcome assessment process being unblinded
d. Subgroup analyses (by Europe/Japan) required to explain heterogeneity (not appropriate to pool).
e. Downgraded by 1 increment for indirectness due to outcome reported as number of events.
f. Downgraded by 2 increments for inconsistency due to the I^2 value of >60%.
g. Downgraded by 2 increments for risk of bias limited information regarding randomisation, allocation concealment, the difference in attrition, unclear how the differences were accounted for, and no pre-specified plan.
h. Downgraded by 2 increments for imprecision (sample size <70)

Table 24: Clinical evidence profile: MRA + ARB + BB versus ARB +BB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA + ARB + BB	ARB +BB	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to drug-related adverse events (follow-up: 52 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	2/23 (8.7%)	1/25 (4.0%)	**RR 2.17** (0.21 to 22.40)	**47 more per 1,000** (from 32 fewer to 856 more)	⨁◯◯◯ Very low[a,b]	CRITICAL
Hyperkalaemia (follow-up: 52 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	1/23 (4.3%)	0/25 (0.0%)	**OR 8.06** (0.16 to 407.60)	**40 more per 1,000** (from 70 fewer to 150 more)[c]	⨁◯◯◯ Very low[a,b]	CRITICAL

ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; MRA: Mineralocorticoid receptor antagonist; OR: Odds ratio; RR: Relative risk
a. Downgraded for 2 increments for risk of bias due to no details provided regarding randomisation, allocation concealment, attrition, or prespecified plan.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.
c. Calculated from risk difference

Table 24: Clinical evidence profile: ARB+ACEI+BB versus ACEI+BB+placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB + ACEI + BB	ACEI + BB + placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) (follow-up: 41 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/1276	-/1272	**HR 0.89** (0.77 to 1.02)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
All-cause mortality (dichotomous) (follow-up: range 24 weeks to 41 months)												
2	randomised trials	not serious	not serious	serious[b]	not serious	none	377/1311 (28.8%)	413/1310 (31.5%)	**RR 0.91** (0.81 to 1.03)	**28 fewer per 1,000** (from 60 fewer to 9 more)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Cardiovascular mortality (HR) (follow-up: 41 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/1276	-/1272	**HR 0.83** (0.71 to 0.97)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
Cardiovascular mortality (dichotomous) (follow-up: 41 months)												
1	randomised trials	not serious	not serious	serious[b]	serious[a]	none	302/1276 (23.7%)	347/1272 (27.3%)	**RR 0.87** (0.76 to 0.99)	**35 fewer per 1,000** (from 65 fewer to 3 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
Unplanned hospitalisation or visits HF related (HF hospitalisation, HR) (follow-up: 41 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/1276	-/1272	**HR 0.83** (0.71 to 0.97)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
Unplanned hospitalisation or visits HF related, HF hospitalisation, dichotomous) (follow-up: 41 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB + ACEI + BB	ACEI + BB + placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[b]	serious[a]	none	309/1276 (24.2%)	356/1272 (28.0%)	**RR 0.87** (0.76 to 0.99)	**36 fewer per 1,000** (from 67 fewer to 3 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
Withdrawal due to drug-related adverse events (follow-up: range 24 weeks to 41 months)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	313/1311 (23.9%)	237/1305 (18.2%)	**RR 1.32** (1.13 to 1.53)	**58 more per 1,000** (from 24 more to 96 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Hyperkalaemia (causing discontinuation) (follow-up: range 24 weeks to 41 months)												
2	randomised trials	not serious	not serious	not serious	not serious	none	47/1311 (3.6%)	9/1305 (0.7%)	**RR 4.97** (2.49 to 9.93)	**27 more per 1,000** (from 10 more to 62 more)	⨁⨁⨁⨁ High	CRITICAL
Falls (symptomatic hypotension as a surrogate) (follow-up: 24 weeks)												
1	randomised trials	not serious	not serious	serious[c]	very serious[a]	none	2/35 (5.7%)	0/33 (0.0%)	**OR 7.19** (0.44 to 117.48)	**60 more per 1,000** (from 40 fewer to 150 more)[d]	⨁◯◯◯ Very low[a,c,d]	CRITICAL

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; BB: Beta-blocker; CI: Confidence interval; HF: Heart Failure; HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.

b. Downgraded by 1 increment for indirectness because events data is used rather than time-to-event data as pre-specified in the protocol.

c. Downgraded by 1 increment outcome indirectness (symptomatic hypotension used as a surrogate for falls)

d. Absolute effects calculated from risk difference.

Table 25: Clinical evidence profile: ARNI+MRA+BB versus ARB+MRA+BB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI + MRA + BB	ARB + MRA + BB	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) (follow-up: 24 weeks)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	-/168	-/168	**HR 1.63** (0.68 to 3.92)	**Not estimable**	⨁◯◯◯ Very low[a,b]	CRITICAL
All-cause mortality (dichotomous) (follow-up: range 12 weeks to 24 weeks)												
2	randomised trials	not serious	not serious	very serious[c]	very serious[d]	none	13/207 (6.3%)	8/207 (3.9%)	**RD 0.02** (-0.02 to 0.07)	**20 more per 1,000** (from 20 fewer to 70 more)	⨁◯◯◯ Very low[c,d]	CRITICAL
Cardiovascular mortality (HR) - Ghafur 2020 (follow-up: 88 days)												
1	randomised trials	serious[e]	serious[f]	not serious	not serious	none	-/50	-/50	**HR 0.37** (0.27 to 0.51)	**Not estimable**	⨁⨁◯◯ Low[e,f]	CRITICAL
Cardiovascular mortality (HR) - Mann 2022 (follow-up: 24 weeks)												
1	randomised trials	not serious	serious[f]	serious[a]	very serious[b]	none	-/168	-/168	**HR 1.58** (0.61 to 4.08)	**Not estimable**	⨁◯◯◯ Very low[a,b,f]	CRITICAL
Cardiovascular mortality (dichotomous) - Ghafur 2020 (follow-up: 88 days)												
1	randomised trials	serious[e]	serious[f]	serious[g]	serious[b]	none	4/50 (8.0%)	11/50 (22.0%)	**RR 0.36** (0.12 to 1.07)	**141 fewer per 1,000** (from 194 fewer to 15 more)	⨁◯◯◯ Very low[b,e,f,g]	CRITICAL
Cardiovascular mortality (dichotomous) Mann 2022 (follow-up: 24 weeks)												
1	randomised trials	not serious	serious[f]	very serious[c]	very serious[b]	none	11/167 (6.6%)	7/168 (4.2%)	**RR 1.58** (0.63 to 3.98)	**24 more per 1,000** (from 15 fewer to 124 more)	⨁◯◯◯ Very low[b,c,f]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI + MRA + BB	ARB + MRA + BB	Relative (95% CI)	Absolute (95% CI)		
Unplanned hospitalisation or visits HF-related (HRs) - Mann 2022 (follow-up: 24 weeks)												
1	randomised trials	not serious	serious[f]	serious[a]	serious[b]	none	-/168	-/168	**HR 1.24** (0.80 to 1.93)	**Not estimable**	⨁◯◯◯ Very low[a,b,f]	CRITICAL
Unplanned hospitalisation or visits HF-related (HRs) - Ghafur 2020 (follow-up: 88 days)												
1	randomised trials	serious[e]	serious[f]	not serious	serious[b]	none	-/50	-/50	**HR 0.80** (0.63 to 1.02)	**Not estimable**	⨁◯◯◯ Very low[b,e,f]	CRITICAL
Unplanned hospitalisaiton or visits HF related (dichotomous) - Gharfur 2020 (follow-up: 88 days)												
1	randomised trials	serious[e]	serious[f]	serious[g]	serious[b]	none	2/50 (4.0%)	10/50 (20.0%)	**RR 0.20** (0.05 to 0.87)	**160 fewer per 1,000** (from 190 fewer to 26 fewer)	⨁◯◯◯ Very low[b,e,f,g]	CRITICAL
Unplanned hospitalisation or visits HF related (dichotomous) - Mann 2022 (follow-up: 24 weeks)												
1	randomised trials	not serious	serious[f]	very serious[c]	serious[b]	none	44/167 (26.3%)	36/168 (21.4%)	**RR 1.23** (0.84 to 1.81)	**49 more per 1,000** (from 34 fewer to 174 more)	⨁◯◯◯ Very low[b,c,f]	CRITICAL
Withdrawal due to drug-related adverse events (discontinuation of drugs due to adverse events) (follow-up: 3 months)												
1	randomised trials	serious[h]	not serious	not serious	very serious[b]	none	1/40 (2.5%)	2/39 (5.1%)	**RR 0.49** (0.05 to 5.16)	**26 fewer per 1,000** (from 49 fewer to 213 more)	⨁◯◯◯ Very low[b,h]	CRITICAL
Hyperkalaemia (follow-up: range 88 days to 24 weeks)												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	29/217 (13.4%)	16/218 (7.3%)	**RR 1.82** (1.03 to 3.24)	**60 more per 1,000** (from 2 more to 164 more)	⨁⨁⨁◯ Moderate[b]	CRITICAL

ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin; BB: Beta-blocker; CI: Confidence interval; HF: Heart Failure; HR: Hazard ratio; MRA: Mineralocorticoid receptor antagonist; RD: Risk difference; RR: Relative risk
a. Downgraded by 1 increment for intervention indirectness because only 78% received combination therapy.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.
c. Downgraded by two increments for indirectness (outcome indirectness because not time-to-event outcome and intervention indirectness because only 78% received combination therapy)
d. Downgraded by two increments for imprecision (calculated using OIS)
e. Downgraded by 1 increment because of some concerns about risk of bias (no information about allocation concealment)
f. Downgraded by 1 increment for inconsistency: Ghafur and Mann studies demonstrated opposite directions for the effect estimate so not appropriate to pool these trials.
g. Downgraded by 1 increment for outcome indirectness because not time-to-event outcome as specified in the protocol.
h. Downgraded by 1 increment because of some concerns about risk of bias (adverse events not pre-specified outcome)

Table 26: Clinical evidence profile: ARNI+MRA+BB versus ACEI+MRA+BB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI+MRA+BB	ACEI+MRA+BB	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) (follow-up: median 27 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/4187	-/4212	**HR 0.84** (0.76 to 0.93)	**Not estimable**	⨁⨁⨁◯ Moderate [a]	CRITICAL
All-cause mortality (dichotomous) (follow-up: range 12 weeks to 33.6 months)												
4	randomised trials	not serious	not serious	serious[b]	serious[a]	none	716/4710 (15.2%)	841/4732 (17.8%)	**RR 0.86** (0.78 to 0.94)	**25 fewer per 1,000** (from 39 fewer to 11 fewer)	⨁⨁◯◯ Low [a,b]	CRITICAL
Cardiovascular mortality (HR) (follow-up: range 27 months to 33.6 months)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	-/4299	-/4323	**HR 0.81** (0.72 to 0.90)	**Not estimable**	⨁⨁⨁◯ Moderate [a]	CRITICAL
Cardiovascular mortality (dichotomous) (follow-up: range 12 weeks to 33.6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI+MRA+BB	ACEI+MRA+BB	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	serious[b]	serious[a]	none	573/4401 (13.0%)	705/4422 (15.9%)	**RR 0.82** (0.74 to 0.91)	**29 fewer per 1,000** (from 41 fewer to 14 fewer)	⊕⊕◯◯ Low [a,b]	CRITICAL

Health-related quality of life (KCCQ- CSS, higher is better, change score) (follow-up: range 3 months to 8 months; Scale from: 0 to 100)

3	randomised trials	not serious	not serious	not serious	not serious	none	4401	4422	-	MD **1.66 higher** (0.72 higher to 2.61 higher)	⊕⊕⊕⊕ High	CRITICAL

Health-related quality of life (KCCQ overall summary score, higher is better, change score) (follow-up: range 3 months to 8 months; Scale from: 0 to 100)

2	randomised trials	not serious	not serious	not serious	not serious	none	3900	3924	-	MD **1.3 higher** (0.61 higher to 1.98 higher)	⊕⊕⊕⊕ High	CRITICAL

Health-related quality of life (EQ-5D, higher is better, change score) (follow-up: 12 weeks; Scale from: 0 to 1)

1	randomised trials	very serious[d]	not serious	not serious	not serious	none	302	302	-	MD **0.01 higher** (0.01 lower to 0.03 higher)	⊕⊕⊕⊕ High	CRITICAL

Health-related quality of life (EQ-VAS, higher is better, change score) (follow-up: 12 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	not serious	none	302	302	-	MD **0.49 higher** (2.08 lower to 3.06 higher)	⊕⊕⊕⊕ High	CRITICAL

Health-related quality of life (SF-12, mental component summary, higher is better, change score) (follow-up: 12 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	not serious	none	302	302	-	MD **0.34 lower** (1.69 lower to 1.01 higher)	⊕⊕⊕⊕ High	CRITICAL

Health-related quality of life (SF-12 physical component summary, higher is better, change score) (follow-up: 12 weeks; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI+MRA+BB	ACEI+MRA+BB	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	302	302	-	MD **0.93 higher** (0.17 lower to 2.03 higher)	⊕⊕⊕⊕ High	CRITICAL

Health-related quality of life (SF-36 mental component score, higher is better, change score) (follow-up: 12 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	not serious	none	103	98	-	MD **0.97 lower** (2.99 lower to 1.05 higher)	⊕⊕⊕⊕ High	CRITICAL

Health-related quality of life (SF-36 physical component score, higher is better, change score) (follow-up: 12 weeks; Scale from: 0 to 100)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	103	98	-	MD **0.45 higher** (1.15 lower to 2.05 higher)	⊕⊕⊕◯ Moderate [a]	CRITICAL

