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[Intervention Review]

Pharmacological interventions for heart failure in people with chronic kidney disease

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ABSTRACT

Background

Approximately half of people with heart failure have chronic kidney disease (CKD). Pharmacological interventions for heart failure in people with CKD have the potential to reduce death (any cause) or hospitalisations for decompensated heart failure. However, these interventions are of uncertain benefit and may increase the risk of harm, such as hypotension and electrolyte abnormalities, in those with CKD.

Objectives

This review aims to look at the benefits and harms of pharmacological interventions for HF (i.e., antihypertensive agents, inotropes, and agents that may improve the heart performance indirectly) in people with HF and CKD.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies through 12 September 2019 in consultation with an Information Specialist and using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included randomised controlled trials of any pharmacological intervention for acute or chronic heart failure, among people of any age with chronic kidney disease of at least three months duration.

Data collection and analysis

Two authors independently screened the records to identify eligible studies and extracted data on the following dichotomous outcomes: death, hospitalisations, worsening heart failure, worsening kidney function, hyperkalaemia, and hypotension. We used random effects meta-analysis to estimate treatment effects, which we expressed as a risk ratio (RR) with 95% confidence intervals (CI). We assessed the risk of bias using the Cochrane tool. We applied the GRADE methodology to rate the certainty of evidence.

Main results

One hundred and twelve studies met our selection criteria: 15 were studies of adults with CKD; 16 studies were conducted in the general population but provided subgroup data for people with CKD; and 81 studies included individuals with CKD, however, data for this subgroup were not provided. The risk of bias in all 112 studies was frequently high or unclear. Of the 31 studies (23,762 participants) with data on CKD patients, follow-up ranged from three months to five years, and study size ranged from 16 to 2916 participants. In total, 26 studies (19,612 participants) reported disaggregated and extractable data on at least one outcome of interest for our review and were included in our meta-analyses.

In acute heart failure, the effects of adenosine A1-receptor antagonists, dopamine, nesiritide, or serelaxin on death, hospitalisations, worsening heart failure or kidney function, hyperkalaemia, hypotension or quality of life were uncertain due to sparse data or were not reported.

In chronic heart failure, the effects of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) (4 studies, 5003 participants: RR 0.85, 95% CI 0.70 to 1.02; $I^2 = 78\%$; low certainty evidence), aldosterone antagonists (2 studies, 34 participants: RR 0.61 95% CI 0.06 to 6.59; very low certainty evidence), and vasopressin receptor antagonists (RR 1.26, 95% CI 0.55 to 2.89; 2 studies, 1840 participants; low certainty evidence) on death (any cause) were uncertain. Treatment with beta-blockers may reduce the risk of death (any cause) (4 studies, 3136 participants: RR 0.69, 95% CI 0.60 to 0.79; $I^2 = 0\%$; moderate certainty evidence).

Treatment with ACEi or ARB (2 studies, 1368 participants: RR 0.90, 95% CI 0.43 to 1.90; $I^2 = 97\%$; very low certainty evidence) had uncertain effects on hospitalisation for heart failure, as treatment estimates were consistent with either benefit or harm. Treatment with beta-blockers may decrease hospitalisation for heart failure (3 studies, 2287 participants: RR 0.67, 95% CI 0.43 to 1.05; $I^2 = 87\%$; low certainty evidence).

Aldosterone antagonists may increase the risk of hyperkalaemia compared to placebo or no treatment (3 studies, 826 participants: RR 2.91, 95% CI 2.03 to 4.17; $I^2 = 0\%$; low certainty evidence). Renin inhibitors had uncertain risks of hyperkalaemia (2 studies, 142 participants: RR 0.86, 95% CI 0.49 to 1.49; $I^2 = 0\%$; very low certainty). We were unable to estimate whether treatment with sinus node inhibitors affects the risk of hyperkalaemia, as there were few studies and meta-analysis was not possible. Hyperkalaemia was not reported for the CKD subgroup in studies investigating other therapies.

The effects of ACEi or ARB, or aldosterone antagonists on worsening heart failure or kidney function, hypotension, or quality of life were uncertain due to sparse data or were not reported.

Effects of anti-arrhythmic agents, digoxin, phosphodiesterase inhibitors, renin inhibitors, sinus node inhibitors, vasodilators, and vasopressin receptor antagonists were very uncertain due to the paucity of studies.

Authors' conclusions

The effects of pharmacological interventions for heart failure in people with CKD are uncertain and there is insufficient evidence to inform clinical practice. Study data for treatment outcomes in patients with heart failure and CKD are sparse despite the potential impact of kidney impairment on the benefits and harms of treatment. Future research aimed at analysing existing data in general population HF studies to explore the effect in subgroups of patients with CKD, considering stage of disease, may yield valuable insights for the management of people with HF and CKD.

PLAIN LANGUAGE SUMMARY

Heart failure drugs in people with chronic kidney disease

What is the issue?

People with heart failure (when the heart doesn't pump blood properly) often need medicine to help with symptoms like fatigue, swelling, and breathing problems. Studies have looked at whether these medicines are harmful or helpful. However, but they do not clarify whether these treatments may help people with heart failure that also have kidney problems (when the kidneys don't remove waste and fluid from the body properly).

What did we do?

We searched for all research studies that assessed the different treatments for heart failure up to September 2019. We evaluated whether medicines prevent death or hospital admissions, or increase risk of harm, for people with kidney disease. We also measured how certain we could be about the effects of these medicines on the body using a system called "GRADE".

What did we find?

We found 31 studies involving 23,762 people with heart failure and chronic kidney disease. Patients were given either a heart failure medicine compared to standard care or a placebo. The treatment they received was decided by random chance. Although there were many

different treatments studied, unfortunately, few of them looked at the same type of medicine. As well, there were many different ways that researchers measured what happened when patients took these medicines. As a result, we could not combine the studies together and clarify the benefits and harms of each treatment. Existing studies cannot really tell us whether medicines used to treat heart failure in the general population are effective or safe for people who have both heart failure and chronic kidney disease.

Conclusions

We are not able to recommend which heart failure medicines are best for people with heart failure and chronic kidney disease. We need more information from large clinical studies. Most of the heart failure studies did not report treatment effects separately based on levels of kidney function. Obtaining this information from existing studies may be helpful to learn more about how to treat heart failure in people with chronic kidney disease.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. ACUTE: Serelaxin versus placebo in patients with heart failure and chronic kidney disease

ACUTE: Serelaxin versus placebo in patients with heart failure and chronic kidney disease

Patient or population: heart failure with chronic kidney disease

Settings: acute, inpatient

Intervention: serelaxin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Serelaxin			
Death (any cause)	42 per 1000	25 per 1000 (14 to 43)	RR 0.59 (0.34 to 1.02)	1395 (2)	⊕⊕⊕⊕ low ^{2,3,4}
Cardiovascular death	97 per 1000	46 per 1000 (20 to 105)	RR 0.47 (0.21 to 1.08)	1395 (2)	⊕⊕⊕⊕ low ^{2,3,4}
Hospitalisation (any cause)	not reported	not reported	--	--	--
Heart failure hospitalisation	not reported	not reported	--	--	--
Worsening heart failure	162 per 1000	115 per 1000 (87 to 149)	RR 0.71 (0.54 to 0.92)	1395 (2)	⊕⊕⊕⊕ low ^{3,4}
Worsening kidney function	86 per 1000	74 per 1000 (32 to 170)	RR 0.86 (0.37 to 1.98)	1395 (2)	⊕⊕⊕⊕ low ^{2,3,4}
Hypotension	48 per 1000	60 per 1000 (39 to 94)	RR 1.26 (0.81 to 1.96)	1395 (2)	⊕⊕⊕⊕ low ^{2,3,4}

Hyperkalaemia	48 per 1000	52 per 1000 (15 to 187)	RR 1.08 (0.30 to 3.87)	234 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
Quality of life	not reported	not reported	--	--	--

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Important study limitations due to risks of bias

² The confidence intervals include potential for important benefits and harms

³ Important and unexplained heterogeneity present (or insufficient data observations to evaluate)

⁴ Insufficient data observations to evaluate

Summary of findings 2. CHRONIC: ACEi or ARB versus placebo in patients with heart failure and chronic kidney disease

CHRONIC: ACEi or ARB versus placebo in patients with heart failure and chronic kidney disease

Patient or population: heart failure with chronic kidney disease

Settings: chronic, outpatient

Intervention: ACEi or ARB

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	ACEi or ARB			
Death (any cause) (follow-up 2 to 3.5 years)	320 per 1000	272 per 1000 (224 to 326)	RR 0.85 (0.70 to 1.02)	5003 (4)	⊕⊕⊕⊕ low ^{2,3,4}
Cardiovascular death	411 per 1000	333 per 1000 (263 to 415)	RR 0.81 (0.64 to 1.01)	1368 (2)	⊕⊕⊕⊕ low ^{2,3,4}

(follow-up 3 to 4 years)					
Hospitalisation (any cause)	not reported	not reported	--	--	--
Heart failure hospitalisation (follow-up 2 to 3.5 years)	546 per 1000	491 per 1000 (235 to 1037)	RR 0.90 (0.43 to 1.90)	1368 (2)	⊕⊕⊕⊕ very low ^{2,3,4}
Worsening heart failure	not reported	not reported	--	--	--
Worsening kidney function	not reported	not reported	--	--	--
Hypotension (ARB; withdrawn from study)	42 per 1000	109 per 1000 (47 to 254)	RR 2.60 (1.12 to 6.07)	332 (1)	⊕⊕⊕⊕ very low ^{3,4}
Hyperkalaemia	not reported	not reported	--	--	--
Quality of life	not reported	not reported	--	--	--

*The **assumed risk** (e.g. the median control group risk across studies) was calculated by dividing the number of participants in the control group that experienced an event by the total number of participants in the control group. The **corresponding risk** was calculated by multiplying the assumed risk with the **relative effect** from the meta-analysis. The 95% CI for the corresponding risk was calculated by multiplying the assumed risk with the lower and upper CI of the risk ratio estimate from the meta-analysis.

CI: Confidence interval; **RR:** Risk Ratio; **ACEi:** angiotensin-converting enzyme inhibitor; **ARB:** angiotensin receptor blocker

GRADE Working Group grades of evidence

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Summary of findings 3. CHRONIC: Beta-blockers versus placebo in patients with heart failure and chronic kidney disease

CHRONIC: Beta-blockers versus placebo in patients with heart failure and chronic kidney disease

Patient or population: heart failure with chronic kidney disease

Settings: chronic, outpatient

Intervention: beta-blockers

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Beta-blockers			
Death (any cause) (follow-up 1 to 2.5 years)	215 per 1000	148 per 1000 (129 to 170)	RR 0.69 (0.60 to 0.79)	3136 (4)	⊕⊕⊕⊕ moderate ^{3,4}
Cardiovascular death (follow-up 1 to 2.5 years)	123 per 1000	65 per 1000 (43 to 100)	RR 0.53 (0.35 to 0.81)	2287 (3)	⊕⊕⊕⊕ low ^{3,4}
Hospitalisation (any cause)	432 per 1000	324 per 1000 (225 to 467)	RR 0.75 (0.52 to 1.08)	1583 (2)	⊕⊕⊕⊕ low ^{2,3,4}
Heart failure hospitalisation (follow-up 1 to 2.5 years)	318 per 1000	213 per 1000 (137 to 334)	RR 0.67 (0.43 to 1.05)	2287 (3)	⊕⊕⊕⊕ low ^{2,3,4}
Worsening heart failure	25 per 1000	34 per 1000	RR 1.36 (0.58 to 3.20)	704 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
Worsening kidney function	no events	no events	--	704 (1)	⊕⊕⊕⊕ very low ^{3,4}
Hypotension	no events	2/356**	RR 5.11 (0.25 to 106.15)	704 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
Hyperkalaemia	not reported	not reported	--	--	--
Quality of life	not reported	not reported	--	--	--

*The **assumed risk** (e.g. the median control group risk across studies) was calculated by dividing the number of participants in the control group that experienced an event by the total number of participants in the control group. The **corresponding risk** was calculated by multiplying the assumed risk with the **relative effect** from the meta-analysis. The 95% CI for the corresponding risk was calculated by multiplying the assumed risk with the lower and upper CI of the risk ratio estimate from the meta-analysis.

** Event rate derived from the raw data. A 'per thousand' rate is non-informative in view of the scarcity of evidence and zero events in the control group

CI: Confidence interval; **RR:** Risk Ratio

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⁴ Insufficient data observations to evaluate

Summary of findings 4. CHRONIC: Aldosterone antagonists versus placebo in patients with heart failure and chronic kidney disease

CHRONIC: Aldosterone antagonists versus placebo in patients with heart failure and chronic kidney disease

Patient or population: heart failure with chronic kidney disease

Settings: chronic, outpatient

Intervention: aldosterone antagonists

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Anti-aldosterone			
Death (any cause) (follow-up 6 to 21 months)	294 per 1000	179 per 1000 (17 to 1,938)	RR 0.61 (0.06 to 6.59)	34 (2)	⊕⊕⊕⊕ very low ^{1,2,3,4}
Cardiovascular death	not reported	not reported	--	--	--
Hospitalisation (any cause)	not reported	not reported	--	--	--
Heart failure hospitalisation	not reported	not reported	--	--	--
Worsening heart failure	not reported	not reported	--	--	--

Worsening kidney function	not reported	not reported	--	--	--
Hypotension	not reported	not reported	--	--	--
Hyperkalaemia follow-up 6-24 months	84 per 1000	243 per 1000 (170 to 350)	RR 2.91 (2.03 to 4.17)	826 (3)	⊕⊕⊕⊖ Low ^{1,4}
Quality of life	not reported	not reported	--	--	--

*The **assumed risk** (e.g. the median control group risk across studies) was calculated by dividing the number of participants in the control group that experienced an event by the total number of participants in the control group. The **corresponding risk** was calculated by multiplying the assumed risk with the **relative effect** from the meta-analysis. The 95% CI for the corresponding risk was calculated by multiplying the assumed risk with the lower and upper CI of the risk ratio estimate from the meta-analysis.

CI: Confidence interval; **RR:** Risk Ratio

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BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is defined by structural (presence of albuminuria) or functional (persistently reduced kidney function) alterations of the kidney that persists for three or more months. CKD is classified according to estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR), using 'G' to denote the GFR category (G1 to G5, with cut-offs at 90, 60, 30 and 15 mL/min/1.73 m²) and 'A' for the ACR category (A1 to A3, with cut-offs at 3 and 30 mg/mol) (Levey 2011). CKD is usually clinically silent until end-stage kidney disease (ESKD) requiring dialysis or kidney transplantation, although complications including fluid retention, hypertension or anaemia are often identified in earlier CKD stages.

Heart failure (HF) results from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support the circulation of blood. People with HF have symptoms of fatigue and breathlessness and signs of fluid retention such as ankle swelling, elevated jugular venous pressure, and pulmonary crackles. Guidelines (McKelvie 2012; Ponikowski 2016; Yancy 2016) restrict HF definition and management recommendations to stages at which symptoms are apparent.

HF can be classified by symptoms or based on measurement of the left ventricular ejection fraction (EF) as below:

Based on symptoms (Yancy 2016)

- Stage I: no limitation of physical activity; ordinary physical activity does not cause symptoms of HF
- Stage II: slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in symptoms of HF
- Stage III: marked limitation of physical activity; comfortable at rest, but less than ordinary activity causes symptoms of HF
- Stage IV: unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

Based on left ventricular EF (Ponikowski 2016)

- HF with preserved EF ($\geq 50\%$; HFpEF)
- HF with reduced EF ($< 40\%$; HFrEF or systolic HF)
- HF with mid-range EF (40% to 49%; HFmrEF).

According to current guidelines (McKelvie 2012; Ponikowski 2016; Yancy 2016) most studies of pharmacological interventions for HF included people with HFrEF, partly because HFrEF is felt to be more severe and possibly because HFpEF is more difficult to diagnose. Because most people with HFrEF also have diastolic dysfunction, and subtle systolic abnormalities are present in people with HFpEF, the terminology based on left ventricle EF (HFrEF/HFpEF) is preferred over the terminology of preserved or reduced 'systolic function' (Ponikowski 2016).

Based on time course and clinical presentation (Ponikowski 2016)

- Chronic HF identifies HF for some time; unchanged symptoms and signs for at least one month define 'stable HF'
- Acute HF could present as decompensation of chronic stable HF, occurrence of de novo HF (e.g. due to a myocardial infarction (MI)), or progression of HF in a subacute (gradual) fashion (e.g. due to progressive dilated cardiomyopathy)

- Congestive HF is a term sometimes used to describe acute or chronic HF with significant evidence of volume overload.

CKD and HF are highly prevalent in the general population. In population-based studies, the prevalence of HF ranges from 0.2% in those aged 18 to 44 years, to 24% in patients 85 years and older (Hemmelgarn 2012). The prevalence of CKD ranges from 1% to 33% in individuals 18 to 44 years and over age 60, respectively (Hemmelgarn 2012). The two conditions often co-exist and 40% to 60% of patients with HF will have evidence of CKD (Shiba 2011). Furthermore, people with both HF and CKD have a greater risk of cardiovascular morbidity and death than people with HF alone (Santoro 2014). As compared to people with either condition alone, those with both HF and CKD have worse quality of life (QoL), a higher risk of morbidity and death, and often require complex multidisciplinary management (Shiba 2011). Criteria to classify cardio-renal syndromes, according to the direction of the organ damage or whether the clinical manifestations are acute or chronic, have been defined by the Acute Dialysis Quality Initiative consensus group (Ronco 2010).

The prevalence of HF and concomitant CKD is increasing. Additionally, CKD may increase the risk of harms associated with HF medication (e.g. spironolactone (Quach 2016)). Therefore, a better understanding of appropriate pharmacological management of HF in this patient population is particularly important.

Description of the intervention

Several pharmacological interventions are used to treat HF. These include:

1. Direct agents
 - Those that reduce peripheral resistance, heart rate or blood volume (anti-hypertensive agents)
 - Those that increase the strength of the heart contraction (positive inotropes)
2. Indirect agents
 - Those that may improve the heart performance indirectly (lipid lowering agents, antiplatelet agents and nutritional supplements)

Guidelines for the general population (Ponikowski 2016; Yancy 2016) make a distinction between:

1. Interventions that are recommended for HFrEF: angiotensin-converting enzyme inhibitors (ACEi), beta-blockers and mineralocorticoid receptor antagonists
2. Interventions that may be beneficial in HFrEF: diuretics, angiotensin receptor neprilysin inhibitor (a single molecule that combines the moieties of valsartan and sacubitril), sinus node I_f channel inhibitors (ivabradine), angiotensin receptor blockers (ARB), hydralazine and isosorbide dinitrate
3. Interventions with uncertain benefits in HFrEF: digoxin and other digitalis glycosides, and n-3 polyunsaturated fatty acids
4. Interventions with unproven benefits in HFrEF: statins, oral anticoagulants and antiplatelet therapy, renin inhibitors
5. Interventions potentially harmful in HFrEF: calcium-channel blockers.

The same guidelines specify that no treatment has yet been shown, convincingly, to reduce morbidity or death in patients with HFpEF (Ponikowski 2016).

Interventions for acute HF are supported by a lower level of evidence, according to these guidelines (McKelvie 2012; Ponikowski 2016; Yancy 2016). These interventions include diuretics for congestive HF (loop diuretics, thiazides and mineral-corticoid antagonists), vasodilators for hypertensive HF (nitroglycerin, isosorbide dinitrate, nitroprusside, nesiritide), inotropic agents for hypotensive HF (dopamine, dobutamine, levosimendan, milrinone, enoximone), vasopressors for hypotensive HF (norepinephrine, epinephrine), and digoxin, beta-blockers or amiodarone for atrial fibrillation with high ventricular rate.

How the intervention might work

Pharmacological interventions improve the heart performance by reducing how quickly the heart beats, reducing its workload, or by increasing the strength of the cardiac muscle directly or indirectly. In the general population, there is strong evidence to support the use of renin-angiotensin-aldosterone system (RAAS) blockers, beta-blockers and their combination, and moderate levels of evidence for diuretics and inotropes. In the CKD population, these agents are thought to work in the same way. However, most studies of interventions for HF excluded people with CKD because it was felt that these interventions may not have the same benefits in a CKD population, and they may be potentially harmful (Coca 2006; Konstantinidis 2016). For example, RAAS blockers may increase the risk of hyperkalaemia, excessive volume depletion with diuretics may worsen kidney function, and some inotropes may accumulate in CKD and adversely affect cardiac rhythm.

Why it is important to do this review

People with CKD and HF require coordinated care from CKD and HF specialists. Individuals with CKD are at high risk of cardiovascular morbidity and death. A narrative review including 1,076,104 patients found a significantly higher risk of death among HF patients with comorbid CKD, compared to those without baseline CKD (Damman 2014a). They may have the potential for significant benefit more from interventions for HF, but they may also be more vulnerable to the potential harms of these interventions. We do not know if benefits and harms of interventions for HF vary with the severity of CKD. For example, people with more advanced stages of CKD benefit less from interventions for ischaemic heart disease (e.g. statins (Palmer 2012)), and complications from HF dominate as the leading cause of hospitalisation. A systematic review of studies addressing questions about pharmacological interventions for HF in people with CKD is not available. Given the increasing prevalence of HF as eGFR declines, the complex and costly management of people affected by both conditions, and the uncertain benefits and harms of available therapies to treat HF in people who also have CKD, this information is important for patients, healthcare providers and policy makers.

OBJECTIVES

This review aims to look at the benefits and harms of pharmacological interventions for HF (i.e., antihypertensive agents, inotropes, and agents that may improve the heart performance indirectly) in people with HF and CKD.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) evaluating the benefits and harms attributable to any pharmacological interventions for HF in people with CKD.

Types of participants

We included studies in people with HF as defined by the authors. For example, people with HF or people with symptoms of HF in case the term HF or the NYHA classification were not explicitly stated. These included breathlessness, ankle swelling and fatigue that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (Ponikowski 2016). Eligible studies included those in any population age, sex, race, educational status or disease type/severity, and could be conducted in any setting (e.g. community, hospital, nursing home, chronic care institution, or outpatient setting). We included individuals with CKD of any stage (from persistent albuminuria without diminished eGFR to ESKD treated with dialysis or kidney transplantation).

Inclusion criteria

CKD is defined based on the presence of urinary albumin excretion of ≥ 30 mg/mol, or equivalent (marker of kidney damage), or as eGFR < 60 mL/min/1.73 m² (marker of decreased kidney function) for three months or longer regardless of the primary cause of kidney injury. We considered studies that included people with any CKD stage (including stage V treated with dialysis or transplantation); however, we considered definitions used by study authors. HF is a common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with (diastolic dysfunction) or eject blood (systolic dysfunction). Therefore, we considered studies of HF due to left ventricular dysfunction (left-sided HF), with reduced ejection fraction (EF $\leq 40\%$; systolic left-sided HF (HF_{rEF})) or preserved ejection fraction (EF $> 40\%$; diastolic left-sided HF (HF_{pEF} or HF_{mrEF})); or due to right ventricular dysfunction (right-sided HF). We considered studies including people with stable HF or acute HF as described above, similarly, as defined by study authors. We only included studies of at least three months in duration, without publication year or language restriction.

Exclusion criteria

We excluded studies shorter than three months.

Types of interventions

Based on existing recommendations (McKelvie 2012; Ponikowski 2016; Yancy 2016), we considered the following pharmacological intervention for either acute or chronic HF.

Interventions for acute HF

- Diuretics for congestive HF: loop diuretics, thiazides and mineral-corticoid antagonists

- Vasodilators for hypertensive HF: nitroglycerin, isosorbide dinitrate, nitroprusside, nesiritide
- Inotropic agents for hypotensive HF: dopamine, dobutamine, levosimendan, milrinone, enoximone
- Vasopressors for hypotensive HF: norepinephrine, epinephrine
- Digoxin, beta-blockers or amiodarone for atrial fibrillation with high ventricular rate.

Interventions for chronic HF

- The combination of ACEi and beta-blockers with and without mineral-corticoid receptor antagonists
- Diuretics, angiotensin receptor neprilysin inhibitor, sinus node I_f channel inhibitors, ARB, hydralazine and isosorbide dinitrate
- Digoxin and other digitalis glycosides, n-3 polyunsaturated fatty acids, coenzyme Q10, creatine analogues, L-carnitine, thiamine, vitamin D supplementation
- Statins, fibrates, ezetimibe, oral anticoagulants and antiplatelet therapy (cyclooxygenase inhibitors, ADP receptor blockers, PDE inhibitors, PAR-1 antagonists, thromboxane inhibitors, adenosine re-uptake inhibitors, others), renin inhibitors
- Calcium-channel blockers.

For all interventions, we considered any preparation, route of administration, dose, duration, frequency, and combinations.

Given the large number of research questions that this review could potentially address, we focused on the following interventions that are recommended in the non-CKD population.

- Use of ACEi or ARB, and beta-blockers
- Mineralocorticoid receptor antagonists
- Use of diuretics in congestive HF.

The primary focus of this review was to assess whether there is evidence that these treatments for HF are effective and safe in people with concomitant CKD when compared to an active control, placebo or no intervention.

Types of outcome measures

Primary outcomes

- Death (any cause)
- Hospitalisation for decompensated HF

Secondary outcomes

- Cardiovascular death
- Hospitalisation (any cause)
- Worsening HF (reported as a dichotomous outcome by authors)
- Worsening kidney function, including acute kidney injury (reported as a dichotomous outcome by authors)
- Hyperkalaemia
- Hypotension
- Other adverse events due to treatment, worsening of the disease course (syncope/pre-syncope, shortness of breath, and peripheral oedema), and measures of quality of life (QoL) as reported by authors

Search methods for identification of studies

Electronic searches

We searched the [Cochrane Kidney and Transplant Register of Studies](#) up to 12 September 2019 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Hand-searching of kidney-related journals and the proceedings of major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the [Cochrane Kidney and Transplant website](#).

See [Appendix 1](#) for search terms used in strategies for this review.

Searching other resources

We searched the reference lists of review articles, relevant studies and clinical practice guidelines.

Data collection and analysis

Selection of studies

We used the search strategy to identify studies relevant to this review. Two authors screened the titles and abstracts independently and selected studies based on whether they met the patient, intervention, comparator, and design criteria. When necessary, two authors (ML, PR) independently assessed full texts to determine which studies satisfied the full inclusion criteria.

Data extraction and management

Four authors extracted data independently using standard forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of a study existed, reports were grouped together and the publication with the most complete data was used in the analyses.

Assessment of risk of bias in included studies

Four authors independently assessed the following items using the risk of bias assessment tool ([Higgins 2011](#)) (see [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)
- Was knowledge of the allocated interventions adequately prevented during the study (blinding)?
 - Participants and personnel (performance bias)
 - Outcome assessors (detection bias)

- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias (registration, funding, etc.)?

Measures of treatment effect

We used risk ratios (RR) with 95% confidence intervals (CI) to summarize dichotomous outcomes (e.g. death, hospitalisation, kidney failure). Where continuous scales of measurement were reported (e.g. QoL, symptom burden), we assessed the effects of treatment using the mean difference (MD) or the standardised mean difference (SMD) for different scales. We referred to the Cochrane Handbook for Systematic Reviews of Interventions to deal with specific issues (e.g. change scores or time-to-event data) (Higgins 2011). Summary intervention effect measures were estimated in comparisons with at least two studies.

Unit of analysis issues

We referred to the Cochrane Handbook for Systematic Reviews of Interventions to deal with non-standard designs (e.g. as cross-over studies or cluster-randomised studies) (Higgins 2011).

Dealing with missing data

We requested any further information required from the original author by written correspondence (e.g. emailing corresponding authors) and included any relevant information obtained in this manner in the review. We also investigated attrition rates, for example drop-outs, losses to follow-up and withdrawals and critically appraised issues of missing data and imputation methods (for example, last-observation-carried-forward) (Higgins 2011).

Assessment of heterogeneity

In analyses with at least two studies, we assessed heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which described the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). We followed this guide to interpret I^2 values.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depended on both its magnitude and the strength of evidence for heterogeneity (e.g. P-value from the chi-squared test or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

In analyses with at least 10 studies, we planned to use funnel plots to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

We summarized data using random-effects models.

Subgroup analysis and investigation of heterogeneity

In analyses with at least three studies, we investigated potential sources of heterogeneity. We considered participant factors, including demographics (age, sex, race), comorbidity (diabetes, coronary heart disease), type of HF, and stage of CKD. Where possible, we considered agent subclasses (ACEi versus ARB) and dose and duration of therapy, as well as the following pre-specified indicators for subgroup analyses (defining different types of cardiac disease or stages of CKD).

1. The type of HF (right- versus left-sided HF)
2. The nature of the functional impairment of the left ventricle (HFrEF versus HFmrEF or HFpEF)
3. Congestive versus non-congestive acute HF
4. Cardio-renal (acute versus chronic) versus reno-cardiac (acute versus chronic) HF
5. The severity of CKD (defined by levels of urine albumin:creatinine ratio and eGFR; CKD stages 1-5).