Unplanned hospitalisation or visits HF related (first unplanned hospitalisation or visits HF relate, HR) - McMurray 2014 (follow-up: 27 months)

1	randomised trials	not serious	serious[c]	not serious	serious[a]	none	4187	4212	**HR 0.79** (0.71 to 0.88)	**Not estimable**	⊕⊕◯◯ Low [a,c]	CRITICAL

Unplanned hospitalisation or visits HF related (first unplanned hospitalisation or visits HF related, HR) - Tsutsui 2021 (follow-up: 33.6 months)

1	randomised trials	serious[d]	serious[c]	not serious	very serious[a]	none	112 participants -	111 participants	**HR 1.27** (0.70 to 2.29)	**Not estimable**	⊕◯◯◯ Very low [a,c,d]	CRITICAL

Unplanned hospitalisations or visits, HF-related (dichotomous) - McMurray 2014 (follow-up: median 27 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI+MRA+BB	ACEI+MRA+BB	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	Not serious	serious[c]	serious[b]	serious[a]	none	537/4187 (12.8%)	658/4212 (15.6%)	**RR 0.82** (0.74 to 0.91)	**28 fewer per 1,000** (from 41 fewer to 14 fewer)	⨁◯◯◯ Very low [a,b,c]	CRITICAL
Unplanned hospitalisations or visits, HF-related (dichotomous) - Tsutsui 2021 (follow-up: median 33.6 months)												
1	randomised trials	serious[d]	serious[c]	serious[b]	very serious[a]	none	25/111 (22.5%)	20/112 (17.9%)	**RR 1.26** (0.75 to 2.13)	**46 more per 1,000** (from 45 fewer to 202 more)	⨁◯◯◯ Very low [a,b,c,d]	CRITICAL
Withdrawal due to drug-related adverse events (follow-up: range 3 months to 34 months)												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	460/4401 (10.5%)	535/4422 (12.1%)	**RR 0.86** (0.77 to 0.97)	**17 fewer per 1,000** (from 28 fewer to 4 fewer)	⨁⨁⨁◯ Moderate [a]	CRITICAL
Acute kidney injury (renal failure acute) (follow-up: median 27 months)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	95/4203 (2.3%)	93/4229 (2.2%)	**RR 1.03** (0.77 to 1.36)	**1 more per 1,000** (from 5 fewer to 8 more)	⨁⨁◯◯ Low [a]	CRITICAL
Hyperkalaemia - Elevated serum potassium >5.5 mmol/l (follow-up: median 27 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	855/4187 (20.4%)	963/4212 (22.9%)	**RR 0.89** (0.82 to 0.97)	**25 fewer per 1,000** (from 41 fewer to 7 fewer)	⨁⨁⨁◯ Moderate [a]	CRITICAL
Hyperkalaemia - Hyperkalaemia measurement undefined (follow-up: range 3 months to 34 months)												
3	randomised trials	serious[d]	very serious[e]	not serious	very serious[b]	none	44/523 (8.4%)	31/520 (6.0%)	**RR 1.49** (0.68 to 3.25)	**29 more per 1,000** (from 19 fewer to 134 more)	⨁◯◯◯ Very low [a,d,e]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI+MRA+BB	ACEI+MRA+BB	Relative (95% CI)	Absolute (95% CI)		
Falls (symptomatic hypotension as a surrogate) (follow-up: median 27 months)												
1	randomised trials	not serious	not serious	serious[f]	not serious	none	588/4187 (14.0%)	388/4212 (9.2%)	**RR 1.52** (1.35 to 1.72)	**48 more per 1,000** (from 32 more to 66 more)	⨁⨁⨁◯ Moderate [f]	CRITICAL

ACEI: Angiotensin converting enzyme inhibitor; ARNI: Angiotensin receptor-neprilysin; BB: Beta-blocker; CI: Confidence interval; EQ-5D: EuroQoL 5-dimensions questionnaire; EQ-VAS: EuroQoL visual analogue scale; HF: Heart Failure; HR: Hazard ratio; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire – Clinical Summary Scores; KCCQ overall: Kansas City Cardiomyopathy Questionnaire – overall scores; MD: Mean difference; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk; SF-12: Short Form-12 health survey; SF-36: Short Form-36 health survey

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x SMD where no baseline values given) for continuous outcomes. MID for KCCQ is 5; MID for EQ5D is 0.03; MID for EQ5D VAS is 7.39; MID for SF12 mental component score is 4.28; MID for SF12 physical component score is 3.37; MID for SF36 mental component score is 3; MID for SF36 physical component score is 2.

b. Downgraded by one increment for outcome indirectness (events data, not time-to-event data as specified in protocol)

c. Downgraded by 1 increment for inconsistency: McMurray 2014 and Tsutsui 2021 demonstrated opposite directions for the effect estimate so not appropriate to pool these trials.

d. Downgraded by 1 increment because evidence has some concerns for risk of bias (no information about allocation concealment).

e. Downgraded by two increments for inconsistency because of unexplained substantial heterogeneity (I2>60%).

f. Downgraded by one increment for outcome indirectness because symptomatic hypotension used as a surrogate for falls.

Table 27: Clinical evidence profile: ARNI+BB versus ACEI+BB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI + BB v	ACEI + BB	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 12 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	1/231 (0.4%)	1/233 (0.4%)	**RR 1.01** (0.06 to 16.03)	**0 fewer per 1,000** (from 4 fewer to 65 more)	⨁⨁◯◯ Low[a]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARNI + BB v	ACEI + BB	Relative (95% CI)	Absolute (95% CI)		
Health-related quality of life (KCCQ- overall summary score, higher is better, change score) (follow-up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	216	222	-	mean **4.5 higher** (1.69 higher to 7.31 higher)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Hyperkalaemia (K^+>5.3meq/L) (follow-up: 12 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	37/231 (16.0%)	30/233 (12.9%)	**RR 1.24** (0.80 to 1.94)	**31 more per 1,000** (from 26 fewer to 121 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL

ACEI: Angiotensin converting enzyme inhibitor; ARNI: Angiotensin receptor-neprilysin; BB: Beta-blocker; CI: Confidence interval; K^+: Potassium in blood serum; KCCQ overall: Kansas City Cardiomyopathy Questionnaire – overall scores; RR: Relative risk
a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes.
b. Downgraded by one increment for imprecision because the 95% confidence crosses one MID (KCCQ MID=5)

Table 28: Clinical evidence profile: SGLT2i +ACEI/ARB +BB + MRA versus ACEI/ARB+BB+MRA in subgroups with and without type 1 diabetes.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI + BB + MRA	ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) - Diabetes present (follow-up: 16 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/1075	-/1064	**HR 0.78** (0.63 to 0.97)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI + BB + MRA	ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) - Diabetes absent (follow-up: 16 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/1298	-/1307	**HR 0.88** (0.70 to 1.11)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
All-cause mortality (dichotomous) - Diabetes present (follow-up: 18.2 months)												
1	randomised trials	not serious	not serious	serious[c]	serious[a]	none	143/1075 (13.3%)	178/1064 (16.7%)	**RR 0.80** (0.65 to 0.97)	**33 fewer per 1,000** (from 59 fewer to 5 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
All-cause mortality (dichotomous) - Diabetes absent (follow-up: 18.2 months)												
1	randomised trials	not serious	not serious	serious[c]	serious[a]	none	133/1298 (10.2%)	151/1307 (11.6%)	**RR 0.89** (0.71 to 1.11)	**13 fewer per 1,000** (from 34 fewer to 13 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
CV mortality (HR) - Diabetes present (follow-up: 16 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/927	-/929	**HR 0.92** (0.71 to 1.20)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
Cardiovascular mortality (HR) - Diabetes absent (follow-up: 16 months)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/304	-/302	**HR 0.92** (0.68 to 1.24)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
Cardiovascular mortality (dichotomous) - Diabetes present (follow-up: range 16 to 18.2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI + BB + MRA	ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious[b]	serious[a]	none	225/2002 (11.2%)	261/1993 (13.1%)	**RR 0.86** (0.73 to 1.01)	**18 fewer per 1,000** (from 35 fewer to 1 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Cardiovascular mortality (dichotomous) - Diabetes absent (follow-up: range 16 to 18.2 months)												
2	randomised trials	not serious	not serious	serious[b]	serious[a]	none	135/1602 (8.4%)	155/1609 (9.6%)	**RR 0.87** (0.70 to 1.09)	**13 fewer per 1,000** (from 29 fewer to 9 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Health related quality of life (KCCQ clinical summary score, higher is better, change score - Diabetes present) (follow-up: 8 months; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	927	929	-	MD **2.41 higher** (2.35 higher to 2.47 higher)	⨁⨁⨁⨁ High	CRITICAL
Health related quality of life (KCCQ clinical summary score, higher is better, change score - Diabetes absent) (follow-up: 8 months; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious	none	936	938	-	MD **1.1 higher** (1.05 higher to 1.15 higher)	⨁⨁⨁⨁ High	CRITICAL
Unplanned hospitalisation or visits HF related (hospitalisation for HF, HR) - Diabetes present (follow-up: range 16 to 18.2 months)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	-/2002	-/1993	**HR 0.72** (0.61 to 0.85)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
Unplanned hospitalisation or visits HF related (hospitalisation for HF, HR) - Diabetes absent (follow-up: range 16 to 18.2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI + BB + MRA	ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	serious[a]	none	-/1602	-/1609	**HR 0.68** (0.56 to 0.82)	**Not estimable**	⨁⨁⨁◯ Moderate[a]	CRITICAL
Unplanned hospitalisation or visits HF related (hospitalisation for HF, dichotomous) - Diabetes present (follow-up: range 16 to 18.2 months)												
2	randomised trials	not serious	serious[c]	serious[b]	serious[a]	none	363/2002 (18.1%)	513/1993 (25.7%)	**RR 0.71** (0.59 to 0.86)	**75 fewer per 1,000** (from 106 fewer to 36 fewer)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Unplanned hospitalisation or visits HF related (hospitalisation for HF, dichotomous) - Diabetes absent (follow-up: range 16 to 18.2 months)												
2	randomised trials	not serious	serious[c]	serious[b]	serious[a]	none	152/1602 (9.5%)	218/1609 (13.5%)	**RR 0.72** (0.55 to 0.93)	**38 fewer per 1,000** (from 61 fewer to 9 fewer)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Withdrawal due to drug-related adverse events - Diabetes present (follow-up: range 16 to 18.2 months)												
2	randomised trials	not serious	serious[c]	not serious	serious[a]	none	218/2002 (10.9%)	233/1993 (11.7%)	**RR 0.94** (0.79 to 1.11)	**7 fewer per 1,000** (from 25 fewer to 13 more)	⨁⨁◯◯ Low[a]	CRITICAL
Withdrawal due to drug-related adverse events - Diabetes absent (follow-up: range 16 to 18.2 months)												
2	randomised trials	not serious	not serious	not serious	not serious	none	215/1602 (13.4%)	211/1609 (13.1%)	**RR 1.02** (0.87 to 1.18)	**3 more per 1,000** (from 17 fewer to 24 more)	⨁⨁⨁⨁ High	CRITICAL
Hyperkalaemia - Diabetes present (follow-up: 16 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2i + ACEI + BB + MRA	ACEI + BB + MRA + placebo - Diabetes subgroup analysis	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	61/927 (6.6%)	74/929 (8.0%)	**RR 0.83** (0.60 to 1.15)	**14 fewer per 1,000** (from 32 fewer to 12 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL

Hyperkalaemia - Diabetes absent (follow-up: 16 months)

1	randomised trials	not serious	not serious	not serious	very serious[a]	none	48/936 (5.1%)	53/930 (5.7%)	**RR 0.90** (0.62 to 1.32)	**6 fewer per 1,000** (from 22 fewer to 18 more)	⨁⨁◯◯ Low[a]	CRITICAL