Sensitivity analysis

Where possible, we planned to perform sensitivity analyses to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking into account of the risk of bias, as specified
- Repeating the analysis excluding studies of short duration or small studies (using the median as a cut-off)
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). Assumed risk was calculated by dividing the number of participants in the control group that experienced an event by the total number of participants in the control group. Corresponding risk was calculated by multiplying the assumed risk with the risk ratio estimate from the meta-analysis. The 95% CI for the corresponding risk was calculated by multiplying the assumed risk with the lower and upper CI of the risk ratio estimate from the meta-analysis.

We included the following outcomes in the 'Summary of findings' tables.

- Death (any cause)

- Cardiovascular death
- Hospitalisation (any cause)
- Hospitalisation for decompensated HF
- Worsening HF
- Worsening kidney function
- Hyperkalaemia
- Hypotension
- Quality of Life

RESULTS

Description of studies

Results of the search

Our search of the Cochrane Kidney and Transplant specialised register identified 869 records. We identified an additional 78

records using other sources (reference lists of review articles, relevant studies, and clinical practice guidelines) - therefore a total of 947 records (176 studies) were identified. We excluded 61 studies (252 records), either due to a population other than HF (38 studies), a non-pharmacological intervention (5), follow-up shorter than three months (16), or a study design other than a RCT (2) (see [Characteristics of excluded studies](#)).

Overall, 115 studies were eligible. Of these, three are ongoing and awaiting publication of primary data ([PARAGON-HF 2018](#); [RELAX-AHF-2 2017](#); [TMAC 2007](#)) and will be included in a future update of this review. As a result, 112 studies were included in this review ([Figure 1](#)) and are categorised as follows.

Figure 1. Study flow diagram.

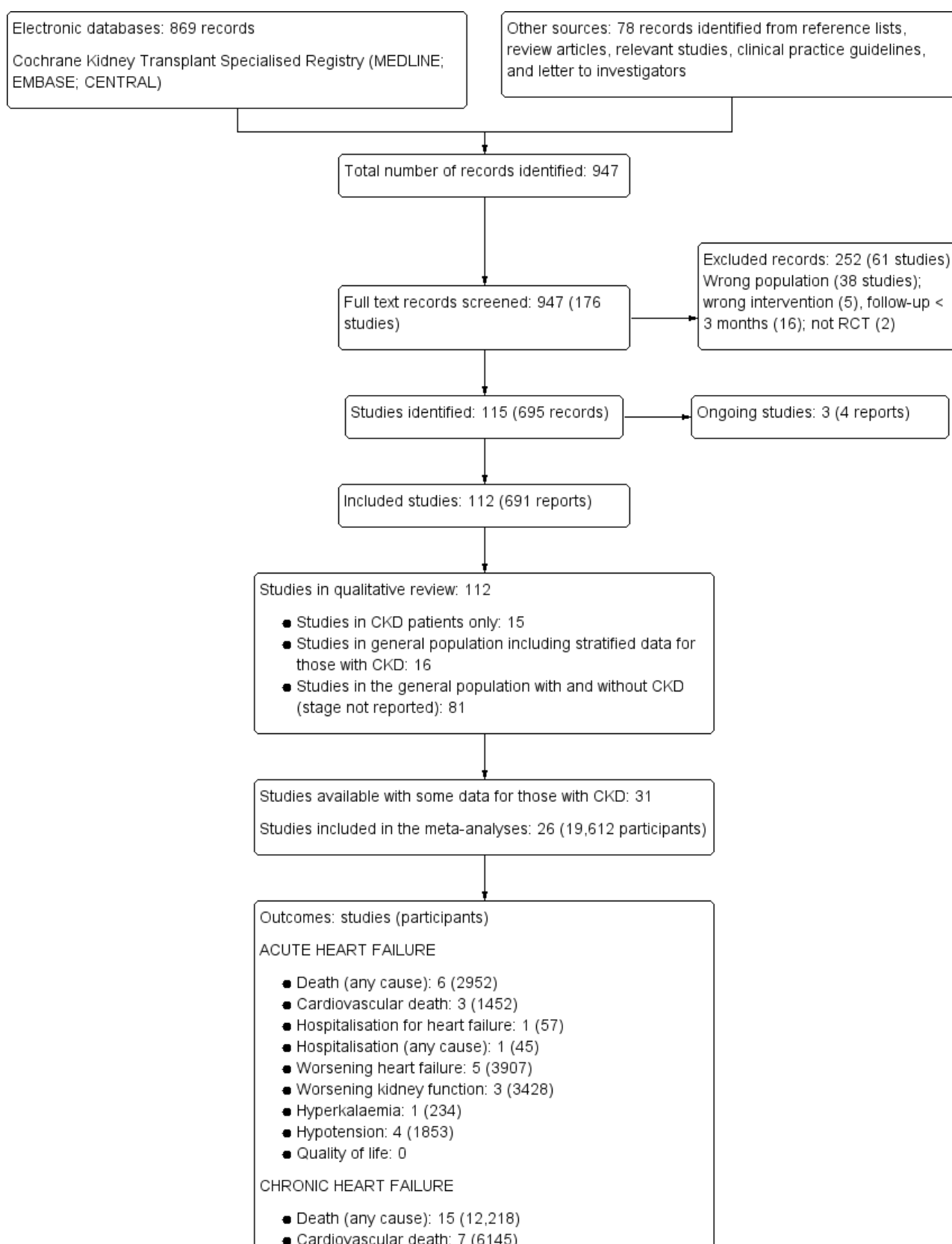


Figure 1. (Continued)

- Death (any cause): 15 (12,218)
- Cardiovascular death: 7 (6145)
- Hospitalisation for heart failure: 7 (5442)
- Hospitalisation (any cause): 2 (1583)
- Worsening heart failure: 2 (745)
- Worsening kidney failure: 5 (2642)
- Hyperkalaemia: 6 (2547)
- Hypotension: 4 (1577)
- Quality of life: 1 (920)

CKD population studies:

- Reported data on CKD patients only (15): [AQUAMARINE 2014](#); [ARIANA-CHF-RD 2016](#); [Cice 1999a](#); [Cice 2001](#); [Cice 2010](#); [FUSION II 2008](#); [Palazzuoli 2014](#); [Pita-Fernandez 2015](#); [Pre-RELAX-AHF 2009](#); [PROTECT 2008](#); [RELAX-AHF 2012](#); [RENO-DEFEND 1 2011](#); [ROSE AHF 2013](#); [Taheri HD 2009](#); [Taheri CAPD 2012](#).

General population studies, including people with CKD:

- Reported data on general population, including both people with and without CKD, and provided stratified data for CKD patients (16): [ALOFT 2008](#); [A-HeFT 2002](#); [CIBIS II 1997](#); [DIAMOND 1999](#); [DIG 1996](#); [EMPHASIS-HF 2010](#); [EVEREST 2005](#); [HEAAL 2008](#); [MERIT-HF 1997](#); [PROMISE 1989](#); [RALES 1995](#); [SAVE 1991](#); [SENIORS 2002](#); [SHIFT 2010](#); [SOLVD \(Treatment\) 1992](#); [Val-HeFT 1999](#)

General population studies, potentially including people with CKD:

- Reported data on general population, including both people with and without CKD, but did not provide stratified data for CKD patients (81): [ABC-HFT 2011](#); [ACTIV in CHF 2003](#); [AIRE 1991](#); [ALIVE 1998](#); [ANZ 1995](#); [ARTS-HF 2015](#); [ASCEND-HF 2009](#); [ASTRONAUT 2011](#); [ATLAS 1999](#); [ATMOSPHERE 2011](#); [Barr 1995](#); [Barr 1997](#); [BEAUTIFUL 2006](#); [Berry 2007](#); [BEST 1995](#); [BETACAR 1999](#); [BLAST-AHF 2015](#); [CAPRICORN 2001](#); [CARMEN 2001](#); [CASINO 2004](#); [CHARM-Added 2003](#); [CHARM-Alternative 2003](#); [CHARM-Preserved 2003](#); [CIBIS I 1994](#); [CIBIS III 2006](#); [COMET 2003](#); [CONSENSUS 1987](#); [COPERNICUS 2001](#); [CORONA 2005](#); [DAD-HF II 2014](#); [de Graeff 1989](#); [ELITE 1995](#); [ELITE II 2000](#); [Erb 2014](#); [EXACT-HF 2013](#); [Fuchs 1995](#); [FUSION I 2004](#); [Giles 1989](#); [GISSI-HF 2004](#); [HORIZON-HF 2008](#); [I-PRESERVE 2008](#); [Jia 2015](#); [Kum 2008](#); [MDC 1993](#); [MMHFT 1992](#); [MOXCON 2003](#); [NAPA 2007](#); [OPTIMAAL 2002](#); [Ozdemir 2007](#); [Pacher 1996](#); [Packer 1986](#); [PARADIGM-HF 2013](#); [PEP-CHF 1999](#); [PRAISE-II 2003](#); [PRIME-II 1997](#); [PROFILE 2002](#); [REACH UP 2010](#); [Risler 1991](#); [SADKO-CHF 2005](#); [Skvortsov 2007](#); [SOLVD \(Prevention\) 1992](#); [SPICE 2000](#); [Statsenko 2007](#); [SWORD 1995](#); [Toblli 2007](#); [TOPCAT 2014](#); [TRACE 1994](#); [ULTIMATE-HFrEF 2013](#); [US-Carvedilol 1996](#); [VALIANT 2000](#); [van den Broek 1995](#); [VERITAS 1 2005](#); [VERITAS 2 2005](#); [V-HEFT I 1986](#); [V-HEFT II 1991](#); [V-HEFT III 1996](#); [Vizzardi 2014](#); [Xamoterol in SHF 1990](#); [Yamada 2013](#); [Yang 2015a](#); [Zhao 2010](#).

Detailed information on the design, participants, intervention, comparator and outcomes of these included studies are summarised in [Characteristics of included studies](#).

Included studies

In total, 31 studies reported data for CKD patients and the characteristics of these 31 studies are reported here. Full details for all studies are summarised in the [Characteristics of included studies](#) table.

Study size, country and year

A total of 23,762 adult CKD participants were randomised; six studies (3892) were in the setting of acute HF and 25 (19,870) were in the setting of chronic HF. The number of CKD participants per group was not provided in two studies ([A-HeFT 2002](#); [DIG 1996](#)). Sample sizes ranged from 16 to 3157 participants and the reported follow-up ranged from 12 weeks to five years.

Ten of 31 studies (32%) were conducted in single-country settings. Three (10%) in Canada or the USA only, and 16 (52%) were in at least three countries. Two studies (6%) did not report this information. Study initiation ranged from 1986 to 2015.

Participants' mean age was reported in 24 (77%) of the 31 studies. The proportion of men ranged between 64.9% and 82.1% and the proportion of people with diabetes ranged between 14.5% and 62.5%. Demographic data for CKD participants (age, sex, diabetes status) were not reported in seven studies ([A-HeFT 2002](#); [ALOFT 2008](#); [DIAMOND 1999](#); [EMPHASIS-HF 2010](#); [EVEREST 2005](#); [HEAAL 2008](#); [PROMISE 1989](#)).

Studies in acute HF (6) included patients who had been admitted for acute decompensated HF ([Palazzuoli 2014](#); [Pre-RELAX-AHF 2009](#); [PROTECT 2008](#); [RELAX-AHF 2012](#); [RENO-DEFEND 1 2011](#); [ROSE AHF 2013](#)). Studies in chronic HF (25) included patients with HFrEF ([A-HeFT 2002](#); [ARIANA-CHF-RD 2016](#); [CIBIS II 1997](#); [Cice 2001](#); [Cice 2010](#); [DIAMOND 1999](#); [DIG 1996](#); [EMPHASIS-HF 2010](#); [EVEREST 2005](#); [FUSION II 2008](#); [HEAAL 2008](#); [MERIT-HF 1997](#); [PROMISE 1989](#); [RALES 1995](#); [SAVE 1991](#); [SENIORS 2002](#); [SHIFT 2010](#); [SOLVD \(Treatment\) 1992](#); [Taheri CAPD 2012](#); [Taheri HD 2009](#); [Val-HeFT 1999](#)), HFpEF ([Cice 1999a](#)), or with no prespecified ejection fraction criteria for inclusion ([ALOFT 2008](#); [AQUAMARINE 2014](#); [Pita-Fernandez 2015](#)).

Interventions

Studies in acute HF evaluated adenosine A1-receptor antagonists ([PROTECT 2008](#); [RENO-DEFEND 1 2011](#)), diuretics ([Palazzuoli 2014](#)), dopamine and nesiritide ([ROSE AHF 2013](#)), and serelaxin ([Pre-RELAX-AHF 2009](#); [RELAX-AHF 2012](#)).

In chronic settings, studies evaluated ARB ([Cice 2010](#); [HEAAL 2008](#); [Pita-Fernandez 2015](#); [Val-HeFT 1999](#)), beta-blockers ([CIBIS II 1997](#); [Cice 2001](#); [MERIT-HF 1997](#); [SENIORS 2002](#)), ACEi ([Cice 2010](#); [SAVE 1991](#); [SOLVD \(Treatment\) 1992](#)), aldosterone antagonists

(EMPHASIS-HF 2010; RALES 1995; Taheri CAPD 2012; Taheri HD 2009), nesiritide (FUSION II 2008), calcium-channel blockers (Cice 1999a), renin inhibitors (ALOFT 2008; ARIANA-CHF-RD 2016), vasopressin receptor antagonists (AQUAMARINE 2014; EVEREST 2005), anti-arrhythmics (DIAMOND 1999), digitalis glycoside (DIG 1996), phosphodiesterase inhibitors (PROMISE 1989), sinus node inhibitors (SHIFT 2010), and vasodilators (A-HeFT 2002).

Of the 31 studies, 28 studies (90%) including a total of 22,893 CKD patients, the intervention was compared with placebo or standard care. Of the remaining studies, two compared different doses of the same drug (HEAAL 2008; Pita-Fernandez 2015) and one compared different IV infusion strategies (continuous versus bolus) of furosemide (Palazzuoli 2014).

Outcomes

Study outcomes included death, hospitalisation, worsening HF, progression of kidney disease, quality of life, and adverse events such as hyperkalaemia and hypotension. Of the 31 studies, nine reported data in a form that could not be extracted for meta-analysis. We contacted the authors of these nine studies and two (22%) were able to provide data (AQUAMARINE 2014; SHIFT 2010). One study investigating calcium-channel blockers (Cice 1999a) did not report any outcomes of interest and was also not included in the meta-analysis. At this time, we do not have extractable data for any outcomes for four studies (A-HeFT 2002; DIG 1996; EMPHASIS-HF 2010; HEAAL 2008) and did not include these studies in our meta-analyses. Of the 81 studies in the general population, 39 had valid author contact information and the authors were emailed to request data on the subset of patients with CKD. No authors have responded to this request, to date.

Combining all intervention types:

- 29 (94%) studies reported on death (any cause), of which 21 provided extractable data and were meta-analysed
- 25 (81%) on hospitalisations for HF, of which eight provided extractable data and were meta-analysed
- 18 (58%) on cardiovascular death, of which ten provided extractable data and were meta-analysed
- 10 (32%) on all-cause hospitalisation, of which three provided extractable data and were meta-analysed
- 11 (35%) reported a dichotomous measure of worsening HF, of which seven were extractable and meta-analysed

- 17 (55%) reported a dichotomous measure of progression of kidney disease, of which eight were extractable and meta-analysed
- 10 (31%) reported a dichotomous measure of hyperkalaemia, of which seven were extractable and meta-analysed
- 15 (48%) reported a dichotomous measure of hypotension, of which eight were extractable and meta-analysed
- 3 (10%) reported a quality of life score, of which one was extractable and analysed

Other secondary outcomes (e.g. dyspnoea, oedema) in CKD populations were not extractable and excluded from analysis.

In summary, 26 studies (19,612 participants) reported disaggregated and extractable data on at least one outcome of interest for our review and were included in our meta-analyses (ALOFT 2008; AQUAMARINE 2014; ARIANA-CHF-RD 2016; CIBIS II 1997; Cice 2001; Cice 2010; DIAMOND 1999; EVEREST 2005; FUSION II 2008; MERIT-HF 1997; Palazzuoli 2014; Pita-Fernandez 2015; Pre-RELAX-AHF 2009; PROMISE 1989; PROTECT 2008; RALES 1995; RELAX-AHF 2012; RENO-DEFEND 1 2011; ROSE AHF 2013; SAVE 1991; SENIORS 2002; SHIFT 2010; SOLVD (Treatment) 1992; Taheri HD 2009; Taheri CAPD 2012; Val-HeFT 1999). Studies were either exclusively in patients with HF and CKD (14) or in the general HF population, but included patients with CKD and stratified results based on kidney function at baseline (12).

Excluded studies

Reasons for exclusion are summarised in the [Characteristics of excluded studies](#) table. In 38 studies, the populations studied had conditions other than HF, five evaluated a non-pharmacological intervention, and 16 measured short-term outcomes (less than three months follow-up)

Risk of bias in included studies

Risk of bias for all 112 included studies is summarised in [Figure 2](#) and [Figure 3](#). In general, the risk of bias was unclear in most studies for many domains. Fifty-four studies (48%) were published after 2005, the year when trial registration became mandatory. Of these, 37 had evidence of registration within a trial registry and 33 reported information on authorship and/or involvement of the study sponsor in data collection, analysis, and interpretation.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ABC-HFT 2011	?	?	-	?	+	+	+
ACTIV in CHF 2003	+	?	+	+	+	+	-
A-HeFT 2002	?	+	+	?	+	+	-
AIRE 1991	+	+	+	+	+	+	?
ALIVE 1998	?	?	+	?	-	+	?
ALOFT 2008	+	+	+	?	-	+	-
ANZ 1995	?	?	+	+	+	+	-
AQUAMARINE 2014	+	?	+	?	+	+	?
ARIANA-CHF-RD 2016	+	?	+	?	+	+	+
ARTS-HF 2015	+	?	+	?	+	+	-
ASCEND-HF 2009	?	?	+	?	+	+	-
ASTRONAUT 2011	?	?	+	+	-	+	-
ATLAS 1999	?	?	+	+	?	+	?
ATMOSPHERE 2011	+	?	+	+	+	+	-
Barr 1995	?	?	+	+	+	+	?
Barr 1997	?	?	+	?	+	+	?
BEAUTIFUL 2006	+	+	+	+	+	+	-
Berry 2007	?	+	+	?	?	?	?
BEST 1995	+	+	+	+	+	+	+
BETACAR 1999	?	?	+	?	-	+	-

Figure 2. (Continued)

BETACAR 1999	?	?	+	?	-	+	-
BLAST-AHF 2015	+	?	+	?	+	+	-
CAPRICORN 2001	+	+	+	?	-	+	?
CARMEN 2001	?	?	+	+	+	+	?
CASINO 2004	?	?	+	?	?	?	?
CHARM-Added 2003	?	?	+	?	+	+	-
CHARM-Alternative 2003	?	?	+	?	+	+	-
CHARM-Preserved 2003	?	?	+	?	+	+	-
CIBIS I 1994	+	?	+	+	+	+	+
CIBIS II 1997	+	+	+	+	-	+	-
CIBIS III 2006	+	+	-	+	-	+	-
Cice 1999a	?	?	+	?	?	-	?
Cice 2001	?	?	+	?	+	+	?
Cice 2010	+	+	+	+	-	+	+
COMET 2003	?	+	+	+	+	+	-
CONSENSUS 1987	+	?	+	+	+	+	-
COPERNICUS 2001	?	?	+	?	+	+	+
CORONA 2005	+	?	-	?	+	+	-
DAD-HF II 2014	+	?	-	-	?	+	+
de Graeff 1989	?	?	-	?	+	?	?
DIAMOND 1999	?	?	+	+	+	+	?
DIG 1996	?	+	+	+	-	+	?
ELITE 1995	?	?	+	+	+	+	-
ELITE II 2000	?	?	+	+	+	+	+
EMPHASIS-HF 2010	+	+	+	+	+	+	?
Erb 2014	+	?	+	?	-	+	+
EVEREST 2005	+	+	+	+	+	+	-
EXACT-HF 2013	?	?	+	?	+	+	?
Fuchs 1995	?	?	+	?	-	+	?
FUSION I 2004	?	?	-	?	+	+	?
FUSION II 2008	+	?	+	+	+	-	?

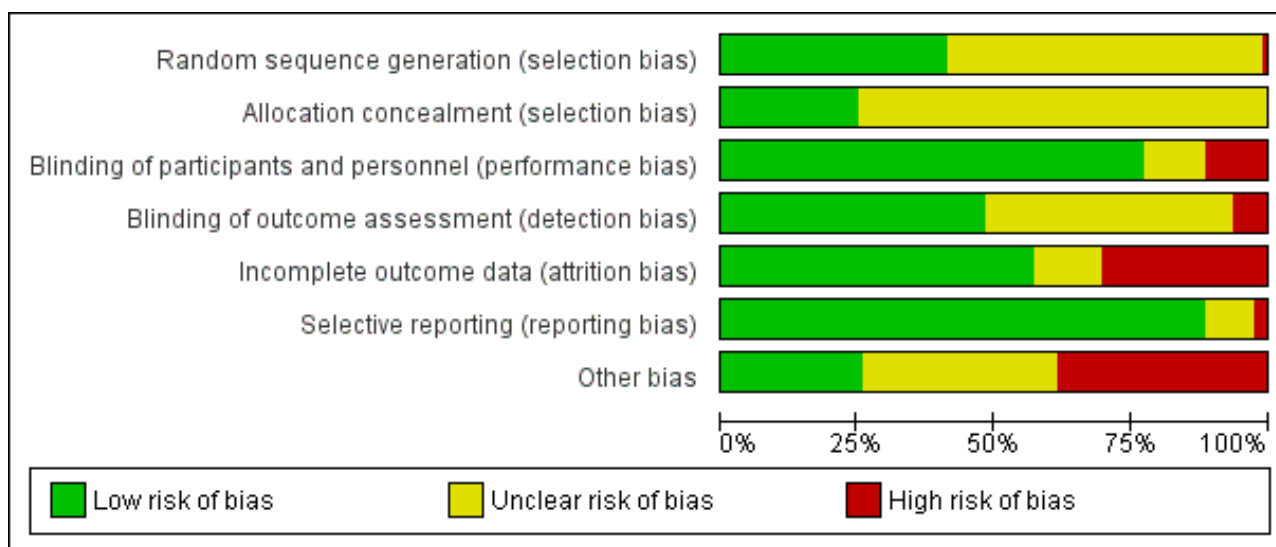
Figure 2. (Continued)

FUSION II 2008	+	?	+	+	+	-	?
Giles 1989	?	?	+	?	+	+	?
GISSI-HF 2004	+	?	+	?	+	+	+
HEAAL 2008	+	+	+	+	-	+	-
HORIZON-HF 2008	?	?	+	?	+	+	?
I-PRESERVE 2008	?	?	?	+	-	+	+
Jia 2015	+	?	-	+	+	+	+
Kum 2008	+	?	-	+	+	+	?
MDC 1993	+	?	?	+	-	+	+
MERIT-HF 1997	+	+	+	+	?	+	?
MMHFT 1992	?	?	+	+	?	+	+
MOXCON 2003	?	?	+	?	+	-	?
NAPA 2007	?	?	+	?	-	+	-
OPTIMAAL 2002	+	+	+	+	+	+	+
Ozdemir 2007	?	?	-	-	-	+	?
Pacher 1996	-	?	+	-	-	+	-
Packer 1986	+	?	-	-	+	+	+
Palazzuoli 2014	+	?	-	-	-	+	+
PARADIGM-HF 2013	+	?	+	+	+	+	-
PEP-CHF 1999	+	+	+	-	+	+	-
Pita-Fernandez 2015	+	?	-	+	+	+	+
PRAISE-II 2003	?	?	+	?	-	?	?
Pre-RELAX-AHF 2009	+	+	+	+	?	+	-
PRIME-II 1997	+	+	?	+	+	+	-
PROFILE 2002	?	?	+	?	-	?	?
PROMISE 1989	?	?	+	+	+	+	?
PROTECT 2008	+	+	+	+	+	+	-
RALES 1995	?	?	+	+	+	+	?
REACH UP 2010	+	?	+	+	+	+	-
RELAX-AHF 2012	+	+	+	+	+	+	-
RENO-DEFEND 1 2011	?	?	+	?	-	+	-

Figure 2. (Continued)

RENO-DEFEND 1 2011	?	?	+	?	-	+	-
Risler 1991	?	?	?	?	?	+	?
ROSE AHF 2013	?	?	+	?	+	+	+
SADKO-CHF 2005	?	?	?	?	?	+	+
SAVE 1991	+	?	+	+	+	+	+
SENIORS 2002	?	+	?	+	-	+	-
SHIFT 2010	+	+	+	+	-	+	-
Skvortsov 2007	?	?	?	?	-	+	?
SOLVD (Prevention) 1992	?	?	+	?	?	+	+
SOLVD (Treatment) 1992	+	+	+	+	+	+	+
SPICE 2000	?	?	+	?	+	+	-
Statsenko 2007	?	?	?	?	+	+	?
SWORD 1995	?	?	+	-	-	+	-
Taheri CAPD 2012	?	?	+	?	-	?	?
Taheri HD 2009	?	?	+	?	-	?	?
Toblli 2007	?	?	+	+	+	+	+
TOPCAT 2014	?	?	+	+	+	+	+
TRACE 1994	+	?	?	+	+	+	-
ULTIMATE-HFrEF 2013	+	?	?	+	-	+	+
US-Carvedilol 1996	?	?	+	+	+	+	-
Val-HeFT 1999	?	?	+	+	-	?	-
VALIANT 2000	+	?	+	+	+	+	-
van den Broek 1995	?	?	+	?	-	+	?
VERITAS 1 2005	?	?	+	?	-	+	-
VERITAS 2 2005	?	?	+	?	-	+	-
V-HEFT I 1986	?	+	?	?	+	+	?
V-HEFT II 1991	?	+	+	+	+	+	?
V-HEFT III 1996	?	+	+	?	?	+	+
Vizzard 2014	?	?	-	+	+	+	+
Xamoterol in SHF 1990	?	?	+	?	-	?	-
Yamada 2013	?	?	?	?	?	?	?
Yang 2015a	?	?	+	+	?	+	+
Zhan 2010	+	?	?	?	-	+	?

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Risk of bias was deemed low for 46 studies, high for one study, and unclear for 65 studies.

Allocation concealment

Risk of bias was deemed low for 28 studies and unclear for the remaining 84 studies.

Blinding

Participants and personnel (performance bias)

Eighty-six studies were judged to be at low risk of bias, 13 did not blind participants or study personnel, and 13 were judged unclear.

Blinding of outcome assessment (detection bias)

Fifty-four studies were judged to be at low risk of bias, either because outcome assessors were blinded or because the outcome measured was unlikely to be influenced by a lack of blinding. Seven studies were judged to be at high risk of bias, and the remaining 51 were judged to be at unclear risk of bias.

Incomplete outcome data

Seventy-four studies were at low risk of attrition bias as < 10% of patients were lost to follow-up and analysis followed an intention-to-treat design. Thirty-four studies were at high risk of attrition bias and 14 studies were judged to be at unclear risk of bias.

Selective reporting

Ninety-nine studies were at low risk of bias, either because a protocol was published or because it was clear that the published report included all expected outcomes. Three studies were at high risk of bias and 10 were judged to be at unclear risk of bias.

Other potential sources of bias

Twenty-nine studies appeared to be free of other sources of bias. Forty-three studies were at high risk of bias, as the study sponsor was involved in the design, data acquisition and/or analysis, or preparation of the manuscript. The remaining 40 studies were deemed to be at unclear risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison ACUTE: Serelaxin versus placebo in patients with heart failure and chronic kidney disease](#); [Summary of findings 2 CHRONIC: ACEi or ARB versus placebo in patients with heart failure and chronic kidney disease](#); [Summary of findings 3 CHRONIC: Beta-blockers versus placebo in patients with heart failure and chronic kidney disease](#); [Summary of findings 4 CHRONIC: Aldosterone antagonists versus placebo in patients with heart failure and chronic kidney disease](#)

Effects in an acute heart failure setting

(See [Summary of findings for the main comparison](#) and [Table 1](#)).

Diuretic bolus versus continuous infusion

[Palazzuoli 2014](#) compared a bolus diuretic versus infusion. Evidence was very uncertain on whether administering furosemide as a bolus compared to a continuous infusion has any impact on cardiovascular death ([Analysis 1.1](#)) or hospitalisation for HF ([Analysis 1.2](#)).

Serelaxin versus placebo

Two studies ([Pre-RELAX-AHF 2009](#); [RELAX-AHF 2012](#)) compared serelaxin to placebo. Treatment with serelaxin had uncertain effects on the risk of death (any cause) ([Analysis 2.1](#) (2 studies, 1395 participants): RR 0.59, 95% CI 0.34 to 1.02; $I^2 = 0\%$; low certainty evidence). Similarly, treatment with serelaxin had uncertain effects on the risk of cardiovascular death ([Analysis 2.2](#) (2 studies, 1395 participants): RR 0.47, 95% CI 0.21 to 1.08;

$I^2 = 55\%$; low certainty evidence). Treatment with serelaxin may reduce the risk of worsening HF in acute chronic HF ([Analysis 2.3](#) (2 studies, 1395 participants): RR 0.71, 95% CI 0.54 to 0.92; $I^2 = 0\%$; low certainty evidence). Treatment with serelaxin had uncertain effects on worsening kidney function ([Analysis 2.4](#) (2 studies, 1395 participants): RR 0.86, 95% CI 0.37 to 1.98; $I^2 = 58\%$; low certainty evidence). It is uncertain whether treatment with serelaxin increases the risk of hyperkalaemia ([Analysis 2.5](#) (1 study, 234 participants): RR 1.08, 95% CI 0.30 to 3.87; very low certainty evidence) or hypotension in acute settings ([Analysis 2.6](#) (2 studies, 1395 participants): RR 1.26, 95% CI 0.81 to 1.96; $I^2 = 0\%$; low certainty evidence).