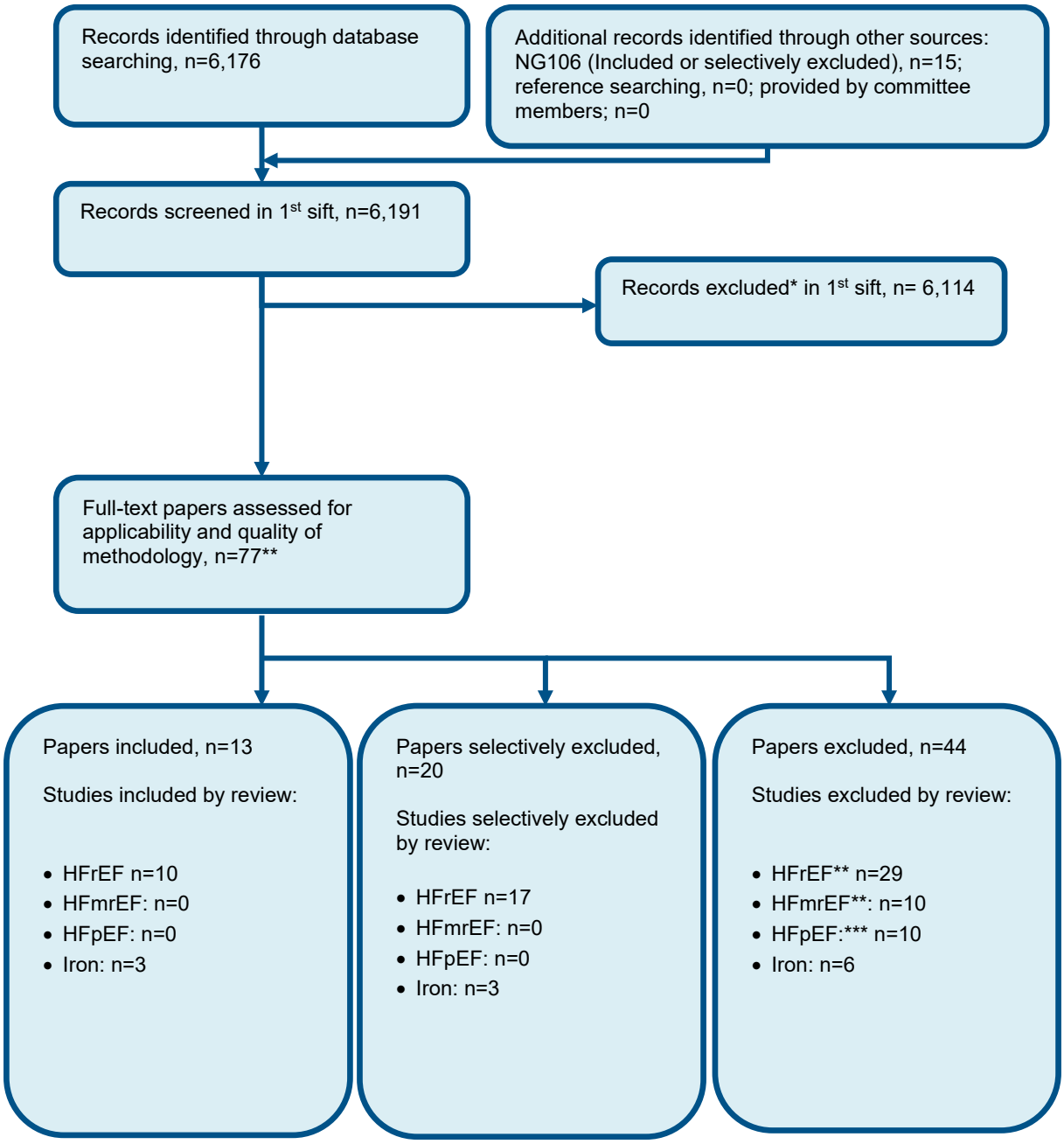
ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BB: Beta-blocker; CI: Confidence interval; HF: Heart failure; HR: Hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MRA: Mineralocorticoid receptor antagonist; RR: Relative risk; SGLT2i: Sodium-glucose co-transporter 2 inhibitor

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group value where no baseline values given) for continuous outcomes; MID for KCCQ = 5.

b. Downgraded by 1 increment for outcome indirectness because not time-to-event outcome as specified in the protocol.

c. Downgraded by 1 increment if I^2 40-60%.

Appendix G Economic evidence study selection



* 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
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Appendix H Economic evidence tables

H.1 Mineral corticoid receptor antagonists

Table 25: Health economic evidence study extraction table: Lee et al 2014

Section	Details for Lee et al 2014
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Discrete-event simulation model based on one RCT. Patient-level data from EMPHASIS-HF used to determine risk equations for each event by fitting a distribution to each time to event. 25,000 patients were simulated and randomly assigned individual time to events based on the risk equations for each model event. Non-CV mortality assumed to be the same for both arms. Patients exit model if death occurs, or ICD or CRT device is implanted. Otherwise patient remained in model until next event occurred. If discontinued treatment with eplerenone, patient returned to standard care. **Country setting:** UK **Perspective:** UK NHS perspective **Time horizon:** Lifetime **Treatment effect duration:** 4 years Best fitting parametric survival models were used to describe time- to-event **Discount rate per year:** Costs: 3.5% Outcomes: 3.5%
Interventions	**Intervention 1:** Standard therapy (ACEI and BBs - in line with trial protocol) **Intervention 2:** Eplerenone (starting dose of 25mg daily increased to 50mg daily after 4 weeks) in addition to standard therapy (as above)
	Population: Patients with chronic systolic heart failure (mean LVEF of 26%); New York Heart Association (NYHA) class II symptoms. **Patient characteristics** Sample size = NR Start age: 69 Male %: 78%

Section	Details for Lee et al 2014
Costs included	**Currency & cost year:** 2011 UK pounds sterling **Cost components incorporated:** Eplerenone drug costs, concomitant medications, eplerenone treatment initiation (two hospital visits and two sets of blood chemistry tests), disease management and monitoring, HF hospitalisation, other cardiovascular hospitalisation, adverse events associated with eplerenone, adverse events associated with standard care, cost of CRT and ICD devices.
Outcomes included	**Primary health outcome(s) in economic analysis:** LYs and QALYs **Key events modelled /analysed:** HRQoL, rates of all-cause mortality and HF hospitalization.
Data Sources	**Effectiveness data:** EMPHASIS-HF RCT - Outcomes: HF hospitalisation, other cardiovascular hospitalisation, new onset atrial fibrillation, CRT/ICD implantation, adverse events, discontinuation of eplerenone, cardiovascular mortality, and non-cardiovascular mortality. Baseline utility values and hospitalisation utility decrements are taken from Göhler et al. 2009, which are estimated from EPHESUS trial using EQ-5D (this trial has been excluded from this review due to having a post-MI population). **Baseline / epidemiological data:** **Quality-of-life weights:** EQ-5D - UK tariff (Sullivan et al. 2011 and Berg et al. 2010), Western Europe weighting (Göhler et al. 2009) Adverse event utility decrements are taken from Sullivan et al. 2011 catalogue of EQ-5D scores for the UK, and the utility decrement for new-onset atrial fibrillation is from Berg et al. 2010. **Costs and/or resource use:** British National Formulary 2011, PSSRU 2011, and the Scottish National Tariff (2010/11).
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £14,275 Intervention 2: £18,559 Incremental (2−1): £4,284 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime QALYs (per patient):** Intervention 1: 4.98 Intervention 2: 6.19 Incremental (2−1): 1.22 (95% CI: NR; p=NR)
Results: Cost-effectiveness	**Incremental cost-effectiveness ratios:** £3,520 per QALY gained (pa) 95% CI: NR

Section	Details for Lee et al 2014
	Probability Intervention 2 cost-effective (£20K/30K threshold): NR
Results: Uncertainty	**Deterministic:** Deterministic sensitivity analysis: Varied key inputs and assumptions (risk equation parameters and utility decrement associated with age) using one-way parameter sensitivity analysis using the 95% CI of the parameter distributions. In all cases ICER remains below £5,500. **Scenario analysis**: Using EMPHASIS-HF data with no extrapolation: ICER = £20,730 2 year time horizon: ICER = £20,101 5 year time horizon: ICER = £6,061 No utility decrement for adverse events, AF or hospitalisations: ICER = £3,558 Increased use of devices: ICER = £3,693 No use of devices: ICER = £2,802 **Probabilistic:** Probabilistic sensitivity analysis for time to event: 100 Monte Carlo simulations gave an overall mean ICER of £6,939 (95% CI: £6,656; £7,222). Probability of eplerenone being cost-effective at £20,000/QALY threshold = 100%.
Health inequalities assessment	Not reported
Comments	**Source of funding:** Pfizer Ltd. **Other:**
Rating: Applicability (Directly/ partially/ not)	**Directly applicable**
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	**Potentially serious limitations** - The analysis is based on estimates of relative treatment effect and resource use from a single study, so does not reflect all available evidence in this area. - There is cross-over between the trial arms. - Utility values are not reported directly from patients of the EMPHASIS-HF trial. - Potential publication bias due to the sponsor of the study.

Abbreviations: 95% CI: 95% confidence interval; BNF: British National Formulary; CRT: cardiac resynchronisation therapy; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICD: Implantable cardioverter defibrillator; ICER: incremental cost-effectiveness ratio; NR: not reported; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years; RCT: randomised controlled trial.

H.2 Sacubitril valsartan

Table 26: Health economic evidence study extraction table: Grant et al. 2020

Section	Details for Grant et al. 2020
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Decision analytic model (Cohort Markov) **Country setting: Canada** **Perspective:** Canadian public health payer, **Time horizon:** 5-year time horizon **Treatment duration:** 27 months, the median duration of follow-up in PARADIGM HF) **Treatment effect duration:** 27 months **Discount rate per year:** Costs: 1.5% Outcomes: 1.5%
Interventions	1. Current care. Initial uptake of 14% after a 9-month guideline recommended medication optimization period, the average rate of ARNI initiation was estimated to be 0.6% per month) 2. Late initiation (Patients had ACEI/ARB, BB, and MRA therapy introduced and up titrated over a period of 9 months) 3. Early initiation (Medication titration took place over 3 months before 4. De novo initiation (Patients were started on ARNI therapy with no preceding trial of ACEI/ARB)
	Population: Simulated cohort of Canadian patients with HFrEF and New York Heart Association functional class II through IV. **Patient characteristics** Sample size =NR Start age: 64 Male %: NR
Costs included	**Currency & cost year:** 2018 Canadian dollars. **Cost components incorporated:** Costing inputs included medication costs, diagnostic imaging costs, and downstream costs of HF hospitalization
Outcomes included	**Primary health outcome(s) in economic analysis:** LYs and QALYs

Section	Details for Grant et al. 2020
	Key events modelled /analysed: HRQoL, rates of all-cause mortality and HF hospitalization.
Data Sources	**Effectiveness data:** Clinical effectiveness inputs, including rates of all-cause mortality and HF hospitalization, were based on the PARADIGM HF trial. **Baseline / epidemiological data:** Change the Management of Patients with Heart Failure (CHAMP-HF) registry for the estimate of the average rate of ARNI initiation for the current care strategy. PARADIGM HF study for patient characteristics and hazard ratios for treatment effects. **Quality-of-life weights:** Health-related quality of life was directly measured in the PARADIGM HF trial using the European Quality of Life - 5 Dimension, 3 Level questionnaire. **Costs and/or resource use:** Alberta Schedule of Medical Benefits, Canadian Institute for Health Information, and the Alberta Drug Benefit List.
Results: costs	**Lifetime Total costs (per patient):** 1. £15,398 2. £17,758 3. £18,075 4. £18,285 Incremental (2-1): £2360 Incremental (3-1): £2677 Incremental (4-1): £2887 (95% CI: NR; p=NR
Results: health outcomes	**Lifetime QALYs (per patient):** 1. 3.28 2. 3.38 3. 3.41 4. 3.42 Incremental (2-1): 0.1 Incremental (3-1): 0.13 Incremental (4-1): 0.14 (95% CI: NR; p=NR)
Results: Cost-effectiveness	**Incremental cost-effectiveness ratios:** 2 vs 1: £23,234 per QALY gained 3 vs 1: £20,714 per QALY gained

Section	Details for Grant et al. 2020
	4 vs 1: £20,054 per QALY gained
Results: Uncertainty	**Deterministic:** Results were sensitive to the mortality effect of sacubitril valsartan and the acquisition cost. Both could potentially push the ICERs above £30,000 per QALY gained. **Probabilistic:** ICER 95% CI: NR At a threshold of £20,000 per QALY gained, the de novo strategy was the most cost-effective strategy in ~50% of simulations.
Health inequalities assessment	Not reported
Comments	**Source of funding:** Canadian Institutes of Health Research Banting Fellowship and an Arthur JE Child Fellowship. **Other:**
Rating: Applicability (Directly/ partially/ not)	Partially applicable - Non-UK setting
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Minor limitations - Effects were from a single trial rather than a systematic review. - Baseline from trial population so might differ from real-world population

Table 27: Health economic evidence study extraction table: McMurray et al. 2016

Section	Details for McMurray et al. 2016
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Decision analytic model (Cohort Markov) plus multivariable regression models for evaluating treatment effect. **Country setting:** UK **Perspective:** NHS and PSS **Time horizon:** Lifetime **Treatment duration:** Lifetime **Treatment effect duration:** Lifetime **Discount rate per year:** Costs: 3.5%; Outcomes: 3.5%

Section	Details for McMurray et al. 2016
Interventions	**Treatment 1:** Enalapril **Treatment 2:** sacubitril/valsartan
Population	**Population:** For the cost-effectiveness estimate, a priori defined subgroups in the PARADIGM-HF with chronic HF-REF was used. **Patient characteristics** Sample size = NR Mean age 1= 63.8, 2=63.8 Male 1= 79.0%, 2=77.4%
Costs included	**Currency & cost year:** 2015 UK pounds **Cost components incorporated:** Pharmacological therapies, hospitalisations, AEs and background medical management, including general practitioner visits and other outpatient contacts
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** Hospitalisation rates, EQ-5D-3L, and adverse event (AE) rates included in the 'alive' health states
Data Sources	**Effectiveness data:** The risks of events were estimated, dependent on patients' baseline characteristics in the PARADIGM-HF trial and treatment (sacubitril/valsartan or enalapril), through multivariable regression models. **Baseline / epidemiological data:** PARADIGM-HF **Quality-of-life weights:** The EQ-5D tariff published by Dolan was applied to EQ-5D responses collected in PARADIGM-HF to generate utility values for each patient for the UK setting. **Costs and/or resource use:** PSSRU, NHS National Schedule of Reference Costs and BNF
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £14,814 Intervention 2: £23,720 Incremental (2-1): £8,906 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime QALYs (per patient):** Intervention 1: 5.06 Intervention 2: 5.58 Incremental (2-1): 0.52 (95% CI: NR; p=NR)