Adenosine A1-receptor antagonists versus placebo

Two studies ([PROTECT 2008](#); [RENO-DEFEND 1 2011](#)) compared adenosine A1 receptor antagonists to placebo. Treatment with adenosine A1-receptor antagonists had uncertain effects on the risk of death (any cause) ([Analysis 3.1](#) (2 studies, 2078 participants): RR 0.71, 95% CI 0.39 to 1.26; $I^2 = 0\%$; low certainty evidence).

Evidence was very uncertain on whether adenosine A1 receptor antagonists have any impact on hospitalisation (any cause) ([Analysis 3.2](#)), worsening HF ([Analysis 3.3](#)), or worsening kidney function ([Analysis 3.4](#)) as only single studies reported these three outcomes.

Dopamine versus placebo

[ROSE AHF 2013](#) compared dopamine to placebo. Evidence was very uncertain on whether dopamine has any impact on death (any cause) ([Analysis 4.1](#)), worsening HF ([Analysis 4.2](#)), or hypotension ([Analysis 4.3](#)).

Nesiritide versus placebo

[ROSE AHF 2013](#) compared nesiritide to placebo. Evidence was very uncertain on whether nesiritide has any impact on death (any cause) ([Analysis 5.1](#)), worsening HF ([Analysis 5.2](#)), or hypotension ([Analysis 5.3](#)).

Effects in a chronic heart failure setting

(See [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); and [Table 1](#)).

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers versus placebo

Four studies ([Cice 2010](#); [SAVE 1991](#); [SOLVD \(Treatment\) 1992](#); [Val-HeFT 1999](#)) compared ACEi or ARB with placebo. Treatment with ACEi or ARB had uncertain effects on death (any cause) ([Analysis 6.1](#) (4 studies, 4003 participants): RR 0.85, 95% CI 0.70 to 1.02; $I^2 = 78\%$; low certainty evidence). In subgroup analysis, there was no evidence that ACEi or ARB had different effects (P for subgroup interaction = 0.91). Treatment with either ACEi or ARB may decrease the risk of cardiovascular death compared to placebo or no treatment ([Analysis 6.2](#) (2 studies, 1368 participants): RR 0.81, 95% CI 0.64 to 1.01; $I^2 = 51\%$; low certainty evidence). Treatment with either ACEi or ARB had uncertain effects on hospitalisation for HF ([Analysis 6.3](#) (2 studies, 1368 participants): RR 0.90, 95% CI 0.43 to 1.90; $I^2 = 97\%$; very low certainty evidence).

Angiotensin receptor blockers (ARB): 50% reduction versus full dose

It was not possible to ascertain the effect of different doses on death (any cause) as only [Pita-Fernandez 2015](#) was designed to examine drug dosing ([Analysis 7.1](#)).

Beta-blockers versus placebo

Four studies ([CIBIS II 1997](#); [Cice 2001](#); [MERIT-HF 1997](#); [SENIORS 2002](#)) compared beta-blockers with placebo. Treatment with beta-blockers may reduce the risk of death (any cause) ([Analysis 8.1](#) (4 studies, 3136 participants): RR 0.69, 95% CI 0.60 to 0.79; $I^2 = 0\%$; moderate certainty evidence) compared with placebo. Treatment with beta-blockers may decrease cardiovascular death ([Analysis 8.2](#) (3 studies, 2287 participants): RR 0.53, 95% CI 0.35 to 0.81; $I^2 = 61\%$; low certainty evidence) or hospitalisation (any cause) ([Analysis 8.3](#) (2 studies, 1583 participants): RR 0.75, 95% CI 0.52 to 1.08; $I^2 = 67\%$; low certainty evidence). Treatment with beta-blockers may decrease hospitalisation for HF ([Analysis 8.4](#) (3 studies, 2287 participants): RR 0.67, 95% CI 0.43 to 1.05; $I^2 = 87\%$; low certainty evidence). Potential causes of high heterogeneity include differences in study year, sample size, location, or use of contaminant ACEi.

Evidence was very uncertain on whether beta-blockers have any impact on worsening HF ([Analysis 8.5](#)), worsening kidney function ([Analysis 8.6](#)), or hypotension ([Analysis 8.7](#)) as only [SENIORS 2002](#) reported these three outcomes.

Aldosterone antagonists versus placebo

Three studies ([RALES 1995](#); [Taheri CAPD 2012](#); [Taheri HD 2009](#)) compared aldosterone antagonists to placebo. Aldosterone antagonists had uncertain effects on death (any cause) compared with placebo ([Analysis 9.1](#) (2 studies, 34 participants): RR 0.61, 95% CI 0.06 to 6.59; $I^2 = 57\%$; very low certainty evidence). Aldosterone antagonists may increase the risk of hyperkalaemia in people with HF and CKD ([Analysis 9.2](#) (3 studies, 826 participants): RR 2.91, 95% CI 2.03 to 4.17; $I^2 = 0\%$; low certainty evidence).

Anti-arrhythmics versus placebo

[DIAMOND 1999](#) compared anti-arrhythmics to placebo. Evidence was very uncertain on whether anti-arrhythmics have any impact on death (any cause) ([Analysis 10.1](#)).

Nesiritide versus placebo

One study [FUSION II 2008](#) compared nesiritide to placebo in a chronic setting. Evidence was very uncertain on whether nesiritide has any impact on death (any cause) ([Analysis 11.1](#)), cardiovascular death ([Analysis 11.2](#)), or quality of life ([Analysis 11.4](#)). There were 196/605 patients with at least one episode of hypotension in the nesiritide group and 55/306 in the placebo group ([Analysis 11.3](#)).

Phosphodiesterase inhibitors versus placebo

[PROMISE 1989](#) compared phosphodiesterase inhibitors to placebo. Evidence was very uncertain on whether phosphodiesterase inhibitors have any impact on death (any cause) ([Analysis 12.1](#)).

Renin inhibitors versus placebo

Two studies ([ALOFT 2008](#); [ARIANA-CHF-RD 2016](#)) compared renin inhibitors to placebo. Evidence was very uncertain on whether

renin inhibitors have any impact on worsening HF (Analysis 13.1) as only ARIANA-CHF-RD 2016 reported this outcome. Treatment with renin inhibitors had uncertain effects on worsening kidney function (Analysis 13.2 (2 studies, 142 participants): RR 1.52, 95% CI 0.22 to 10.33; $I^2 = 36\%$; very low certainty evidence). The risk of hyperkalaemia was uncertain with renin inhibitors (Analysis 13.3 (2 studies, 142 participants): RR 0.86, 95% CI 0.49 to 1.49; $I^2 = 0\%$; very low certainty evidence). The risk of hypotension was uncertain with renin inhibitors (Analysis 13.4 (2 studies, 142 participants): RR 1.44, 95% CI 0.62 to 3.31; $I^2 = 0\%$; very low certainty evidence).

Sinus node inhibitors versus placebo

One study (SHIFT 2010) compared sinus node inhibitors to placebo. Evidence was very uncertain on whether sinus node inhibitors have any impact on cardiovascular death (Analysis 14.1), hospitalisation for HF (Analysis 14.2), or worsening kidney function (Analysis 14.3). There were 14/780 patients with at least one episode of hyperkalaemia in the sinus node inhibitor group and 27/799 in the placebo group (Analysis 14.4).

Vasopressin receptor antagonists versus placebo

Two studies (AQUAMARINE 2014; EVEREST 2005) compared vasopressin receptor antagonists to placebo. Vasopressin receptor antagonists had uncertain effects on death (any cause) (Analysis 15.1 (2 studies, 1840 participants): RR 1.26, 95% CI 0.55 to 2.89; $I^2 = 41\%$; low certainty evidence). Evidence was very uncertain on whether vasopressin receptor antagonists have any impact on HF hospitalisations (Analysis 15.2) or worsening kidney function (Analysis 15.3), as only AQUAMARINE 2014 reported these two outcomes.

DISCUSSION

Summary of main results

In this systematic review of HF therapies in people with CKD, we identified 112 studies: 15 studies reported data on CKD patients only; 16 studies included both people with and without CKD, and provided stratified data for CKD patients; and 81 studies included people with and without CKD, however data for those with CKD was not available. Twenty-six studies with disaggregated and extractable data in people with CKD were included in our meta-analyses. In acute settings, six studies investigated dopamine, nesiritide, furosemide (dose reduction), serelaxin, and adenosine A1 receptor antagonists. Based on the level of evidence available, it is uncertain whether these therapies make any difference to death, hospitalisations, or adverse effects including worsening kidney function, hyperkalaemia, or hypotension. In chronic settings, 18 studies investigated ACEi, ARB, aldosterone antagonists, anti-arrhythmic, beta-blockers, digoxin, phosphodiesterase inhibitors, renin inhibitors, sinus node inhibitors, vasodilators, and vasopressin receptor antagonists. It is uncertain whether these interventions make any difference to death, hospitalisations, or harms, as the number of studies available was low. Due to few data observations, studies with zero events in both arms, and situations where only single studies were available for clinical outcomes, meta-analysis was not possible for most of the review outcomes, particularly for harms.

Considering that CKD is a significant independent predictor of worse outcome in acute or chronic HF (Grande 2017; Smith 2006), knowledge about benefits and harms of recommended

interventions for HF in this patient population is important. Insufficient evidence is available to inform decision-making.

Overall completeness and applicability of evidence

Of the 112 included studies, quantitative data on CKD patients could be extracted in only 23% of studies. In total, 26 studies were eligible for meta-analysis. Due to the diversity of drug classes and outcomes available, few summary estimates of the effects were possible. Meta-analysis in acute settings was not performed. Meta-analysis for death (any cause) was only possible for ACEi/ARB, anti-aldosterone, beta-blockers, and vasopressin receptor antagonists. Meta-analysis for cardiovascular death was only possible for ACEi/ARBs and beta-blockers. Re-hospitalisation for HF was meta-analysed only for ACEi/ARB and beta-blockers. Analyses for harms were only possible for renin inhibitors (worsening kidney function and hyperkalaemia) and aldosterone antagonists (hyperkalaemia). Overall, the certainty of the evidence across most interventions and outcomes was very low due to the limited number of studies. Treatment with beta-blockers may reduce risk of all-cause or cardiovascular death; however, the certainty was moderate and low, respectively. Furthermore, due to the few number of studies in each meta-analysis, sub-group analyses by type of HF (systolic or diastolic) or level of kidney failure were not possible.

Quality of the evidence

Of the 112 studies, the risks of bias were generally high, or unclear. The risk of selection bias was unclear in the majority of studies due to unclear randomisation methods or allocation concealment. Over three-quarters of studies blinded participants and nearly half blinded outcome assessors. The majority reported on outcomes as per a pre-specified protocol. Over 70% of studies followed an intention-to-treat approach. Nearly one-third were at high risk of attrition bias. In most studies, the study sponsor was involved in the study or their role was unclear.

Potential biases in the review process

Although based on a peer-reviewed protocol and conducted using methods developed by Cochrane, our review has limitations mostly related to lack of data availability. Data for CKD populations that could be extracted for meta-analysis were only available in 23% of studies. Considering that our review was broad in scope and included a variety of pharmacological interventions and outcomes, availability of more data on interventions and outcome would be key to obtaining summary measures of effect. Of the studies in the CKD population (or subgroup analyses), the definition of CKD varied and ranged from having eGFR < 60 mL/min/1.73 m² to being on dialysis. Many of the studies did not specify the stage of CKD among patients with an eGFR < 60 mL/min/1.73 m², which may be problematic as the effect or safety of these interventions likely differs based on early versus advanced CKD. Further, many of these studies defined CKD by a baseline eGFR, which may not represent a true CKD diagnosis if not confirmed with a second measure three months apart. Generalisation of findings to people with HF and CKD requires additional data, some of which could be made available from studies already completed.

Agreements and disagreements with other studies or reviews

Our review only identified six studies that assessed interventions for acute HF with a follow-up of at least three months: investigating

dopamine or nesiritide (1 study), serelaxin (2), adenosine A1 receptor antagonists (2) and diuretics (1). We were unable to estimate risk of any outcome for studies investigating diuretics, nesiritide, or dopamine in an acute setting. No significant reduction in risk of death (any cause) was found for adenosine A1 receptor antagonists; however, the certainty of the evidence was low. No other analyses could be performed for this intervention due to limited data. Serelaxin did not significantly reduce risk of all-cause or cardiovascular death nor increase the risk of worsening kidney function or hypotension. There appeared to be a decrease in risk of worsening HF; however, the certainty of evidence for all analyses in this intervention group was very low. Previous research has suggested that kidney impairment may affect the response to interventions for acute decompensated HF, such as tolvaptan (Ikeda 2017). Further data are needed to clarify whether reduced kidney function hampers the efficacy of the interventions for HF or leads to excess harm. While we acknowledge that MI and HF often are physiopathologically related and overlap, to address the specific question of this review, we excluded studies that examined pharmacological interventions in people with acute MI without HF.

The ACC/AHA Clinical Practice Guidelines for people with HF (Yancy 2017) recommend the use of renin-angiotensin system inhibition (with ACEi or ARB) in conjunction with beta-blockers and aldosterone antagonists, in selected patients with chronic HFrEF. Of note, the guidelines mention that treatment with ACEi and ARBs should be administered with caution to people with HFrEF renal insufficiency, and further, that aldosterone antagonists may be beneficial for people with HFpEF only if their eGFR > 30 mL/min/1.73 m² (Yancy 2017). Further, a 2014 review exploring the efficacy of HF interventions suggested a benefit among people with moderate CKD (i.e. stage 3), but the evidence in those with more advanced CKD (stage 4 to 5) is unknown (Damman 2014b). Our review was unable to differentiate CKD stage due to limited data accessibility. However, we found that beta-blockers may reduce risk of all-cause and cardiovascular death in people with HF who also have CKD. Pooling studies administering ARB or ACEi found no significant risk reduction in the CKD population for any outcome; however, one study (Cice 2010) reported that treatment with ARB significantly reduced the risk of cardiovascular death as well as hospitalisation for HF. We searched the OVID database and found three reviews that evaluated the combination of ARB and ACEi versus a single agent (Heran 2012; Kuenzli 2010; Lee 2004). While reviews have shown a significant benefit of ARB versus placebo (Heran 2012; Lee 2004) and a similar effect of ARB versus ACE inhibitors (Heran 2012; Kuenzli 2010; Lee 2004), we were unable to find any published reviews of studies comparing the effects of ACEi versus placebo. The Cochrane Database of Systematic Reviews reports protocols currently investigating a number of interventions: ACEi or ARB (http://www.cochrane.org/CD003040/VASC_are-angiotensin-receptor-blockers-arbs-an-effective-treatment-for-heart-failure) and beta-blockers (http://www.cochrane.org/CD012897/VASC_beta-blockers-heart-failure). This research will be important to ensure guidelines are based on high quality systematic reviews of RCTs.