Section	Details for McMurray et al. 2016
Results: Cost-effectiveness	**Incremental cost-effectiveness ratios:** 2 vs 1: £17,100 per QALY gained
Results: Uncertainty	**Deterministic:** Deterministic sensitivity analysis showed that results were most sensitive to the extrapolation of mortality, duration of treatment effect and time horizon, but were robust to other structural changes, with most scenarios associated with ICERs below the threshold. **Probabilistic:** In the UK, the expected ICER from the PSA was £18,000 (95% CI £8,900 to £34,700). At cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained, the probabilities that sacubitril/valsartan was cost-effective were 68% and 94%, respectively
Health inequalities assessment	Not reported
Comments	**Source of funding:** Novartis AG **Other:**
Rating: Applicability (Directly/ partially/ not)	Directly applicable
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations - Effects were from a single trial rather than a systematic review - Baseline from trial population so might differ from real-world population - Funded by manufacturer

Table 28: Health economic evidence study extraction table: Park et al. 2019

Section	Details for Park et al. 2019
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Decision analytic model (Cohort Markov) **Country setting:** South Korea **Perspective:** Health care sector (including out of pocket payments) **Time horizon:** Lifetime **Treatment duration:** Lifetime **Treatment effect duration:** Lifetime **Discount rate per year:** Costs: 5%; Outcomes: 5%
Interventions	**Intervention 1:** ARB (Candesartan or Valsartan) **Intervention 2:** Enalapril **Intervention 3:** Sacubitril valsartan

Section	Details for Park et al. 2019
Population	**Population:** Patients with Heart Failure with Reduced Ejection Fraction (EF<35%) and NYHA II-IV **Baseline characteristics** Mean age = 63.8 Male = 78%
Costs included	**Currency & cost year:** 2017 US dollars (presented here as 2020 UK pounds – converted back to South Korean Won using exchange rate reported then converted to pounds using OECD Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx) **Cost components incorporated:** medical costs, including medication, monitoring, hospitalization, adverse events (outpatient visits and tests) and terminal care.
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** hospitalisation, death, adverse events (hypotension, cough, elevated creatinine, elevated potassium)
Data Sources	**Effectiveness data:** 3 vs 2 from PARADIGM-HF RCT. 1 assumed to be equally as effective as 2 but had higher rates of raised creatine and potassium based on a network meta-analysis of 10 RCTs. **Baseline / epidemiological data:** Non-cardiovascular mortality from South Korean lifetables. **Quality-of-life weights:** value of utility surveyed from the general South Korean population according to the 5-level EuroQol-5 dimensions was used. One hundred face-to-face interviewees were selected through quota sampling according to age, sex, and region from the general population to reflect the utility decremented because of the events. The following health states were surveyed: alive, hospitalization, and AEs (eg, cough, hypotension) **Costs and/or resource use:** Hospitalisation rates were from PARADIGM-HF. Hospitalisation costs were from a retrospective cohort study of 6 hospitals in South Korea.
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £16,647 Intervention 2: £16,250 Intervention 3: £22,945 Incremental (3−1): £6,299 Incremental (2−1): £6,695 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime QALYs (per patient):** Intervention 1: 0.515 Intervention 2: 0.515 Intervention 2: 0.574 Incremental (3−1): 0.59 Incremental (2−1): 0.59 (95% CI: NR; p=NR)
Results: cost-effectiveness	**Incremental cost-effectiveness ratios:** 3 vs 1: £10,632 per QALY gained 3 vs 2: £11,300 per QALY gained
Results: Uncertainty	**Deterministic:** Results were below £20,000 per QALY for all sensitivity analyses including:

Section	Details for Park et al. 2019
	• Price of sacubitril valsartan • Discount rate • Distribution assumed for survival • Hospitalisation cost • Utility weights **Probabilistic:** ICER 95% CI: Not reported Probability Intervention 3 cost-effective (at £18,000 per QALY) 3 vs 1: 89.0% 3 vs 2: 87.6%
Health inequalities assessment	Not reported
Comments	**Source of funding:** Novartis Korea Ltd. H. Kim and S. Kim are an employee of Novartis Korea, Ltd. **Other:** [e.g., assumptions/omissions that may have impacted the conclusions]
Rating: Applicability (Directly/ partially/ not)	Partially applicable Korean cost perspective Korean utility values
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	- Potentially serious limitations - Effects were from a single trial rather than a systematic review - Baseline from trial population so might differ from real-world population - Funded by manufacturer

Abbreviations: ARB=angiotensin 2 receptor blockers; CI= confidence interval; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; QALY=quality-adjusted life-year; RCT=randomised controlled trial.

Table 29: Health economic evidence study extraction table: Van der Pol et al. 2019

Section	Details for Van der Pol et al. 2019
Study details	**Economic analysis type:** Cost-utility analysis **Model type:** Decision analytic model (Cohort Markov) **Country setting:** Germany **Perspective:** German Statutory Health Insurance **Time horizon:** Lifetime **Treatment duration:** Lifetime **Treatment effect duration:** Lifetime **Discount rate per year:** Costs: 3%; Outcomes: 3%
Interventions	**Intervention 1:** Candesartan **Intervention 2:** Enalapril **Intervention 3:** Sacubitril valsartan
Population	**Population:** Patients with HF-REF, as described in PARADIGM-HF **Baseline characteristics** Start age = 64 Male = NR%

Section	Details for Van der Pol et al. 2019
Costs included	**Currency & cost year:** 2018 euros (presented here as 2018 UK pounds – converted using OECD Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx) **Cost components incorporated:**
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** Hospitalisations and survival
Data Sources	**Effectiveness data (mortality and hospitalisation):** Intervention 3 vs Intervention 2 were from PARADIGM-HF RCT Intervention 2 vs Intervention 1 were from Indirect comparison of SOLVD and CHARM-alternative RCTs **Baseline / epidemiological data:** PARADIGM-HF RCT **Quality-of-life weights:** EQ-5D-3L UK tariff. **Costs and/or resource use:** Hospitalisation rates were from the PARADIGM-HF RCT. Outpatient care costs were added monthly to all patients in the model and consisted of both general practitioner and cardiologist costs, visited on average 1.8 times annually, distributed equally. Unit costs were from standard German sources.
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £6,930 Intervention 2: £6,854 Intervention 3: £21,614 Incremental (3−1): £14,684 Incremental (3−2): £14,760 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime QALYs (per patient):** Intervention 1: 4.81 Intervention 2: 4.90 Intervention 3: 5.72 Incremental (3−1): 0.91 Incremental (3−2): 0.82 (95% CI: NR; p=NR)
Results: cost-effectiveness	**Incremental cost-effectiveness ratios:** 3 vs 1: £16,096 per QALY gained 3 vs 2: £18,047 per QALY gained 2 dominated 1
Results: Uncertainty	**Deterministic:** Results were sensitive to the price of sacubitril valsartan and the mortality effect of sacubitril valsartan **Probabilistic:** ICER 95% CI: NR Probability Intervention 3 was most cost-effective (£20/£30K threshold): ~50%/~80%
Health inequalities assessment	Not reported
Comments	**Source of funding:** Dr. Postma received grants and honoraria from various pharmaceutical companies, including the company marketing the drug of interest in the paper. This study was, however, not financially supported and was performed on the authors own initiative. **Other:**

Section	Details for Van der Pol et al. 2019
Rating: Applicability (Directly/ partially/ not)	Partially applicable - German cost perspective - German utility values
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations - Effects were from a single trial rather than a systematic review - Baseline from trial population so might differ from real-world population

Abbreviations: CI= confidence interval; DA=deterministic analysis; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; PSS= Personal Social Services; QALY=quality-adjusted life-year; RCT=randomised controlled trial.

H.3 SGLT2 inhibitors

Table 30: Health economic evidence study extraction table: McEwan et al. 2020

Section	Details for McEwan et al. 2020
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Decision analytic model (Cohort Markov) **Country setting:** UK **Perspective:** NHS and PSS **Time horizon:** Lifetime **Treatment duration:** Lifetime but with 7% discontinuation per year **Treatment effect duration:** Lifetime while on treatment **Discount rate per year:** Costs: 3.5%; Outcomes: 3.5%
Interventions	**Intervention 1:** Standard therapy, i.e. RAASi (94%), BB (96%) and MRA (71%) **Intervention 2:** Dapagliflozin (10mg once daily) + Standard therapy
Population	**Population:** Adults with heart failure with reduced (<=40%) ejection fraction (HFrEF) DAPA-HF trial population: NYHA class II-IV and were optimally treated with pharmacological and device therapy. Patients were excluded if they had hypotension, systolic blood pressure >95 mmHg, estimated glomerular filtration rate <30 mL/min/1.73 m2 (or rapidly declining renal function), or type 1 diabetes mellitus. **Patient characteristics** Sample size = NR Mean age 1= 66.5, 2=66.2 Male 1= 77.0%, 2=76.2%
Costs included	**Currency & cost year:** 2019 UK pounds **Cost components incorporated:** Treatment, monitoring and adverse events. Heart failure hospitalisation. Background heart failure resource use (contact with primary care, cardiologist visits and A&E referrals with additional costs included

Section	Details for McEwan et al. 2020
	for patients with comorbid T2DM).
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** Transitions between quartiles of KCCQ-TSS stratified by presence/absence of Type 2 diabetes Heart failure hospitalisation constant by trial arm Mortality – Weibull distribution – adjusted for time-updated KCCQ-TSS and trial arm Adverse events: volume depletion, worsening renal function, episodes of major hypoglycaemia, fracture, diabetic ketoacidosis, amputation, urinary tract infection and genital infection.
Data Sources	**Effectiveness data:** RCT: DAPA-HF (Mean follow-up 18.2 months) **Baseline / epidemiological data:** RCT: DAPA-HF **Quality-of-life weights:** EQ-5D-3L UK tariff (mapped from EQ-5D-5L). **Costs and/or resource use:** Hospitalisation – DAPA HF
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £13,628 Intervention 2: £16,408 Incremental (2-1): £2,780 (95% CI: NR; p=NR) **Lifetime Treatment costs (per patient):** Intervention 1: £1,917 Intervention 2: £4,287 Incremental (2-1): £2,370 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime QALYs (per patient):** Intervention 1: 4.13 Intervention 2: 4.61 Incremental (2-1):0.48 (95% CI: NR; p=NR) **Life-years (per patient):** Intervention 1: 5.62 Intervention 2: 6.20 Incremental (2-1):0.58 (95% CI: NR; p=NR) **Lifetime heart failure hospitalisations (per 1000 patients):** Intervention 1: 925 Intervention 2: 820 Incremental (2-1):-105 (95% CI: NR; p=NR)
Results: Cost-effectiveness	**Incremental cost-effectiveness ratios:** 2 vs 1: £5,822 per QALY gained (DA)
Results: Uncertainty	**Deterministic:** **Subgroups** Across all subgroups the ICER ranged from £5,400-£6,800 per QALY gained: • age (≤65 vs. >65 years); • Heart failure duration (≤2 years vs. >2 years);

Section	Details for McEwan et al. 2020

	• prior heart failure hospitalisation (yes/no),
	• Type 2 Diabetes (yes/no),
	• ischaemic aetiology (yes/no);
	• ≤ median vs. > median
	  ○ left ventricular ejection fraction,
	  ○ N-terminal pro B-type natriuretic peptide
	  ○ body mass index,
	  ○ creatinine
	  ○ KCCQ-TSS
	Probabilistic: ICER 95% CI: NR
	Probability Intervention 2 cost-effective (£20K/30K threshold): 96%/97%

Health inequalities assessment	Not reported
Comments	**Source of funding:** Astra Zeneca **Other:**
Rating: Applicability (Directly/ partially/ not)	Directly applicable
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations - Effects were from a single trial rather than a systematic review - Baseline from trial population so might differ from real-world population - Funded by manufacturer

Abbreviations: BB=Beta-blockers; CI=confidence interval; DA=deterministic analysis; analysis; KCCQ-TSS= Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; MRA=Mineralcorticoid receptor antagonists; NR=not reported; NYHA=New York Heart Association; PSS=Personal Social Services; QALY=quality-adjusted life-year; RAASi= renin-angiotensin-aldosterone system inhibitors.

Table 31: Health economic evidence study extraction table: Miller et al. 2023

Section	Details for Miller et al. 2023
Study details	**Economic analysis type:** Cost-utility analysis **Model type:** Markov model adapted from the McEwan et al. 2020 model. The key modifications applied to the economic model were as follows. The analysis was restricted to the sub-population of DAPA-HF with a history of prior hospitalisation for heart failure (HHF); consequently, all-cause and cardiovascular mortality in addition to risk of HHF were conditional upon this population sub-group. They evaluated the cost-effectiveness of dapagliflozin based on timing of initiation. To estimate the incidence of HHF, negative binominal generalized estimating equation models were developed using the full DAPA-HF trial in which prior HHF was included as a covariate. **Country setting:** UK

Section	Details for Miller et al. 2023
	Perspective: NHS and PSS **Time horizon/Follow-up:** Lifetime **Treatment duration:** Lifetime but with 7% discontinuation per year **Treatment effect duration:** Lifetime while on treatment **Discount rate per year:** Costs: 3.5%; Outcomes: 3.5%
Interventions	**Intervention 1:** Standard therapy **Intervention 2:** Standard therapy + dapagliflozin 10mg (12-month delayed initiation) **Intervention 3:** Standard therapy + dapagliflozin (immediate initiation)
Population	**Population:** Patients with New York Heart Association class II, III or IV HF and a left ventricular ejection fraction of 40% or less to receive either dapagliflozin 10 mg once daily or placebo, in addition to recommended therapy. The sub-population of DAPA-HF with a history of prior HHF. **Patient characteristics** Sample size = NR Mean age = 65.92 Male = 77%
Costs included	**Currency & cost year:** 2019 UK pounds **Cost components incorporated:** UK specific and event-specific costs were applied as a one-off cost in the model with each occurrence of an event. Costs describing background resource use associated with HFrEF were applied to all patients and included contact with primary care, cardiologist visits and emergency department referrals with additional costs included for patients with comorbid Type 2 Diabetes Mellitus**.**
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** The model captured clinically relevant events including all-cause mortality, first and recurrent HHF, urgent HF visits, and adverse events. The following treatment-specific adverse events were included in the economic model based on data collected in DAPA-HF: volume depletion, worsening renal function, episodes of major hypoglycaemia, fracture, diabetic ketoacidosis, amputation, and urinary tract infection. For Intervention 2, event rates, costs, and transition probabilities for the standard therapy model were applied during the first 12 months with costs and transition probabilities for the dapagliflozin model applied after 12 months.