Following appropriate ACEi/ARB dose-adjustment based on eGFR may be important for people with HF and impaired kidney function (Grande 2017). This was addressed in only one study (Pita-Fernandez 2015), which found that reducing the dose of ACEi by 50% in people with HF and CKD resulted in an improvement in anaemia and kidney function, decreased protein C, and improved

survival. Further research into dose-adjustment for people with CKD may be important for preventing the progression of kidney failure.

The effect of beta-blockers did not significantly reduce the risk of all-cause or cardiovascular death in a study including people over 70 years of age (SENIORS 2002), which is consistent with findings from the general population (Grossman 2002). While that study appears to show a trend toward an increased risk of worsening HF with beta-blockers, the estimate of this effect was imprecise. An observational study reported that beta-blocker use in patients with HF and CKD was safe and effective in reducing risk of death or hospitalisations (Chang 2013), but RCTs in this population are warranted (Franco Peláez 2016). Insufficient data are available on potential harms, including hypotension and acute kidney injury in people with CKD.

Our review reported an uncertain effect of aldosterone antagonists on death (any cause). Other research investigating the use of aldosterone antagonists in people on dialysis (with or without HF) reported a protective effect with respect to all-cause and cardiovascular death (Quach 2016). However, hyperkalaemia may be a concern in this patient population. The authors of the same review were unable to provide any recommendations due to insufficient sample size and the quality of the study. Due to the potential risk of hyperkalaemia in CKD patients who also have HF (as we found pooling the results of three studies), further work investigating the safety and efficacy of aldosterone antagonists, and other agents that block the renin-angiotensin system, is warranted.

Our review found a significant protective effect of aliskiren on reducing the risk of worsening HF in one study (ARIANA-CHF-RD 2016). However, while not significant, a trend suggesting a potential harmful effect on kidney function with administration of aliskiren was reported in two studies (ALOFT 2008; ARIANA-CHF-RD 2016). Other research has suggested that aliskiren is safe for use in people with CKD due to its anti-proteinuric effect (Persson 2013). However, much of the research done pertains to the treatment of hypertension and findings may not necessarily apply to HF populations. Furthermore, risks of hyperkalaemia with this intervention could be of concern for patients with CKD (Morishita 2013).

There are a number of additional therapies for the treatment of HF (Lothar 2016). Our review identified studies investigating anti-arrhythmics (dofetilide), digoxin, phosphodiesterase inhibitors (milrinone), sinus node inhibitors (ivabradine), and vasopressin receptor antagonists (tolvaptan). Evidence on the safety and efficacy of these interventions in people with CKD is limited and further research is needed before any conclusions may be drawn about their use in this patient population. As the co-occurrence of HF and CKD appears to be increasing (Conrad 2018), a better understanding of how to manage this patient population, particularly with a focus on the potential harms of conventional therapies, is important.

AUTHORS' CONCLUSIONS

Implications for practice

- In accordance with current guidelines, pharmacological interventions for HF should be used in caution in patients with

comorbid renal insufficiency. Systematic review of the existing literature didn't change the certainty of evidence around the using interventions for HF in people with CKD.

- While most analyses did not suggest a reduced risk of death or hospitalisation, the limited certainty of this evidence suggests a lack of evidence, not a lack of benefit, on these interventions. No changes to clinical practice are advised at this time until further information becomes available.
- Evidence on the appropriateness of the use of HF therapies is limited by: (1) the relatively small number of studies from which CKD data could be extracted to inform each comparison:outcome combination; and (2) the fact that people with advanced CKD are often under-represented in general HF studies.
- Available data suggest beta-blockers may reduce risk of death. However, high-quality studies enrolling patients with CKD are needed to increase the level of certainty for this effect.
- There is low certainty that anti-aldosterone interventions lead to hyperkalaemia. Information on the risk of other harms for most therapies is limited.
- Studies assessing interventions for acute decompensated HF compared outcomes within the first six months only.

Implications for research

- A better understanding of the risks of harms associated with HF interventions in people with CKD is needed.
- While the evidence surrounding the efficacy and safety of HF interventions is strong in the general population, exploring whether the same applies to people with CKD is important because these people may potentially gain more benefits from these interventions but also suffer from more harms. Future

studies comparing risk between non-CKD patients with those with CKD will help guide this knowledge.

- The stage of CKD should be considered when exploring the impact of kidney disease on the efficacy or safety of HF interventions. Including patients with a very low baseline eGFR (including those receiving kidney replacement therapy) will help inform practice for patients with advanced CKD and HF.
- Although the majority of HF studies did not exclude participants with CKD, subgroup analyses by CKD were not available in most studies.
- Future research aimed at analysing existing data in general population HF studies to explore the effect in sub-groups of patients with CKD may yield valuable insights for the management of people with HF and CKD.
- One of the limitations of this systematic review is the inability to access the data generated by RCTs of pharmacological interventions for HF that included people with CKD. Removing existing barriers to study data would promote more rapid advancement of new knowledge, improve patient care, and the use of resources in health systems.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

A-HeFT 2002

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: June 2001 to July 2004 - Duration of follow-up: 18 months
Participants	- Country: USA - Setting: multicentre (161 sites); outpatient - Inclusion criteria: HF (NYHA class III or IV, LVEF $\leq$ 35%); on HF therapy (ACEi, ARB, beta-blockers, digoxin, spironolactone, and diuretics for at least 3 months); and African American - Total number of study participants (CKD cohort): 181 (17.2% of total cohort); numbers per group not reported - Mean age $\pm$ SD (years) (CKD cohort): not reported - Sex (M/F) (CKD cohort): not reported - CKD stage (CKD cohort): chronic renal insufficiency (not defined) - DM (CKD cohort): not reported - Exclusion criteria: females who were pregnant, nursing, or of childbearing age who were not practicing effective contraception; acute MI, acute coronary syndrome, or stroke within the previous 3 months; cardiac surgery or PCI within 3 months or the likelihood of a requirement for such procedures during the study; significant valvular heart disease, hypertrophic or restrictive cardiomyopathy, active myocarditis, or uncontrolled hypertension; cardiac arrest or life-threatening arrhythmias within the previous 3 months (unless they had been treated with an implantable defibrillator); treatment with parenteral inotropes within 1 month before randomisation; likely need to undergo cardiac transplantation during the study period; symptomatic hypotension; presence of an illness other than HF that was likely to result in death within the study period; inability to comprehend or complete the QoL assessment instrument; contraindications to nitrate or hydralazine therapy
Interventions	Treatment group - Fixed-dose combination of 37.5 mg of hydralazine HCl and 20 mg of isosorbide dinitrate 3 times/day (dose adjustment as per protocol) Control group - Placebo
Outcomes	- Composite score that weighted all-cause death (18 months), first hospitalisation for HF (18 months) and change in QoL (6 months) - Individual components of the primary composite score - Cause-specific death - Total number of HF hospitalisations - Total number of all hospitalisations - Total days in-hospital - Overall QoL throughout the study - Number of unscheduled emergency room and office/clinical visits - Changes in LV ejection fraction, LV internal diastolic diameter - LV wall thickness at 6 months - Change in BNP level at 6 months

A-HeFT 2002 (Continued)

- Newly recognized need for cardiac transplantation

Notes

- Secondary analysis
- Funding: sponsor was NitroMed, Inc (Lexington, Mass)
- Authors did not report screening information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; all patients randomised were included in the final analysis
Selective reporting (reporting bias)	Low risk	Rationale, design, and methodology paper published
Other bias	High risk	Sponsor involved in preparation of manuscript

ABC-HFT 2011

Methods

- Study design: RCT
- Study duration: July 2006 to July 2008
- Duration of follow-up: 24 months

Participants

- Country: USA
- Setting: single centre
- Inclusion criteria: ADHF and admission BNP levels > 500 pg/mL
- Number: treatment group (44); control group (45)
- Mean age $\pm$ SD (years): treatment group (66.8 $\pm$ 17.2); control group (68.6 $\pm$ 14.1)
- Sex (M/F): treatment group (23/21); control group (25/20)
- CKD stage: SCr > 2.5 mg/dL at admission was an exclusion criterion
- DM: treatment group (30%); control group (36%)
- Exclusion criteria: women who were pregnant or lactating at the time of enrolment; < 18 years; symptomatic hypotension (SBP < 90 mm Hg) or cardiogenic shock; asymptomatic patients; BNP < 500 pg/mL; known allergy to E. coli-derived products, or any history of anaphylactic reactions to nesiritide or nitroglycerin; history of dialysis, SCr > 2.5 mg/dL at admission; current participant in a clinical study

Interventions

Treatment group

ABC-HFT 2011 (Continued)

- Nitroglycerin: 10 to 200 µg/min, IV for 48 hours
- Standard treatment

Control group

- Nesiritide: 2 µg/kg optional bolus followed by 0.01 µg/kg/min infusion, IV for 48 hours
- Standard treatment.

Outcomes	• Changes in renal and neurohormonal markers • Relationship between vasodilator infusion duration and nephrotoxicity (change in SCr, BUN, and CrCl at 24 and 48 hours of infusion) • Median length of stay, need for dialysis, and symptomatic hypotension • Acute changes observed during vasodilator therapy were correlated with death and rehospitalisation at 3 and 6 months
Notes	• Funding: Scios Speakers Bureau • Authors report the number of patients screened, but no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10 % of lost to follow-up; all patients randomised were included in the final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

ACTIV in CHF 2003

Methods	• Study design: double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 RCT • Study duration: not reported • Duration of follow-up: 2 months
Participants	• Country: USA; Argentina • Setting: multicentre (45 sites); inpatient period of up to 10 days, followed by a 7-week (49 to 51 days) outpatient period

ACTIV in CHF 2003 (Continued)

- Inclusion criteria: LVEF < 40% within 1 year of admission and systemic congestion as evidenced by JVD, rales, or peripheral oedema after initial in-hospital therapy for HF
- Number: treatment group 1 (78); treatment group 2 (84); treatment group 3 (77); control group (80)
- Mean age $\pm$ SD (years): treatment group 1 (62 ± 14); treatment group 2 (62 ± 13); treatment group 3 (62 ± 14); control group (60 ± 14)
- Sex (M/F): treatment group 1 (53/25); treatment group 2 (50/34); treatment group 3 (61/16), control group (60/20)
- CKD stage (SCr): treatment group 1 (2.01 ± 0.85); treatment group 2 (1.82 ± 0.33); treatment group 3 (2.07 ± 0.85); control group (1.75 ± 0.27)
- DM: treatment group 1 (50%), treatment group 2 (45.2%); treatment group 3 (45.5%), control group (46.3%)
- Exclusion criteria: women of child bearing age; cardiac surgery within 60 days; MI, sustained ventricular tachycardia, or ventricular fibrillation within 30 days; angina at rest; primary valvular disease; hypertrophic cardiomyopathy; stroke within the last 6 months; significant hepatic, kidney, or hematologic dysfunction; SBP < 110 mm Hg; use of drugs known to inhibit cytochrome P 3A4 enzyme within 7 days of randomisation, except for amiodarone, which should not have been taken within 10 weeks of randomisation; use of NSAIDs or of aspirin at a dose of more than 700 mg/d; substance or alcohol abuse; uncontrolled DM; urinary tract obstruction; morbid obesity; or malignancy or other terminal illness

Interventions	Treatment group 1 • Tolvaptan 30 mg/d Treatment group 2 • Tolvaptan 60 mg/d Treatment group 3 • Tolvaptan 90 mg/d Control group • Placebo
Outcomes	• Change in body weight at 24 hours after the administration of the first dose of study drug • Worsening HF at 60 days after randomisation, defined as hospitalisation for HF, unscheduled visit for HF to an emergency department or outpatient clinic associated with need for either increased therapy or new therapy for HF, or death • Changes in dyspnoea, JVD, rales, oedema, body weight (at discharge and in the outpatient setting), urine output (inpatient), serum electrolyte levels, length of hospital stay after randomisation, use of diuretics, and patient-and physician-assessed symptom scales
Notes	• Funding: Otsuka Maryland Research Institute • Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported

ACTIV in CHF 2003 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The clinical event committee based at the Duke Clinical Research Institute adjudicated all serious adverse events, cause of hospitalisation, and mode of death, blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10 % of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in study design and data analysis

AIRE 1991

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: not reported - Duration of follow-up: 6 months (minimum)
Participants	- Countries: 14 - Setting: multicentre (144 site) - Inclusion criteria: ≥ 18 years admitted to coronary care, intensive care, or general medical units with a definite acute MI and clinical evidence of HF at any time after the index acute MI - Number: treatment group (1004); control group (982) - Mean age $\pm$ SD (years): treatment group (64.9 ± 10.8); control group (65.1 ± 10.8) - Sex (M/F): treatment group (734/270); control group (727/255) - CKD stage: not reported - DM: treatment group (12%); control group (12%) - Exclusion criteria: severe HF (usually NYHA grade IV), HF of primary valvular or congenital aetiology, unstable angina, or any of the recognised contraindications to ACEi treatment
Interventions	Treatment group - Ramipril: 2.5 or 5 mg twice/day Control group - Placebo: twice/day
Outcomes	- Death (any cause) (primary outcome) - Severe/resistant HF - Reinfarction - Stroke
Notes	- Funding: supported by Hoechst - Authors do not report the number of patients screened and reasons for screen failure

Risk of bias

AIRE 1991 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study randomisation code was prepared by the statistician of the Independent Adjudicating Panel
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent adjudicating panel was responsible for the clinical definitions of the outcomes. The study data were analysed by the statistician on this panel
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10 % of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

ALIVE 1998

Methods	- Study design: placebo-controlled, double-blind RCT - Study duration: not reported - Duration of follow-up: 12 months
Participants	- Countries: 26 - Setting: multicentre (483 sites) - Inclusion criteria: documented MI within the previous 5 to 21 days, and had an LVEF of 15% to 35%, determined at least 1 day after the MI; NYHA I-III - Number: treatment group (1691), control group (1690) - Mean age $\pm$ SD (years): treatment group (60 $\pm$ 10); control group (61 $\pm$ 11) - Sex (M/F): treatment group (1318/373), control group (1318/372) - CKD stage: not reported - DM: treatment group (26%); control group (25%) - Exclusion criteria: history of torsade de pointes; unstable angina pectoris or a high-degree heart block; QTc interval of 450 ms; resting heart rate 50 BPM; NYHA class IV congestive HF; implantable cardioverter-defibrillator; serum potassium of 4 mEq/L; amiodarone use within 1 month before enrolment, current use of class I or III anti-arrhythmic drugs
Interventions	Treatment group - Azimilide: 100 mg Control group - Placebo
Outcomes	Death (any cause)