Section	Details for Miller et al. 2023
Data Sources	**Effectiveness data:** RCT DAPA-HF **Baseline / epidemiological data:** RCT DAPA-HF **Quality-of-life weights:** EQ-5D-3L UK tariff. **Costs and/or resource use.** DAPA-HF trial, UKPDS 84. NHS Reference Costs, and PSSRU
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £13,224 Intervention 2: £16,660 3: £16,912 **Incremental - Compared to standard therapy** 2 vs 1: £3436. 3 vs 1: £3688 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime QALYs (per patient):** Intervention 1: 4.023 Intervention 2: 4.614. Intervention 1: 4.662 **Incremental - Compared to standard therapy** 2 vs 1: 0.591. 3 vs 1: 0.639 (95% CI: NR; p=NR)
Results: Cost-effectiveness	**Incremental cost-effectiveness ratios compared to standard therapy:** 2 vs 1: £5,821/QALY 3 vs 1: £5,779/QALY **Net health benefit at £20,000 per QALY gained (in descending order):** Intervention 3: 3.816 QALYs Intervention 2: 3.781 QALYs Intervention 1: 3.362 QALYs **Full incremental analysis:** See Table 10
Results: Uncertainty	**Deterministic:** The cost-effectiveness of immediate and 12-month delayed initiation of dapagliflozin compared to standard therapy was stable across a range of deterministic sensitivity analyses. The ICER of immediate compared to 12-month delayed initiation of dapagliflozin was most sensitive to benefit and cost discounting parameters as well as intervention costs. **Probabilistic:** ICER 95% CI: NR At £20 000 per QALY gained, immediate initiation of dapagliflozin was cost-effective in >99% of simulations.
Health inequalities assessment	Not reported
Comments	**Source of funding:** This work was supported by AstraZeneca **Other:**
Rating: Applicability	Directly applicable

Section	Details for Miller et al. 2023
(Directly/ partially/ not)	
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations - Effects were from a single trial rather than a systematic review - Baseline from trial population so might differ from real-world population - Funded by manufacturer

Abbreviations: CI=confidence interval; DA=deterministic analysis; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; PSS: Personal Social Services; QALY=quality-adjusted life-year.

Table 32: Incremental cost-effectiveness results: Miller et al. 2023

Interventions in ascending order of cost	Costs per person	QALYs per person	Incremental cost*	Incremental QALYs*	Incremental cost per QALY gained*	Incremental cost per QALY gained**
Standard therapy	£13,224	4.023				
Standard therapy + Dapagliflozin (12-month delayed initiation)	£16,660	4.614	£3436	0.591	£5,820	Extendedly dominated
Standard therapy + Dapagliflozin (immediate initiation)	£16,912	4.662	£252	0.048	£5,263	£5,779

QALY=quality-adjusted life-year
** Compared with row above*
*** Compared with the next non-dominated row above*

Table 33: Health economic evidence study extraction table: Reifsnider et al. 2020

Section	Reifsnider et al. 2020
Study details	**Economic analysis type:** Cost-utility analysis **Model type:** Decision analytic model (Discrete-event simulation). EMPA-REG OUTCOME trial HF subpopulation data was used to estimate event-specific time-to-event distributions and baseline characteristics. **Country setting:** UK **Perspective:** NHS and PSS **Time horizon/Follow-up**: Lifetime **Treatment duration:** Lifetime **Treatment effect duration:** Lifetime while on treatment **Discount rate per year: Costs:** 3.5%; Outcomes: 3.5%
Interventions	**Intervention 1:** Standard of Care (SOC) **Intervention 2:** SOC + Empagliflozin 10mg
Population	**Population:** Participants with HF at baseline, enrolled in the EMPA-REG OUTCOME trial. The population consisted of adults with T2D and atherosclerotic CVD. Inclusion was not restricted to reduced left ventricular ejection fraction or to specific New York Heart Association classes. **Patient characteristics** Sample size =706 Mean age (standard deviation) = 64.5 (8.8) Male = 70%
Costs included	**Currency & cost year:** 2018 UK pounds **Cost components incorporated:** UK specific and event-specific costs were applied as a one-off cost in the model with each occurrence of an event. Costs describing background resource use associated with HFrEF were applied to all patients and included contact with primary care, cardiologist visits and emergency department referrals with additional costs included for patients with comorbid T2DM.
Outcomes included	**Primary health outcome(s) in economic analysis:** QALYs **Key events modelled /analysed:** First, and subsequent, hospitalization for worsening HF, CV death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina, transient ischaemic attack, revascularization, macroalbuminuria, renal injury, and renal failure.

Section	Reifsnider et al. 2020
Data Sources	**Effectiveness data:** EMPA-REG OUTCOME trial HF **Baseline / epidemiological data:** EMPA-REG OUTCOME trial HF **Quality-of-life weights:** Model utility multipliers were obtained from a study of the health-related quality of life of diabetes-related chronic conditions based on an analysis of 20,705 patients with diabetes and valid EQ-5D scores who participated in the 2000–2011 Medical Expenditure Panel Survey. They were then applied to a baseline tariff value for the UK. **Costs and/or resource use:** UK Prospective Diabetes study, a secondary analysis of the Study of Heart and Renal Protection (SHARP), NHS reference costs, NG28.
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £16,829 Intervention 2: £18,197 2 vs 1: £1,367 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime QALYs (per patient):** Intervention 1: 5.62 Intervention 2: 6.27 2 vs 1: 0.65 (95% CI: NR; p=NR):
Results: Cost-effectiveness	**Incremental cost-effectiveness ratio:** 2 vs 1: £2093 per QALY gained
Results: Uncertainty	**Deterministic:** In the analyses with a 10-year time horizon and higher event management costs, empagliflozin with SoC dominated SoC (was more effective and less costly) when . Variations in the discount rate to costs, the price of empagliflozin, and the discount rate to QALYs were most influential on the ICER. All scenarios produced ICERs well below the WTP threshold of £20 000 per QALY. **Probabilistic:** ICER 95% CI: NR Empagliflozin was cost-effective at a threshold of £20 000 per QALY in 91% of iterations .
Health inequalities assessment	**NR**
Comments	**Source of funding:** Boehringer Ingelheim International GmbH. **Other:**

Section	Reifsnider et al. 2020
Rating: Applicability (Directly/ partially/ not)	Directly applicable UK perspective
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations - Effects were from a single trial rather than a systematic review - Baseline from trial population so might differ from real-world population - Subgroup analysis of trial that informed the model was not powered to detect a difference in primary outcomes - Funded by manufacturer

Table 34: Health economic evidence study extraction table: Tafazzoli et al. 2023

Section	Tafazzoli et al 2023
Tafazzoli et al, 2023	**Economic analysis type:** Cost-utility analysis **Model type;** Markov cohort model with monthly cycles comparing empaglifozin 10mg plus Standard of Care (SoC) vs. SoC alone was developed to simulate patients' progression through health states based on the Kansas City Cardiomyopathy Questionnaire (KCCQ).The model consisted of five states that encompassed KCCQ-CSS quartiles and death. **Country setting:** UK **Perspective:** NHS and PSS **Time horizon/Follow-up**: Lifetime **Treatment duration:** Lifetime but with some discontinuation **Treatment effect duration:** Lifetime unless discontinued **Discount rate per year: Costs:** 3.5%; Outcomes: 3.5%
Interventions	**Intervention 1:** Standard of care (SoC) **Intervention 2:** Empaglifozin10mg added to standard of care 20% were receiving an angiotensin receptor–neprilysin inhibitor (ARNI) as part of SoC
Population	**Population:** The modelled cohort was representative of patients in the EMPEROR-Reduced trial. Patients were initially distributed into KCCQ-CSS quartiles. Half the patients had history of type 2 diabetes (T2D), 48% had an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2. **Patient characteristics** Start age: 67 yrs Male: 76% Sample size = NR
Costs included	**Currency & cost year:** 2021 British pounds **Cost components incorporated:** drug acquisition, management of clinical events, disease management

Section	Tafazzoli et al 2023
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** Treatment was assumed to reduce the risk of mortality and hospitalisation for heart failure (HHF) and influence the likelihood of transitions between KCCQ-CSS health states.
Data Sources	**Effectiveness data:** EMPEROR-Reduced trial **Baseline / epidemiological data:** EMPEROR-Reduced trial, Office of National Statistics **Quality-of-life weights:** EQ-5D-3L UK tariff. **Costs and/or resource use:** costing databases and published literature DAPA HF trial, UKPDS 84 study, MIMS, NHS Reference Costs, and PSSRU
Results: costs	**Lifetime Total costs (per patient):** Intervention 1: £15,475 Intervention 2: £16,661 **Incremental** 2 vs 1: £1185 (95% CI: NR; p=NR)
Results: health outcomes	**Lifetime/Life years, QALYs (per patient):** Intervention 1: 5.62 Intervention 2: 5.81 **Incremental** 2 vs 1: 0.18 (95% CI: NR; p=NR)
Results: Cost-effectiveness	**Incremental cost-effectiveness ratios:** **Compared to standard therapy:** 2 vs 1: £6152
Results: Uncertainty	**Deterministic:** Empaglifozin10mg plus SoC remained cost-effective compared with SoC alone in DSA at £ 20,000 per QALY. The cost of HHF was the most influential parameter followed by the cost of Empagliflozin. **Probabilistic:** ICER 95% CI: NR The PSA results found that the mean ICERs for the UK was £6061/QALY. The chance of empagliflozin plus SoC vs. SoC being cost-effective at WTP thresholds of £20,000/QALY UK was 79.6%.
Health inequalities assessment	Not reported
Comments	**Source of funding:** Boehringer Ingelheim **Other:**
Rating: Applicability (Directly/ partially/ not)	Directly applicable
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations - Effects were from a single trial rather than a systematic review - Baseline from trial population so might differ from real-world population - Funded by manufacturer

Abbreviations: CI=confidence interval; DA=deterministic analysis; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; PSS: Personal Social Services; QALY=quality-adjusted life-year.

H.4 Quadruple therapy

Table 35 Health economic evidence study extraction table: Van et al 2024

Section	Details for Van et al 2024
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Decision analytic model (Microsimulation) **Country setting:** Canada **Perspective:** Single payer perspective (e.g. British Columbia ministry of health) **Time horizon:** Lifetime **Treatment duration:** Lifetime **Treatment effect duration:** Lifetime **Discount rate per year:** Costs:1.5% Outcomes: 1.5%
Interventions	**Intervention 1**: Traditional sequencing, initiate ACEI/ARBs, followed by BB, MRA, ARNI and finally SGLT2i **Intervention 2:** SGLT2i followed by: MRA, ARNI, BB Strategies 3 and 4 initiate two treatments together, then prioritise initiation over titration **Intervention** 3: SGLT2i and BB, followed by ARNI, MRA (rapid titration) **Intervention** 4: ARNI and BB, followed by MRA then SGLT2i **Intervention** 5: Initiate ARNI, BB & SGLT2i, then initiate MRA and titrate other treatments **Intervention** 6: Initiate ARNI, BB, MRA & SGLT2i then titrate treatments Strategies 1 and 2 initiate one medication at a time prioritising titration over initiation of the next treatment. Strategies 3 and 4 initiate two treatments together, then prioritise initiation over titration. For each strategy a: bi-weekly titration, b: weekly titration
Population	**Population:** Adults with heart failure with reduced ejection fraction (HFrEF) **Patient characteristics** Sample size = NR Mean age =NR Refers to the mean survival range based on 60 year old patient Percentage male not reported Baseline data based on the placebo arm of SOLVD (1991) n =1284 age 61, ejection fraction 24.9, Male 79.8%
Costs included	**Currency & cost year:** 2022 Canadian dollars (presented here as 2022 UK pounds – converted using OECD Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx) **Cost components incorporated:** Treatment (drug and titration costs) and Heart failure hospitalisation.

Section	Details for Van et al 2024
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** Heart failure hospitalisation All cause mortality Adverse events rates: hypotension, bradycardia, hyperkalaemia and renal impairment only considered in terms of quality of life decrements and whether they were dose limiting
Data Sources	**Effectiveness data:** Risk ratio for treatments versus placebo: ACE or ARB: Target dose: Bœuf-Gibot et al 2021, Flather et al 2000 Sub-target dose: Turgeon et al 2019tARNI (all doses): McMurray et al 2014, Bœuf-Gibot et al 2021, Gao et al 2023, Vardeny et al (2016) PARADIGM-HF, Mohebi et al 2022 BB all doses: Turgeon et al 2019, Shibeta et al 2001, McAlister et al 2009, Barron et al 2013, Wikstrand et al 2002, Bristow et al 1996, Simon et al 2003 MRA all doses: Berbenetz et al 2016, Serenelli et al 2020, Ferreira et al 2019 EMPHASIS-HF SGLT2: Zannad et al 2020 meta-analysis of the EMPEROR-Reduced and DAPA-HF trials, Butler et al 2020, Ferreira et al (2022). **Baseline / epidemiological data:** SOLVD Yuself et al 1991 **Quality-of-life weights:**). Heart failure outpatient and hospital admission Armoiry et al 2020, adverse events: hypotension Ademi et al 2017, Bradycardia Sullivan et al 2005, Hyperkalemia: Widen et al 2020, Renal impairment Salcedo et al 2019 **Costs and/or resource use:** Hospitalisation: Patient cost estimator 2022, in office visits: MSC payment schedule 2023, Drug costs: BC PharmaCare Formulary Search 2022
Results: costs	**Lifetime Total costs (per patient):** Intervention 1a: £42,749 Intervention 1b: £43,801 Intervention 2a: £43,294 Intervention 2b: £44,081 Intervention 3a: £43,698 Intervention 3b: £44,288 Intervention 4a: £43,788 Intervention 4b: £44,340 Intervention 5a: £43,815 Intervention 5b: £44,356 Intervention 6a: £43,830 Intervention 6b: £44,370 (95% CI: NR; p=NR) **Lifetime incremental costs** Compared with intervention 1a Intervention 1a: - Intervention 1b: £1,052 Intervention 2a: £545 Intervention 2b: £1,332 Intervention 3a: £948 Intervention 3b: £1,538 Intervention 4a: £1,038 Intervention 4b: £1,591

Section	Details for Van et al 2024
	Intervention 5a: £1,066 Intervention 5b: £1,607 Intervention 6a: £1,080 Intervention 6b: £1,621
Results: health outcomes	**Lifetime QALYs (per patient):** Compared with intervention1a Intervention 1a: 9.55 Intervention 1b: 9.63 Intervention 2a: 9.61 Intervention 2b: 9.67 Intervention 3a: 9.70 Intervention 3b: 9.71 Intervention 4a: 9.71 Intervention 4b: 9.71 Intervention 5a: 9.71 Intervention 5b: 9.72 Intervention 6a: 9.72 Intervention 6b: 9.72 (95% CI: NR; p=NR) **Lifetime incremental QALYs (per patient):** Compared with intervention1a Intervention 1a: - Intervention 1b: 0.08 Intervention 2a: 0.06 Intervention 2b:0.12 Intervention 3a:0.15 Intervention 3b:0.16 Intervention 4a: 0.16 Intervention 4b:0.16 Intervention 5a: 0.17 Intervention 5b: 0.17 Intervention 6a: 0.17 Intervention 6b: 0.17 (95% CI: NR; p=NR) **Life-years (per patient): not reported**
Results: Cost-effectiveness	**Incremental cost-effectiveness ratios:** Compared with intervention 1a Intervention: 1a: - Intervention: 1b: £12,578 Intervention: 2a: £8,494 Intervention: 2b: £11,467 Intervention: 3a: £6,250 Intervention: 3b: £9,587

Section	Details for Van et al 2024
	Intervention: 4a: £6,577 Intervention: 4b: £9,727 Intervention: 5a: £6,448 Intervention: 5b: £9,590 Intervention: 6a: £6,387 Intervention: 6b: £9,485
Results: Uncertainty	**Deterministic:** One way sensitivity analysis found discount rate, incidence rate of death, and heart failure hospital admissions had the greatest impact on NMB. However all remaining under the willingness to pay (WTP) threshold of £27,963 (CA$50,000) per QALY. Subgroups **Probabilistic:** Based on the cost-effectiveness acceptability curve strategy 6a was identified as the most optimal strategy based on a WTP threshold of £7,830 (CA$14,000) per QALY and had a 75% probability of being the optimal choice at a WTP of £27,963 (CA$50,000) per QALY.:
Health inequalities assessment	Not reported
Comments	**Source of funding:** None
Rating: Applicability (Directly/ partially/ not)	Partially applicable Canadian payer perspective, not fully representative of UK costs and utilities
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations - Not all relevant costs were included (adverse event costs and treatment monitoring costs). - The baseline data and assumptions are from a study 20 years old which may not be reflective of current practice

Appendix I Health economic model

The health economic modelling can be found in the economic analysis report for chronic heart failure with reduced ejection fraction.

Appendix J Excluded studies

J.1 Clinical studies

Table 36: Studies excluded from the clinical review

Study	Exclusion reason
(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*
(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*
(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*
(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*
(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) New beta blocker reduces heart failure mortality by two-thirds. Geriatrics 51(1): 16-19	- Publication type not relevant to review protocol *commentary article*
(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*
(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*
(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)	- Population not relevant to this review protocol *Acute MI*

Study	Exclusion reason
Study Investigators. Lancet (London, England) 342(8875): 821-828	
(2024) The efficacy of dapagliflozin in a hierarchical kidney outcome in heart failure. Nature Medicine 30(5): 1253	- Not a peer-reviewed publication
(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*
, 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 resynchronisation 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
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*

Study	Exclusion reason
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 (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.*

Study	Exclusion reason
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 *SR checked for refs 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
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	- Comparator in study does not match that specified in this review protocol *within-class comparison*

Study	Exclusion reason
myocardial energy substrate utilization. European journal of heart failure 7(4): 618-23	
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
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 in Chronic Heart Failure. Cardiovascular drugs and therapy 26(6): 131-143	- Population not relevant to this review protocol *Mixed EF not matching either reduced or mildly reduced ejection fraction definitions. Results are not separated.*
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 *SR checked - no additional studies identified*
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.*
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*
Alzahrani, Talal, Tiu, John, Panjrath, Gurusher et al. (2018) The effect of angiotensin-converting enzyme inhibitors on clinical outcomes in	- Population not relevant to this review protocol *Mildly reduced EF*

Study	Exclusion reason
patients with ischemic cardiomyopathy and midrange ejection fraction: a post hoc subgroup analysis from the PEACE trial. Therapeutic advances in cardiovascular disease 12(12): 351-359	
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 effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
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, 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 Meta-Analysis of Randomized Controlled Trials Erratum. Journal of cardiovascular pharmacology 83(4): 359	- Publication type not relevant to review protocol *erratum*
Anonymous. (2004) Individualising heart failure patients to beta-blocker therapy. Cardiovascular journal of South Africa : official journal for Southern Africa Cardiac Society [and] South	- Conference abstract

Study	Exclusion reason
African Society of Cardiac Practitioners 15(2): 88-91	
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 INFLAMMATION IN CHRONIC HEART FAILURE?. Archives of the Balkan Medical Union 59(3): 259	- Study design not relevant to this review protocol *Retrospective cohort*
Balmforth, Craig, Simpson, Joanne, Shen, Li et al. (2019) Outcomes and Effect of Treatment According to Etiology in HFrEF: An Analysis of	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
PARADIGM-HF. JACC. Heart failure 7(6): 457-465	*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 coronary artery disease. The American journal of cardiology 76(17): 1259-1265	- Duration of follow up <3 months
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*

Study	Exclusion reason
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 Inhibition in Black Americans: Data From the PIONEER-HF Trial. JACC. Heart failure 8(10): 859-866	- Duration of follow up <3 months *Follow-up period was 8 weeks*
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

Study	Exclusion reason
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*
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 peritoneal dialysis with diabetes and heart failure with preserved ejection fraction. Clinical nephrology 102(5): 295-305	- Population not relevant to this review protocol *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	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
maximal and submaximal exercise capacity and neurohumoral activation in patients with congestive heart failure. American heart journal 149(5): 938e1-7	
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
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*
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	- Study does not contain an intervention relevant to this review protocol *HFrEF: no combination treatment*

Study	Exclusion reason
trial. International journal of cardiology 167(1): 151-156	
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*
Braunwald, Eugene, Domanski, Michael J, Fowler, Sarah E et al. (2004) Angiotensin-converting-enzyme inhibition in stable coronary artery disease. The New England journal of medicine 351(20): 2058-68	- Population not relevant to this review protocol *Mildly reduced ejection fraction.*
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 dilated or ischemic cardiomyopathy. Bucindolol Investigators. Circulation 89(4): 1632-1642	- Study does not contain an intervention relevant to this review protocol *Bucindolol*
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*

Study	Exclusion reason
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, 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*
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	- Population not relevant to this review protocol *Pooled population with HFrEF and HFpEF participants*

Study	Exclusion reason
Ejection Fraction Spectrum. JACC. Heart failure 11(4): 375-388	
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 definition 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)*
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 definition*
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
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*
Cadrin-Tourigny, Julia, Shohoudi, Azadeh, Roy, Denis et al. (2017) Decreased Mortality With Beta-Blockers in Patients With Heart Failure and	- Study design not relevant to this review protocol

Study	Exclusion reason
Coexisting Atrial Fibrillation: An AF-CHF Substudy. JACC. Heart failure 5(2): 99-106	*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 in Heart Failure (EMPHASIS-HF). European journal of heart failure 17(7): 707-16	- Secondary publication of an included study that does not provide any additional relevant information
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 does not contain an intervention relevant to this review protocol *Isosorbide dinitrate/hydralazine*

Study	Exclusion reason
Study Group. Journal of cardiac failure 5(3): 178-187	
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 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*

Study	Exclusion reason
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*
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)*
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	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
Failure. Journal of the American College of Cardiology 81(15): 1443-1455	
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*
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*

Study	Exclusion reason
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 Reduced or Preserved Ejection Fraction: A Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial. JAMA cardiology	- Population not relevant to this review protocol *LVEF too preserved*
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-	- Population not relevant to this review protocol

Study	Exclusion reason
year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. Journal of the American College of Cardiology 41(9): 1438-44	*Population is dilated cardiomyopathy due to haemodialysis*
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 COPERNICUS trial. Journal of cachexia, sarcopenia and muscle 8(4): 549-556	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*
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*
Cleland, John G F, Bunting, Karina V, Flather, Marcus D et al. (2018) 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 39(1): 26-35	- Population not relevant to this review protocol *Mildly reduced ejection fraction*

Study	Exclusion reason
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 function: insights from the SENIORS trial. European journal of heart failure 11(9): 872-880	- Comparator in study does not match that specified in this review protocol *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*

Study	Exclusion reason
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*
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., 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*

Study	Exclusion reason
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 Inhibition in Heart Failure. JACC. Heart failure 6(6): 489-498	- Secondary publication of an included study that does not provide any additional relevant information *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	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
a randomized, placebo-controlled study in patients with congestive heart failure. American heart journal 144(2): e3	*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
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	- Publication type not relevant to review protocol

Study	Exclusion reason
candesartan on nonfatal myocardial infarction and cardiovascular death in patients with heart failure. JAMA 294(14): 1794-8	*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 heart failure and preserved ejection fraction. American heart journal 162(6): 966-972.e10	- Population not relevant to this review protocol *LVEF ≥45% and mean not reported*
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, 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 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, 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 Prespecified Analysis of the FINEARTS-HF Trial. Circulation 151(1): 45-58	- Duplicate reference
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	- Population not relevant to this review protocol *Mildly reduced/preserved ejection fraction.*

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 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, 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*

Study	Exclusion reason
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 randomized, double-blind, active-controlled study. American heart journal 239: 1-10	- Duration of follow up <3 months *Follow up for 6 weeks*
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 *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*

Study	Exclusion reason
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 152(1): 86-92	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis describing the participants who had AF and factors associated with AF. AF 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*
Edes I; Gasior Z; Wita K (2005) Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
ENECA study. European journal of heart failure 7(4): 631-639	*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*
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.*

Study	Exclusion reason
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*
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	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
EMPEROR-Reduced. European journal of heart failure 24(4): 708-715	*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*
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-	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
Reduced. Journal of the American College of Cardiology 77(11): 1397-1407	*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*
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	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
Characteristics, Correlates of Recovery, and Survival: Results From the Valsartan Heart Failure Trial. Circulation. Heart failure 9(7)	*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
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	- Systematic review indirectly matches the review protocol: used as source of primary studies

Study	Exclusion reason
of randomized controlled trials. Heart failure reviews 26(1): 165-171	
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*
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	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
congestive heart failure. Perfusion 24(5): 162-170	
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*
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
Ghali JK, Wikstrand J, Van Veldhuisen DJ et al. (2009) The influence of renal function on clinical outcome and response to beta-blockade in	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). Journal of cardiac failure 15(4): 310-318	*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
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)*

Study	Exclusion reason
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 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, 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*
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

Study	Exclusion reason
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*
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*

Study	Exclusion reason
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*
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 with severe congestive heart failure. Circulation 99(8): 990-992	- Comparator in study does not match that specified in this review protocol *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*

Study	Exclusion reason
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*
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.	- Population not relevant to this review protocol *Acute MI and range of chronic HF*

Study	Exclusion reason
Archives of medical science : AMS 19(3): 565-576	
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*
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	- Study does not contain an intervention relevant to this review protocol

Study	Exclusion reason
failure: results of an ELITE trial substudy. Evaluation of Losartan in the Elderly. European journal of heart failure 1(4): 385-393	*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 failure: A systematic review and meta-analysis of randomized controlled trials. Frontiers in cardiovascular medicine 9: 1071387	- Systematic review does not contain a protocol intervention
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

Study	Exclusion reason
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 diabetes mellitus with acute myocardial infarction. American heart journal 266: 188-197	- Population not relevant to this review protocol *Acute MI hospitalised patients.*
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	- Systematic review indirectly matches the review protocol: used as source of primary studies

Study	Exclusion reason
review and meta-analysis. Age and ageing 46(1): 18-25	*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. (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	- Population not relevant to this review protocol