ALIVE 1998 (Continued)

- Notes
- Funding: Health Care Research Center, Procter & Gamble Pharmaceuticals Inc, Cincinnati, Ohio
 - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10 % of lost to follow up with differences between groups; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

ALOFT 2008

Methods	• Study design: double-blind, parallel-group, placebo-controlled RCT • Study duration: May 2005 to February 2007 • Duration of follow-up: 12 weeks
Participants	• Countries: 9 • Setting: multicentre (75 sites); outpatient • Inclusion criteria: HF (NYHA class II - IV); essential hypertension; on ACEi or ARB, and beta-blocker; BNP > 100 pg/mL • Total number of study participants (CKD cohort): 99 (32.8% of total cohort; treatment group (50); control group (49) • Mean age $\pm$ SD (years) (CKD cohort): not reported • Sex (M/F) (CKD cohort): not reported • CKD stage (CKD cohort): eGFR < 60 (but SCr > 2.0 mg/dL or on dialysis excluded) • DM (CKD cohort): not reported • Exclusion criteria: treatment with both an ACEi and an ARB; HF related to obstructive valve disease or hypertrophic, restrictive, or infective cardiomyopathy; pregnancy; lung disease; SBP > 90 mm Hg; serum potassium > 5.1 mmol/L; SCr > 2.0 mg/dL (or on dialysis); MI; cerebrovascular accident, transient ischaemic attack, or coronary revascularization within 6 months; cardiac resynchronization device or implantable cardioverter defibrillator; malignancy or other disease likely to greatly limit life expectancy, adherence to protocol, or absorption to study drug

ALOFT 2008 (Continued)

Interventions	Treatment group - Aliskiren: 150 mg once/day for 12 weeks Control group - Placebo
Outcomes	- Incidence of kidney dysfunction - Symptomatic hypotension - Hyperkalaemia - Cardiac function (pro-BNP, NYHA class, aldosterone, echocardiographic measures, BP, heart rate, neurohumoral and inflammatory biomarkers, LVEF, dyspnoea) - Death (any cause) - QoL
Notes	- Funding: This study was funded by Novartis, which also funded the core echocardiography laboratory at the Brigham and Women's Hospital - Authors report the number of patients screened, but no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was randomised using a validated, automated system
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% patients lost to follow up. Only reported outcomes on those that completed study
Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented
Other bias	High risk	Sponsor involved in data analysis and manuscript preparation

ANZ 1995

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: not reported - Duration of follow-up: 6 months
Participants	Countries: Australia, New Zealand

ANZ 1995 (Continued)

- Setting: multicentre (20 sites)
- Inclusion criteria: (1) chronic stable HF due to ischaemic heart disease (defined as a documented history of MI, typical angina, an exercise ECG positive for ischaemia, or angiographic evidence of coronary disease); (2) LVEF by radionuclide ventriculography < 45%; and (3) current NYHA functional class II or III or previous NYHA class II-IV.
- Number: treatment group (207); control group (208)
- Mean age $\pm$ SD (years): treatment group (67 ± 7.2); control group (67 ± 7.3)
- Sex (M/F): treatment group (157/50); control group (176/32)
- CKD stage: not reported (excluded if baseline SCr > 250 μ mol/L)
- DM: not reported
- Exclusion criteria: current NYHA class IV; heart rate < 50 BPM; sick sinus syndrome; second- or third-degree heart block; SBP < 90 mm Hg or BP > 160/100 mm Hg; treadmill exercise duration < 2 or > 18 minutes (modified Naughton protocol); coronary event or procedure (MI, unstable angina, coronary artery bypass surgery, or coronary angioplasty) within the previous 4 weeks; primary myocardial or valvular disease; current treatment with a beta-blocker, beta-agonist, or verapamil; insulin-dependent DM; chronic obstructive airways disease; hepatic disease (serum transaminase > 3 times normal); kidney impairment (SCr > 250 μ mol/L); or any other life-threatening noncardiac disease

Interventions	Treatment group • Carvedilol: 6.25 mg twice/week Control group • Matching placebo
Outcomes	• Changes in LVER (6 months) • Treadmill exercise duration from baseline (before commencing study treatment) • Changes in LV dimensions • 6-minute walk distance • Symptoms of HF and angina • Patient's perceived level of exertion (Borg scale)
Notes	• Funding: this study was funded by a grant from SmithKline Beecham • Authors do not report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on methods used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent data monitoring committee reviewed outcomes.
Incomplete outcome data (attrition bias)	Low risk	Principal outcome analyses involved all patients grouped according to their original randomised treatment allocation. < 10% lost to follow-up

ANZ 1995 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	High risk	Funded by a grant from SmithKline Beecham

AQUAMARINE 2014

Methods	- Study design: open-label, parallel-group RCT - Study duration: December 2011 to January 2015 (enrolment) - Duration of follow-up: 90 days
Participants	- Country: Japan - Setting: multicentre (14 sites); outpatient - Inclusion criteria: admitted to hospital with acute HF and CKD (eGFR 15 to 60 mL/min/1.73 m²) - Number: treatment group (108); control group (109) - Mean age $\pm$ SD (years): treatment group (72.99 $\pm$ 8.90); control group (72.95 $\pm$ 10.24) - Sex (M/F): 141/76 - CKD stage: eGFR 15 to 60 mL/min/1.73 m²(not on dialysis) - DM: 44.2% - Exclusion criteria: requiring mechanical circulatory support; consciousness disturbance; hypernatraemia (serum Na at admission > 147 mEq/L); volume depletion; cardiac shock; allergy or contraindication for tolvaptan; acute coronary syndrome; Chronic HD
Interventions	Treatment group - Tolvaptan: 15 mg once/day for 2 days - Conventional therapy (continued as per physician decision) Control group - Conventional therapy
Outcomes	- Urine Output (48 hours) - Worsening of kidney function (%) - Dose of diuretics use within 48 hours - Net fluid loss (48 h) - Change in BNP from baseline to 48 h - Change in body weight from baseline to 48 h - Length of hospital stay - Changes in dyspnoea and oedematous symptoms* - Adverse events - In-hospital death - Death (any cause) - Readmission for HF
Notes	- Funding: The AQUAMARINE study was funded by the Japan Heart Foundation of Multicentre Grant - Authors did not report screening information *Unable to estimate relative rate of improvement of dyspnoea, oedema, or rales as number at risk not reported

AQUAMARINE 2014 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using a web-based randomisation system
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; not all patients randomised were included in final analysis for death (any cause) or heart-failure hospitalisation, but this was a secondary outcome of the study
Selective reporting (reporting bias)	Low risk	Design and rationale paper published
Other bias	Unclear risk	The study appears to be free of other sources of bias

ARIANA-CHF-RD 2016

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: May 2009 to August 2012 (enrolment) - Duration of follow-up: 6 months
Participants	- Country: Netherlands - Setting: single centre; outpatient - Inclusion criteria: CHF (NYHA class II-IV and LVEF $\leq$ 45%) and CKD (eGFR 30 to 60 mL/min/1.73 m²) - Number: treatment group (27); control group (14) - Mean age $\pm$ SD (years): treatment group (69 $\pm$ 10); control group (67 $\pm$ 6) - Sex (M/F): 32/7 - CKD stage: eGFR 30 to 60 mL/min/1.73 m² - DM: 25.6% - Exclusion criteria: known hypersensitivity to study drug or ACEi; concomitant treatment with both ARB and aldosterone receptor antagonist; symptomatic hypotension; acute HF; history of stroke, acute coronary syndrome, PCI or angioplasty within past 3 months; serum potassium > 5.2 mmol/L; right HF due to severe pulmonary disease
Interventions	Treatment group - Aliskiren: 300 mg once/day for 6 months Control group - Matching placebo

ARIANA-CHF-RD 2016 (Continued)

Outcomes	• Change in renal blood flow • Changes in kidney function, N-terminal pro-BNP, left ventricular function, BP and neurohormones • Hyper/hypokalaemia • Hypotension
Notes	• Funding: "This trial was sponsored by an investigational grant of Novartis AG. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents." • Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised treatment allocation using an automated computer system
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow up. Final analysis did not include participants that discontinued study
Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented
Other bias	Low risk	The study was supported by Novartis, but the authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents

ARTS-HF 2015

Methods	• Study design: double-blind, phase 2b RCT • Study duration: June 2013 to August 2014 • Duration of follow-up: 3 months
Participants	• Countries: 25 (Europe, North America, Asia, other countries) • Setting: multicentre (173 sites) • Inclusion criteria: worsening CHF requiring hospitalisation and treatment with IV diuretics; T2DM and/or CKD (i.e. an eGFR of > 30 mL/min/1.73 m² in patients with T2DM and 30 to 60 mL/min/1.73 m² in patients without T2DM); have been receiving treatment with evidence-based therapy for HF for at least the previous 3 months; have a medical history of a left ventricular ejection fraction of ≤ 40% within the previous 12 months.

ARTS-HF 2015 (Continued)

- Number: treatment group 1 (173); treatment group 2 (165); treatment group 3 (169); treatment group 4 (170); treatment group 5 (165); control group (224)
- Mean age $\pm$ SD (years): treatment group 1 (72.5 ± 9.7); treatment group 2 (71.8 ± 10.6); treatment group 3 (69.3 ± 9.8); treatment group 4 (71.3 ± 10.23); treatment group 5 (69.2 ± 10.2); control group (72.4 ± 9.9)
- Sex (M/F): treatment group 1 (135/37); treatment group 2 (126/37); treatment group 3 (124/43); treatment group 4 (128/41); treatment group 5 (132/31); control group (170/51)
- CKD stage (eGFR): treatment group 1 (52 ± 16); treatment group 2 (52 ± 16); treatment group 3 (55 ± 20); treatment group 4 (53 ± 17); treatment group 5 (55 ± 19); control group (52 ± 18)
- DM: not reported
- Exclusion criteria: acute de novo HF or acute inflammatory heart disease; acute coronary syndromes in the last 30 days before the screening visit; cardiogenic shock or valvular heart disease requiring surgical intervention; left ventricular assist device or awaiting heart transplantation; stroke or transient ischaemic attack within 3 months before screening

Interventions	Treatment group 1 • Finerenone: 2.5 to 5 mg Treatment group 2 • Finerenone: 5 to 10 mg Treatment group 3 • Finerenone: 7.5 to 15 mg Treatment group 4 • Finerenone: 10 to 20 mg Treatment group 5 • Finerenone: 15 to 20 mg Control group • Eplerone: 25 to 50 mg, once/day
Outcomes	• Efficacy (percentage of responders; i.e. the number of patients with a decrease in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of $> 30\%$ from baseline to day 90) and safety of different oral doses of finerenone given once/day • A composite endpoint of death from any cause, CV hospitalisation, or emergency presentation for worsening CHF until day 90 • Change in efficacy biomarker (B-type natriuretic peptide, NT-proBNP, galectin 3, and N-terminal pro-collagen III propeptide) • Change in scores on HRQoL questionnaires (the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the five-dimension European Quality of Life Questionnaire (EuroQoL)) • Effects on the following safety parameters were assessed: (i) biomarker of organ injury (troponin T and cystatin C); (ii) vital signs; (iii) laboratory parameters (including potassium and SCr concentrations, and eGFR); (iv) incidence of adverse events including those of special interest (i.e. an increase in serum potassium concentration to at least 5.6 mmol/L leading to discontinuation or emergency presentation for worsening CHF after starting treatment with the study drug)
Notes	• Funding: Bayer Pharma AG • Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported

Risk of bias

ARTS-HF 2015 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out centrally by an interactive voice/web response system
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical endpoints have been adjudicated by the event committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10 % of lost to follow-up; not all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in writing the manuscript

ASCEND-HF 2009

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: May 2007 to August 2010 - Duration of follow-up: 180 days
Participants	- Countries: North America, Europe, Latin America, Asia-Pacific region - Setting: multicentre (398 sites) - Inclusion criteria: hospitalised for HF occurring within 24 hours before they received their first IV treatment for HF, or if they had received a diagnosis of ADHF < 48 hours after hospitalisation for another cause - Number: treatment group (3496); control group (3511) - Mean age (IQR): 67 years (56 to 76) - Sex (M/F): 4616/2391 - CKD stage (median SCr, IQR) (mg/dL): treatment group (1.2, 1.0 to 1.5); control group (1.2, 1.0 to 1.6) - DM: not reported - Exclusion criteria: high risk of hypotension (SBP < 100 mm Hg or 110 mm Hg with the use of IV nitroglycerin); other contraindications for vasodilators; treatment with dobutamine (at a dose $\geq$ 5 µg/kg/min); treatment with milrinone or levosimendan within the previous 30 days; persistent uncontrolled hypertension; acute coronary syndrome; normal level of BNP or NT-proBNP; severe pulmonary disease; ESKD during receipt of RRT; clinically significant anaemia
Interventions	Treatment group Nesiritide: continuous infusion of 0.010 µg/kg/min for 24 hours or more for up to 7 days (optional IV bolus (2 µg/kg) administered prior) Control group

ASCEND-HF 2009 (Continued)

- Placebo

Outcomes	• Change in self-reported dyspnoea 6 and 24 hours after study-drug initiation • Composite end point of rehospitalisation for HF and death from any cause during the period from randomisation to day 30 • Death at day 180 (any cause)
Notes	• Funding: Scios Inc. • Details on screening not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; authors used a modified intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Rationale and design published prior; all pre-specified outcomes included in analysis
Other bias	High risk	Study conduct was directed by the sponsor

ASTRONAUT 2011

Methods	• Study design: prospective, multicentre, double-blind, placebo-controlled RCT • Study duration: May 2009 to December 2011 • Duration of follow-up: 11.3 months (median)
Participants	• Countries: North and South America, Europe, Asia • Setting: multicentre (316 sites) • Inclusion criteria: history of CHF defined as requiring standard therapy for 30 days or longer prior to the index hospitalisation, LVEF $\leq$ 40%, elevated levels of natriuretic peptides (BNP > 400 pg/mL or NT-proBNP > 600 pg/mL), signs and symptoms of fluid overload that required hospitalisation • Number: treatment group (821); control group (818) • Mean age $\pm$ SD (years): treatment group (64.7 $\pm$ 12.4); control group (64.5 $\pm$ 11.9) • Sex (M/F): treatment group (637/171); control group (610/197) • CKD stage (eGFR): treatment group (67.3 $\pm$ 20); control group (66.1 $\pm$ 19.9) • DM: treatment group (39.5%); control group (42.5%)