Study	Exclusion reason
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	*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 ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nature medicine 28(9): 1956-1964	- Population not relevant to this review protocol *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	- Secondary publication of an included study that does not provide any additional relevant information
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	- Secondary publication of an included study that does not provide any additional relevant information
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	- Comparator in study does not match that specified in this review protocol *hydralazine*

Study	Exclusion reason
Cooperative Studies Group. Circulation 87(6suppl): vi32-9	
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
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	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
congestive heart failure. Heart (British Cardiac Society) 92(5): 625-30	
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
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*

Study	Exclusion reason
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.*
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)*
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*

Study	Exclusion reason
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
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*
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*
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	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
American College of Cardiology 83(20): 1973-1986	*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*
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

Study	Exclusion reason
Kotecha, Dipak, Manzano, Luis, Altman, Douglas G et al. (2013) Individual patient data meta-analysis of beta-blockers in heart failure: rationale and design. Systematic reviews 2: 7	- Population not relevant to this review protocol *Mildly reduced ejection fraction*
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 of the American College of Cardiology 38(5): 1463-1469	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
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%*
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*
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, Phillip H, Dooley, Daniel J, Fonarow, Gregg C et al. (2018) Similar clinical benefits	- Population not relevant to this review protocol

Study	Exclusion reason
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	*<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*
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	- Secondary publication of an included study that does not provide any additional relevant information
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	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies

Study	Exclusion reason
Review and Network Meta-Analysis. Cardiorenal medicine 14(1): 570-580	*all included studies already identified and man relevant studies missing*
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, 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-HeFT study. European journal of heart failure 15(11): 1236-1244	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*
Leung, M., Wong, V.W., Heritier, S. et al. (2013) Rationale and design of a randomized trial on	- Publication type not relevant to review protocol

Study	Exclusion reason
the impact of aldosterone antagonism on cardiac structure and function in diabetic cardiomyopathy. Cardiovascular Diabetology 12(1): 139	*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, 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
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

Study	Exclusion reason
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, 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*
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.*

Study	Exclusion reason
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 *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 data*

Study	Exclusion reason
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*
Lund, Lars H, Claggett, Brian, Liu, Jiankang et al. (2018) 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 20(8): 1230-1239	- Population not relevant to this review protocol *Mildly reduced ejection fraction*
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 chronic congestive heart failure. Chinese new medicine 5(14): 1265-1266	- Full text unavailable
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	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment*

Study	Exclusion reason
Reduction in Mortality and morbidity (CHARM) programme. European heart journal 29(11): 1377-85	
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*
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*
Marcy, Todd R and Ripley, Toni L (2006) Aldosterone antagonists in the treatment of heart failure. American journal of health-system	- Review article but not a systematic review *Narrative review*

Study	Exclusion reason
pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 63(1): 49-58	
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	- Secondary publication of an included study that does not provide any additional relevant information
Massie BM, Armstrong PW, Cleland JG et al. (2001) Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure: results from the ATLAS trial. The Assessment of Treatment with Lisinopril and Survival. Archives of internal medicine 161(2): 165-171	- Comparator in study does not match that specified in this review protocol *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	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
Antagonists in Patients With Heart Failure and Impaired Renal Function. Journal of the American College of Cardiology 83(24): 2426-2436	*pools 2 studies with different comparisosn 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* - 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 L et al. (2024) Finerenone and Kidney Outcomes in Patients	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
with Heart Failure: The FINEARTS-HF Trial. Journal of the American College of Cardiology	*FINEARTS-HF analysis: Outcome data not stratified by LVEF*
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
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 adverse outcomes in DAPA-HF. European journal of heart failure 24(6): 1066-1076	- Secondary publication of an included study that does not provide any additional relevant information *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 (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*
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*
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*

Study	Exclusion reason
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, 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, 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 Reduction in Mortality and morbidity (CHARM)-Added trial. American heart journal 151(5): 985-91	- Population not relevant to this review protocol *Subgroup not of relevance to the protocol.*
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.*

Study	Exclusion reason
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 clinical conditions in patients with idiopathic dilated cardiomyopathy. Journal of the American College of Cardiology 24(7): 1678-1687	- Comparator in study does not match that specified in this review protocol *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
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	- Conference abstract

Study	Exclusion reason
dispersion. Therapeutic Research 28(11): 2235-2242	
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
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

Study	Exclusion reason
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 atrial fibrillation: insights from SENIORS. European journal of heart failure 14(10): 1171-8	- Study does not contain any outcome data relevant to this review protocol
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*
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*

Study	Exclusion reason
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.*
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.*
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*

Study	Exclusion reason
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 morbidity (CHARM) programme. European journal of heart failure 7(4): 650-6	- Population not relevant to this review protocol *Population includes MI or HF with hypertension*
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
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 trials. Journal of cardiovascular electrophysiology 34(5): 1277-1285	- Study does not contain any outcome data relevant to this review protocol
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	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
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	
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
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*

Study	Exclusion reason
Ozdemir, Murat, Arslan, Ugur, Turkoglu, Sedat et al. (2007) Losartan improves heart rate variability and heart rate turbulence in heart failure due to ischemic cardiomyopathy. Journal of cardiac failure 13(10): 812-7	- Population not relevant to this review protocol *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; 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, 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*

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) 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, 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, 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, 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*
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	- Data not reported in an extractable format or a format that can be analysed

Study	Exclusion reason
advanced heart failure. Minerva cardioangiologica 53(4): 321-8	*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 comparisosn 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 *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

Study	Exclusion reason
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 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	- Study does not contain any outcome data relevant to this review protocol *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	- Population not relevant to this review protocol *Analysed populations includes patients with and without HF*

Study	Exclusion reason
failure: findings from EMPA-REG OUTCOME. ESC heart failure 7(6): 3401-3407	
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*
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 morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet (London, England) 362(9386): 759-766	- Publication type not relevant to review protocol *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*
Pfeffer, MA, Domanski, M, Rosenberg, Y et al. (1998) Prevention of events with angiotensin-converting enzyme inhibition (the PEACE study design). Prevention of Events with Angiotensin-Converting Enzyme Inhibition. American journal of cardiology 82(3a): 25H-30H	- Population not relevant to this review protocol *Mildly reduced ejection fraction*
Piccirillo, Gianfranco, Quaglione, Raffaele, Nocco, Marialuce et al. (2002) Effects of long-term beta-blocker (metoprolol or carvedilol)	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
therapy on QT variability in subjects with chronic heart failure secondary to ischemic cardiomyopathy. The American journal of cardiology 90(10): 1113-7	*Within drug class comparison*
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. Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine 341(10): 709-717	- Comparator in study does not match that specified in this review protocol *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	- Duration of follow up <3 months *Follow-up was 6 weeks*

Study	Exclusion reason
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	
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 dysfunction and heart failure. Journal of the American College of Cardiology 46(3): 425-31	- Population not relevant to this review protocol *Population comprised of acute MI patients*
Pitt B, Pfeffer MA, Assmann SF et al. (2014) Spironolactone for heart failure with preserved ejection fraction. The New England journal of medicine 370(15): 1383-1392	- Population not relevant to this review protocol *Mildly reduced ejection fraction*
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*

Study	Exclusion reason
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 research in cardiology : official journal of the German Cardiac Society 112(7): 911-922	- Study does not contain any outcome data relevant to this review protocol
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)*

Study	Exclusion reason
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 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	- Population not relevant to this review protocol *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	- Population not relevant to this review protocol *Comprised of a population with mixed EF status*

Study	Exclusion reason
Heart Failure with Reduced Ejection Fraction Patients. Journal of clinical medicine 11(10)	
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, 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
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*

Study	Exclusion reason
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 Survival Study in Heart Failure (EMPHASIS-HF). Circulation. Heart failure 7(1): 51-58	- 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*
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*

Study	Exclusion reason
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 Activity?. Cardiovascular drugs and therapy 33(1): 87-95	- Protocol for an excluded study
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	- Conference abstract *Conference abstract*

Study	Exclusion reason
from the PARADISE MI trial. European journal of heart failure	
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. (2018) Impact of systolic blood pressure on the safety and tolerability of initiating and up-titrating sacubitril/valsartan in patients with heart failure and reduced ejection fraction: insights from the TITRATION study. European journal of heart failure 20(3): 491-500	- Secondary publication of an included study that does not provide any additional relevant information *Post hoc analysis/ retrospective subgroup of RCT*
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*
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. (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. (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 Changes in Cardiac Structure and Function in Heart Failure With	- Population not relevant to this review protocol *preserved ejection fraction*

Study	Exclusion reason
Preserved Ejection Fraction and the Impact of Spironolactone. Circulation. Heart failure 8(6): 1052-1058	
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*
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*
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

Study	Exclusion reason
	- 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 *SR 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*
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 protoco
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*

Study	Exclusion reason
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
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	- Study does not contain an intervention relevant to this review protocol *Monotherapy with background therapy of digoxin*

Study	Exclusion reason
failure. Journal of the American College of Cardiology 44(9): 1825-30	
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 Decompensation: The PARADIGM-HF Trial. JACC. Heart failure 4(10): 816-822	- Secondary publication of an included study that does not provide any additional relevant information
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*
Solomon, Scott D, Claggett, Brian, Lewis, Eldrin F et al. (2016) Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. European heart journal 37(5): 455-62	- Population not relevant to this review protocol *Mildly reduced/preserved ejection fraction*
Solomon, Scott D, McMurray, John J V, Anand, Inder S et al. (2019) Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. The New England journal of medicine 381(17): 1609-1620	- Population not relevant to this review protocol *Mildly reduced/preserved ejection fraction*
Solomon, Scott D, Vaduganathan, Muthiah, L Claggett, Brian et al. (2020) Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation 141(5): 352-361	- Population not relevant to this review protocol *Mildly reduced/preserved ejection fraction*
Solomon, SD, McMurray, JJV, Vaduganathan, M et al. (2024) Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. The New England journal of medicine	- Population not relevant to this review protocol *Mildly reduced/preserved ejection fraction*
Solomon, SD, Ostrominski, JW, Vaduganathan, M et al. (2024) Baseline characteristics of patients with heart failure with mildly reduced or	- Population not relevant to this review protocol *Mildly reduced/preserved ejection fraction*

Study	Exclusion reason
preserved ejection fraction: The FINEARTS-HF trial. European journal of heart failure 26(6): 1334-1346	
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*
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*

Study	Exclusion reason
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 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*
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*
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*

Study	Exclusion reason
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
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	- Study does not contain any outcome data relevant to this review protocol

Study	Exclusion reason
Angiotensin II Receptor Antagonist in Hypertensive Patients with Congestive Heart Failure Study. Current therapeutic research, clinical and experimental 64(2): 81-94	
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., 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
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, M, Claggett, BL, Lam, CSP et al. (2024) Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial. European journal of heart failure 26(6): 1324-1333	- Population not relevant to this review protocol *Mildly reduced/preserved ejection fraction.*
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).	- Comparator in study does not match that specified in this review protocol *HFrEF: not combination treatment in control group*

Study	Exclusion reason
Journal of the American College of Cardiology 60(20): 2082-2089	
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*
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 *Too 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*

Study	Exclusion reason
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*
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	- Population not relevant to this review protocol *Less than 80% of the population matches the protocol.*

Study	Exclusion reason
analysis of TOPCAT trial. ESC heart failure 11(1): 475-482	
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*
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.*
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	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
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	*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; 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.*
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
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 from 91 randomized controlled trials. Cardiovascular diabetology 18(1): 47	- Study does not contain an intervention relevant to this review protocol *Diabetic drugs for people with T2DM.*
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.*

Study	Exclusion reason
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 info*
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)*
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*

Study	Exclusion reason
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, 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	~~Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection~~
Zannad, Faiez, Ferreira, Joao Pedro, Gregson, John et al. (2022) Early changes in estimated glomerular filtration rate post-initiation of	- Study design not relevant to this review protocol

Study	Exclusion reason
empagliflozin in EMPEROR-Reduced. European journal of heart failure 24(10): 1829-1839	*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
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
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 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	- Population not relevant to this review protocol *Patients recruited post MI.*
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	- Study not reported in English *Non-English language study (Chinese)*

Study	Exclusion reason
Ejection Fraction. Chinese pharmaceutical journal 58(14): 1339-1342	
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 *ref 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 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	- Study design not relevant to this review protocol *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 37 MRA studies excluded from the economic review

Study	Code [Reason]
Ademi, Zanfina, Pasupathi, Kumar, Krum, Henry et al. (2014) Cost-effectiveness of Eplerenone in Patients with Chronic Heart Failure. American Journal of Cardiovascular Drugs 14(3): 209-216	- Selectively exclude - UK study available
Ademi, Zanfina; Pasupathi, Kumar; Liew, Danny (2016) Cost-Effectiveness of Eplerenone Compared to Usual Care in Patients With Chronic Heart Failure and NYHA Class II Symptoms, an Australian Perspective. Medicine 95(18): e3531	- Selectively exclude - UK study available
Athanasakis, Kostas, Bilitou, Aikaterini, Lee, Dawn et al. (2016) Cost-effectiveness of eplerenone in NYHA class II chronic heart failure patients with reduced LVEF: an analysis for Greece. ClinicoEconomics and Outcomes Research 8(null): 583-590	- Selectively exclude - UK study available
Thanh, Nguyen X., Ezekowitz, Justin A., Tran, Dat T. et al. (2016) Cost-effectiveness of Eplerenone for the Treatment of Systolic Heart Failure with Mild Symptoms in Alberta, Canada. American Journal of Cardiovascular Drugs 16(5): 365-376	- Selectively exclude - UK study available
Zhang, Zefeng, Mahoney, Elizabeth M., Kolm, Paul et al. (2010) Cost-effectiveness of Eplerenone in Patients with Heart Failure after Acute Myocardial Infarction Who were Taking Both ACE Inhibitors and β-Blockers. American Journal of Cardiovascular Drugs 10(1): 55-63	- Wrong population

Table 38: Sacubitril valsartan studies excluded from the economic review

Study	Code [Reason]
Ademi, Zanfina, Pfeil, Alena M, Hancock, Elizabeth et al. (2017) Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. Swiss medical weekly 147: w14533	- Selectively exclude (in favour of McMurray)
Borges, Margarida, Afonso-Silva, Marta, Laires, Pedro A et al. (2020) Cost-effectiveness of sacubitril/valsartan for the treatment of patients with heart failure with reduced ejection fraction in Portugal. Expert review of pharmacoeconomics & outcomes research 20(2): 199-205	- Selectively exclude (in favour of McMurray)
Chin, Ken Lee, Zomer, Ella, Wang, Bing H et al. (2020) Cost-Effectiveness of Switching Patients With Heart Failure and Reduced Ejection Fraction to Sacubitril/Valsartan: The Australian Perspective. Heart, lung & circulation 29(9): 1310-1317	- Selectively exclude (in favour of McMurray)
Gandjour, Afschin and Ostwald, Dennis A (2018) Sacubitril/Valsartan (LCZ696): A Novel Treatment for Heart Failure and its Estimated Cost-effectiveness, Budget Impact, and Disease Burden Reduction in Germany. PharmacoEconomics 36(10): 1285-1296	- Selectively exclude (in favour of McMurray)

Study	Code [Reason]
Giorgi, Mariano A, Boissonnet, Carlos P, Luque, Paula Soledad et al. (2023) Cost-effectiveness in unstable economies: the case of sacubitril/valsartan in heart failure with reduced ejection fraction in Argentina. Health economics review 13(1): 13	- Wrong perspective - non-OECD
Liang, Lin, Bin-Chia Wu, David, Aziz, Mohamed Ismail Abdul et al. (2018) Cost-effectiveness of sacubitril/valsartan versus enalapril in patients with heart failure and reduced ejection fraction. Journal of medical economics 21(2): 174-181	- Wrong perspective - non-OECD
Perera, Kanila, Ademi, Zanfina, Liew, Danny et al. (2021) Sacubitril-valsartan versus enalapril for acute decompensated heart failure: a cost-effectiveness analysis. European journal of preventive cardiology 28(9): 966-972	- Wrong subpopulation
Ramos, Isaac Corro, Versteegh, Matthijs M, de Boer, Rudolf A et al. (2017) Cost-effectiveness of the Angiotensin Receptor Neprilysin Inhibitor Sacubitril/Valsartan for Patients with Chronic Heart Failure and Reduced Ejection Fraction in the Netherlands: A Country Adaptation Analysis Under the Former and Current Dutch Pharmacoeconomic Guidelines. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 20(10): 1260-1269	- Selectively exclude (in favour of McMurray)
Zaca, Valerio (2018) Sacubitril/valsartan or an implantable cardioverter-defibrillator in heart failure with reduced ejection fraction patients: a cost-effectiveness analysis. Journal of cardiovascular medicine (Hagerstown, Md.) 19(10): 597-605	- Wrong intervention/comparator

Table 39 SGLT2i studies excluded from the economic review

Study	Code [Reason]
Abushanab, Dina, Chbib, Salma, Kaddoura, Rasha et al. (2024) Cost-effectiveness of add-on dapagliflozin for heart failure with reduced ejection fraction patients without diabetes. Journal of medical economics 27(1): 404-417	- Wrong perspective - non-OECD
Bhatt, Ankeet S, Vaduganathan, Muthiah, Claggett, Brian L et al. (2024) Cost-effectiveness of Dapagliflozin for Heart Failure Across the Spectrum of Ejection Fraction: An Economic Evaluation Based on Pooled, Individual Participant Data From the DELIVER and DAPA-HF Trials. Journal of the American Heart Association 13(5): e032279	- Wrong perspective - US
Davis, Jason A, Booth, David, McEwan, Phil et al. (2024) Cost-effectiveness of dapagliflozin for patients with heart failure across the spectrum of ejection fraction: A pooled analysis of DAPA-HF and DELIVER data. European journal of heart failure 26(3): 664-673	- Wrong population

Study	Code [Reason]
Garcia-Moll, Xavier, Croci, Francesco, Sole, Alexandra et al. (2024) A cost-effectiveness analysis of empagliflozin for heart failure patients across the full spectrum of ejection fraction in Spain: combined results of the EMPEROR-Preserved and EMPEROR-Reduced trials. Expert review of cardiovascular therapy 22(13): 131-139	- Wrong population
Gil-Rojas, Yaneth; Lasalvia, Pieralessandro; Garcia, Angel (2022) Cost-utility of dapagliflozin plus standard treatment compared to standard treatment for the management of heart failure with reduced ejection fraction in Colombia. Expert review of pharmacoeconomics & outcomes research 22(4): 655-663	- Selectively exclude (in favour of McEwan)
Hallinen, Taru, Kivela, Santtu, Soini, Erkki et al. (2023) Cost-Effectiveness of Empagliflozin in Combination with Standard Care versus Standard Care Only in the Treatment of Heart Failure Patients in Finland. ClinicoEconomics and outcomes research : CEOR 15: 1-13	- Selectively exclude (in favour of Taffazoli)
Kim, Eui-Soon, Park, Sun-Kyeong, Cho, Daniel Sung-Ho et al. (2024) Eligibility and Cost-Utility Analysis of Dapagliflozin in Patients with Heart Failure Across the Whole Spectrum of Ejection Fraction in South Korea. American journal of cardiovascular drugs : drugs, devices, and other interventions 24(2): 313-324	- Selectively exclude (in favour of McEwan)
Kim, Eui-Soon, Park, Sun-Kyeong, Youn, Jong-Chan et al. (2024) Real-World Eligibility and Cost-Effectiveness Analysis of Empagliflozin for Heart Failure in Korea. Journal of Korean medical science 39(1): e8	- Selectively exclude (in favour of Taffazoli)
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	- Preserved or mildly reduced ejection fraction
Liao, Chia-Te, Yang, Chun-Ting, Kuo, Fang-Hsiu et al. (2021) Cost-Effectiveness Evaluation of Add-on Empagliflozin in Patients With Heart Failure and a Reduced Ejection Fraction From the Healthcare System's Perspective in the Asia-Pacific Region. Frontiers in cardiovascular medicine 8: 750381	- Selectively exclude (in favour of Taffazoli)
Liao, Chia-Te, Yang, Chun-Ting, Toh, Han Siong et al. (2021) Cost-effectiveness evaluation of add-on dapagliflozin for heart failure with reduced ejection fraction from perspective of healthcare systems in Asia-Pacific region. Cardiovascular diabetology 20(1): 204	- Selectively exclude (in favour of McEwan)
Montilla, Precious Juzenda, Aquino, Camilo Oliver, Cunanan, Elaine et al. (2025) Cost-utility analysis of empagliflozin for heart failure in the Philippines. Journal of medical economics 28(1): 157-167	- Wrong perspective - non-OECD
Ong, Siew Chin; Low, Joo Zheng; Linden, Stephan (2023) Cost-effectiveness of adding empagliflozin to the standard of care for	- Wrong perspective - non-OECD

Study	Code [Reason]
patients with heart failure with reduced ejection fraction from the perspective of healthcare system in Malaysia. Frontiers in pharmacology 14: 1195124	
Parizo, Justin T, Goldhaber-Fiebert, Jeremy D, Salomon, Joshua A et al. (2021) Cost-effectiveness of Dapagliflozin for Treatment of Patients With Heart Failure With Reduced Ejection Fraction. JAMA cardiology 6(8): 926-935	- Wrong perspective - US
Savira, Feby, Wang, Bing H, Kompa, Andrew R et al. (2021) Cost-effectiveness of dapagliflozin in chronic heart failure: an analysis from the Australian healthcare perspective. European journal of preventive cardiology 28(9): 975-982	- Selectively exclude (in favour of McEwan)
Tsutsui, Hiroyuki, Sakamaki, Hiroyuki, Momomura, Shin-Ichi et al. (2023) Cost-effectiveness analysis of empagliflozin in patients with heart failure with reduced ejection fraction in Japan based on the EMPEROR-Reduced trial. Journal of cardiology 81(6): 522-530	- Selectively exclude (in favour of Taffazoli)

Table 40: Quadruple therapy studies excluded from the economic review

Study	Code [Reason]
Dixit, Neal M, Parikh, Neil U, Ziaeian, Boback et al. (2023) Economic Modeling Analysis of an Intensive GDMT Optimization Program in Hospitalized Heart Failure Patients. Circulation. Heart failure 16(12): e011218	- Wrong perspective - US
Dixit, Neal M, Parikh, Neil U, Ziaeian, Boback et al. (2023) Cost-Effectiveness of Comprehensive Quadruple Therapy for Heart Failure With Reduced Ejection Fraction. JACC. Heart failure 11(5): 541-551	- Wrong perspective - US
Faridi, Kamil F, Dayoub, Elias J, Ross, Joseph S et al. (2022) Medicare Coverage and Out-of-Pocket Costs of Quadruple Drug Therapy for Heart Failure. Journal of the American College of Cardiology 79(25): 2516-2525	- Wrong perspective - US
Huang, Yun, Zhou, Hua, Fang, Chongbo et al. (2024) Cost-Effectiveness of New Quadruple Therapy Compared With Standard Treatment for Patients With Heart Failure in China. Journal of cardiovascular pharmacology 83(1): 86-92	- Wrong perspective - non-OECD
Yan, Brandon W; Spahillari, Aferdita; Pandya, Ankur (2023) Cost-Effectiveness of Quadruple Therapy in Management of Heart Failure With Reduced Ejection Fraction in the United States. Circulation. Cardiovascular quality and outcomes 16(6): e009793	- Wrong perspective - US

Table 41: Intensive titration studies excluded from the economic review

Study	Code [Reason]
Dixit, Neal M, Parikh, Neil U, Ziaeian, Boback et al. (2023) Economic Modeling Analysis of an Intensive GDMT Optimization Program in Hospitalized Heart Failure Patients. Circulation. Heart failure 16(12): e011218	- Wrong perspective - US

Table 42: Other medicines excluded from the economic review

Study	Code [Reason]
Adena, Michael A; Hamann, Gary; Sindone, Andrew P (2019) Cost-Effectiveness of Ivabradine in the Treatment of Chronic Heart Failure. Heart, lung & circulation 28(3): 414-422	- Wrong intervention/comparator
Alkhatib, Nimer, Sweitzer, Nancy K, Lee, Christopher S et al. (2021) Ex Ante Economic Evaluation of Arg389 Genetically Targeted Treatment with Bucindolol versus Empirical Treatment with Carvedilol in NYHA III/IV Heart Failure. American journal of cardiovascular drugs : drugs, devices, and other interventions 21(2): 205-217	- Wrong intervention/comparator
Alsumali, Adnan, Lautsch, Dominik, Liu, Rongzhe et al. (2021) Budget Impact Analysis of Vericiguat for the Treatment of Chronic Heart Failure with Reduced Ejection Fraction Following a Worsening Event. Advances in therapy 38(5): 2631-2643	- Not economic evaluation
Bakhai, Ameet, Palaka, Eirini, Linde, Cecilia et al. (2018) Development of a health economic model to evaluate the potential benefits of optimal serum potassium management in patients with heart failure. Journal of medical economics 21(12): 1172-1182	- Wrong intervention/comparator
Claxton, Lindsay, Simmonds, Mark, Beresford, Lucy et al. (2022) Coenzyme Q10 to manage chronic heart failure with a reduced ejection fraction: a systematic review and economic evaluation. Health technology assessment (Winchester, England) 26(4): 1-128	- Wrong intervention/comparator

Study	Code [Reason]
Di Stasi, F., Scalone, L., De Portu, S. et al. (2005) Cost-effectiveness analysis of bisoprodol treatment for heart failure. Italian Heart Journal 6(12): 950-955	- EU perspective - Wrong intervention/comparator
Di Tanna, Gian Luca, Angell, Blake, Urbich, Michael et al. (2022) A Proposal of a Cost-Effectiveness Modeling Approach for Heart Failure Treatment Assessment: Considering the Short- and Long-Term Impact of Hospitalization on Event Rates. PharmacoEconomics 40(11): 1095-1105	- Wrong intervention/comparator
Elendu, Chukwuka, Amaechi, Dependable C, Elendu, Tochi C et al. (2024) Cost-effectiveness of ace inhibitors versus ARBs in heart failure management. Medicine 103(36): e39496	- Wrong perspective - US - Wrong intervention/comparator
Krittayaphong, Rungroj; Yadee, Jirawit; Permsuwan, Unchalee (2019) Cost-Effectiveness Analysis of the Adjunctive Therapy of Ivabradine for the Treatment of Heart Failure with Reduced Ejection Fraction. ClinicoEconomics and outcomes research : CEOR 11: 767-777	- Wrong intervention/comparator
Kurdi, A.I.B.; Elliott, R.A.; Chen, L.-C. (2019) Clinical and economic implications of therapeutic switching of angiotensin receptor blockers to angiotensin-converting enzyme inhibitors: A population-based study. Journal of Hypertension 37(6): 1285-1293	- Wrong population
Lassnig, Alexander, Rienmueller, Theresa, Kramer, Diether et al. (2019) A novel hybrid modeling approach for the evaluation of integrated care and economic outcome in heart failure treatment. BMC medical informatics and decision making 19(1): 229	- Wrong intervention/comparator