ASTRONAUT 2011 (Continued)

- Exclusion criteria: MI, cardiac surgery, or stroke within 3 months prior to enrolment; presence of ventricular assist devices or any type of mechanical support; history of a cardiac transplant or listed for transplant at time of enrolment; haemodynamically significant uncorrected primary cardiac valvular disease; right HF due to pulmonary disease; eGFR < 40 mL/min/ 1.73 m²; serum sodium < 130 mEq/L; serum potassium > 5.0 mEq/L; comorbid conditions with an expected survival of < 3 years

Interventions	Treatment group • Aliskiren: 150 or 300 mg/day Control group • Placebo
Outcomes	• The first occurrence of CV death or rehospitalisation for HF at 6 months (i.e. 190 days) after randomisation. • The first occurrence of CV death or rehospitalisation for HF within 12 months of randomisation. • The first CV event (defined as CV death, HF hospitalisation, nonfatal MI, nonfatal stroke, and resuscitated sudden death) within 12 months; death (any cause) within 6 and 12 months; changes from baseline in NT-proBNP level (at months 1, 6, and 12); and QoL (activities of daily living, assessed by the Kansas City Cardiomyopathy Questionnaire at months 1, 6, and 12)
Notes	• Funding: Novartis Pharma • Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All potential study end points were adjudicated by a blinded clinical event committee (Brigham and Women's Hospital, Harvard Medical School)
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10 % of lost to follow-up; not all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in the design, conduct, and management of the study

ATLAS 1999

Methods	• Study design: RCT
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ATLAS 1999 (Continued)

	- Study duration: October 1992 to September 1997 - Duration of follow-up: ranged from 39 to 58 months (median 45.7)
Participants	- Countries: 19 - Setting: multicentre (287 sites) - Inclusion criteria: NYHA class II, III, or IV symptoms of HF associated with a LVEF $\leq$ 30% despite treatment with diuretics for $\geq$ 2 months; patients with class II symptoms were required to have received treatment for HF in an emergency room or hospital within 6 months - Number: treatment group (1596); control group (1568) - Mean age $\pm$ SD (years): treatment group (63.6 ± 10.3); control group (63.6 ± 10.5) - Sex (M/F): treatment group (1265/331); control group (1251/317) - CKD stage: not reported but SCr $>$ 2.5 mg/dL was an exclusion criterion - DM: not reported - Exclusion criteria: acute coronary Ischaemic event or revascularization procedure within 2 months; history of sustained or symptomatic ventricular tachycardia; known to be intolerant of ACEi; SCr $>$ 2.5 mg/dL; any noncardiac disorder that could limit survival
Interventions	Treatment group - Lisinopril: 20 mg/day (low dose lisinopril) Control group - Lisinopril: 40 mg/day (high dose lisinopril)
Outcomes	- Death (any cause) - CV death, CV hospitalisations, death (any cause combined with CV hospitalisations, and CV death combined with CV hospitalisations)
Notes	- Funding: Zeneca Pharmaceuticals - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All end points were adjudicated according to prespecified criteria by an End Points Committee blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information regarding lost-to-follow-up to permit judgement; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes presented

ATLAS 1999 (Continued)

Other bias	Unclear risk	Insufficient information to permit judgement
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ATMOSPHERE 2011

Methods	- Study design: double-blind, double-dummy treatment RCT - Study duration: March 2009 to December 2013 - Duration of follow-up: 36.6 months (median)
Participants	- Countries: 43 (North America, Latin America, Western Europe, Central Europe, Asia and Pacific region) - Setting: multicentre (789 sites) - Inclusion criteria: CHF with NYHA class II to IV symptoms and an LVEF $\leq 35\%$; BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or, if they had been hospitalised for HF within the previous 12 months, a BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL); must have been receiving stable doses of an ACEi (equivalent to at least 10 mg of enalapril/day) and of a beta-blocker at the time of enrolment - Number: treatment group 1 (2340); treatment group 2 (2336); control group (2340) - Mean age $\pm$ SD (years): treatment group 1 (63.3 ± 12.06); treatment group 2 (63.3 ± 11.71); control group (63.2 ± 11.65) - Sex (M/F): treatment group 1 (1808/532); treatment group 2 (1837/499); control group (1846/494) - CKD stage (eGFR): treatment group 1 (74 ± 23); treatment group 2 (74 ± 22); control group (74 ± 27) - DM: treatment group 1 (26.8%); treatment group 2 (27.9%); control group (28.4%) - Exclusion criteria: symptomatic hypotension; SBP < 95 mm Hg at screening (or < 90 mm Hg at randomisation); eGFR < 40 mL/min/1.73 m² (or < 35 mL/min/1.73 m² at randomisation or a decline of $> 25\%$ in the eGFR between screening and randomisation); serum potassium ≥ 5.0 mmol/L at screening (or ≥ 5.2 mmol/L at randomisation); history of inability to take ACEi
Interventions	Treatment group 1 - Aliskiren: 300 mg once/day Treatment group 2 - Enalapril: 5 or 10 mg twice/day Control group - Combination therapy
Outcomes	- Composite of death from CV causes or a first hospitalisation for HF - Change from baseline to 12 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score and the change in the NT-proBNP concentration from baseline to 4 months (this outcome was removed after the protocol was amended)
Notes	- Funding: Novartis - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Voice-based computerized randomisation system
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported

ATMOSPHERE 2011 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A clinical-event committee adjudicated deaths and major CV outcomes in a blinded fashion, using prespecified criteria
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in the analysis

Barr 1995

Methods	- Study design: prospective double-blind RCT - Study duration: not reported - Duration of follow-up: 2 months
Participants	- Country: UK - Setting: single centre - Inclusion criteria: NYHA II to III congestive HF - Number: treatment group (28); control group (14) - Mean age $\pm$ SD (years): treatment group (68 ± 3); control group (70 ± 2) - Sex (M/F): treatment group (22/6); control group (10/4) - CKD stage (eGFR): treatment group (74 ± 11); control group (75 ± 15) - DM: not reported - Exclusion criteria: not reported
Interventions	Treatment group - Spironolactone: 50 to 100 mg/day Control group - Placebo
Outcomes	Death in CHF
Notes	- Funding: not reported - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Barr 1995 (Continued)

Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind assessment of all end points
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Barr 1997

Methods	- Study design: prospective triple-blind RCT - Study duration: not reported - Duration of follow-up: 12 months
Participants	- Country: UK - Setting: single centre - Inclusion criteria: NYHA class I to II CHF (few or no symptoms), and with ECG evidence of left ventricular systolic dysfunction and LVEF > 35%; all patients had evidence of coronary artery disease - Number: treatment group (21); control group (20) - Mean age $\pm$ SD (years): treatment group (66 ± 8); control group (66 ± 8) - Sex (M/F): treatment group (19/2); control group (19/1) - CKD stage (eGFR): treatment group (85 ± 21); control group (79 ± 20) - DM: not reported - Exclusion criteria: not reported
Interventions	Treatment group - Enalapril: 2.5 to 20 mg/day Control group - Placebo
Outcomes	Death in CHF
Notes	- Funding: This study was supported by Merck, Sharp & Dohme Hoddessdon - Authors did not report screening information.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Barr 1997 (Continued)

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

BEAUTIFUL 2006

Methods	- Study design: multicentre, international, double-blind placebo-controlled RCT - Study duration: December 2004 to December 2006 (screening) - Duration of follow-up: 17 to 36 months
Participants	- Countries: 33 - Setting: multicentre (781 sites) - Inclusion criteria: ≥ 55 years for nondiabetic patients or ≥ 18 years for diabetic patients (type 1 or 2); evidence of coronary artery disease, in sinus rhythm with a resting heart rate of ≥ 60 BPM, with a LVEF $< 40\%$, and with left ventricular dilation - Number: treatment group (5479); control group (5438) - Mean age $\pm$ SD (years): treatment group (65.3 ± 8.5); control group (65.0 ± 8.4) - Sex (M/F): treatment group (4540/939); control group (4507/931) - CKD stage: not reported (patients ineligible if known severe kidney disease) - DM: treatment group (37%); control group (37%) - Exclusion criteria: (1) unlikely to cooperate in the study or with inability or unwillingness to give informed consent; (2) pregnant or breast-feeding women or women of childbearing potential; (3) recent (< 6 months) MI or coronary revascularization or with a history of stroke or cerebral transient ischaemic attack within the preceding 3 months or scheduled for revascularization (PCI and coronary artery bypass graft); (4) at least 1 of the following criteria: (a) implanted pacemaker or implantable cardioverter defibrillator; (b) valvular disease likely to require surgery within the next 3 years; (c) sick sinus syndrome, sinoatrial block, congenital long QT, complete atrioventricular block; (d) severe or uncontrolled hypertension (SBP > 180 mm Hg or DBP > 110 mm Hg); (e) current severe symptoms of HF (NYHA class IV); (f) expectation of death from other illness during the course of the study; (g) with known severe liver disease or kidney disease; (h) requiring or likely to require the following medications: macrolide antibiotics, cyclosporin, gestodene, antiretroviral drugs or azole antifungals such as ketoconazole or with known hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
Interventions	Treatment group

BEAUTIFUL 2006 (Continued)

- Ivabradine: target dose 7.5 mg twice/day

Control group

- Matched placebo

Outcomes	• Composite of CV death and hospital admission for acute MI or new onset or worsening of HF • Death (any cause) • Cardiac death (death from MI or HF, or death related to a cardiac procedure) • CV death (defined as cardiac death, death from a vascular procedure, presumed arrhythmic death, stroke death, other vascular death, or sudden death of unknown cause) or admission to hospital for new-onset or worsening HF • Composite of admission to hospital for fatal and non-fatal acute MI or unstable angina • Coronary revascularization • CV death • Admission to hospital for HF • Admission to hospital for MI
Notes	• Funding: Servier, France. All authors have received fees, research grants, or both from Servier • Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-allocation schedule was computer-generated by non-adaptive balanced randomisation
Allocation concealment (selection bias)	Low risk	An independent organization supervised randomisation. A central interactive voice-response system and an interactive web-response system was used to ensure investigators were unaware of treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An endpoint validation committee, blinded to the allocation of randomised study medication, will review outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised included in analysis; < 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	All authors have received fees, research grants, or both from Servier

Berry 2007

Methods	• Study design: randomised, parallel-group, double-blind RCT • Study duration: not reported
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Berry 2007 (Continued)

	Duration of follow-up: 12 weeks
Participants	- Country: UK - Setting: single centre - Inclusion criteria: NYHA class I to III and LVEF < 40% and taking an optimal maintenance dose of both a beta-blocker and either an ACEi or an ARB for at least 30 days - Number: treatment group (20), control group (20) - Mean age $\pm$ SD (years): treatment group (65 ± 7.4); control group (59 ± 9.5) - Sex (M/F): 31/9 - CKD stage: not reported (included patients with SCr ≤ 220 μmol/L) - DM: 10% - Exclusion criteria: use of potassium-sparing diuretics; SCr > 220 μmol/L; serum potassium >5 mmol/L before randomisation
Interventions	Treatment group - Spironolactone 25 mg/day for 3 months Control group - Placebo
Outcomes	- Blood and urine assays - Heart rate - QT interval dispersion - Cardiopulmonary exercise testing - HRQoL - Safety
Notes	- Funding: not reported - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Randomisation procedure performed by the hospital pharmacy clinical trials unit
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and patients were blinded to the allocated treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	< 10% of patients withdrew from study; insufficient information to permit judgement regarding intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Berry 2007 (Continued)

Other bias	Unclear risk	Insufficient information to permit judgement
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BEST 1995

Methods	- Study design: double-blind, multicentre RCT - Study duration: May 1995 to December 1998 (patients randomised) - Duration of follow-up: 12 months
Participants	- Countries: Canada, USA - Setting: multicentre (90 sites) - Inclusion criteria: compensated congestive HF due to idiopathic dilated cardiomyopathy or coronary disease with ejection fraction 10.35, are in NYHA class III or IV, and are taking an ACEi, digitalis, and if needed, a diuretic - Number: treatment group (1354); control group (1354) - Mean age $\pm$ SD (years): treatment group (60 ± 12.6); control group (60 ± 12.3) - Sex (M/F): treatment group (1068/286); control group (1047/307) - CKD stage: not reported (patients were ineligible if SCr ≥ 3.0 mg/dL) - DM: treatment group (37%); control group (34%) - Exclusion criteria: reversible cause of HF; uncorrected primary valvular disease; untreated thyroid disease; obstructive or hypertrophic cardiomyopathy; pericardial disease; amyloidosis; active myocarditis; a malfunctioning artificial heart valve; history of MI within the previous 6 months; candidates for heart transplantation; undergone a revascularization procedure (a percutaneous transluminal intervention or a coronary-artery bypass procedure) within the previous 60 days; unstable angina (requiring treatment with more than 6 nitroglycerin tablets/week); heart rate slower than 50 BPM; undergoing treatment with other investigational agents; life expectancy of less than 3 years; active liver disease or if they had haematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that could adversely affect the safety or the efficacy of the study drug; decompensated HF; active abusers of alcohol or illicit drugs; taken any of the following: calcium-channel-blocking agents (including amlodipine), theophylline, tricyclic antidepressants, monoamine oxidase inhibitors, or beta-agonists within 1 week before the base-line evaluation; beta-adrenergic-blocking agents within 30 days before the base-line evaluation; flecainide, encainide, propafenone, or disopyramide within 2 weeks before randomisation; or amiodarone within 8 weeks before the baseline evaluation
Interventions	Treatment group - Bucindolol: 6.25mg, 12.5 mg, 25mg, 50mg, or 100mg twice/day Control group - Matched placebo
Outcomes	- Death (any cause) - CV death, death due to worsening HF, sudden death - QoL, hospitalisation and cost, LVEF after 3 and 12 months of therapy, MI
Notes	- Funding: National Heart, Lung, and Blood institute and the Department of Veterans Affairs Cooperative Studies Program; Incara Pharmaceuticals supplied bucindolol and placebo - Authors do not report the number of patients screened or reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
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BEST 1995 (Continued)

Random sequence generation (selection bias)	Low risk	Treatment was assigned by an adaptive balancing scheme ("biased coin" randomisation)
Allocation concealment (selection bias)	Low risk	A central coordinating centre randomly assigned patients to treatment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The cause of death was adjudicated by a central end-points committee whose members were blinded to the treatment-group assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

BETACAR 1999

Methods	- Study design: double-blind RCT - Study duration: March 1999 to June 2001 - Duration of follow-up: 21 months
Participants	- Countries: 4 - Setting: multicentre (29 sites) - Inclusion criteria: stable CHF of NYHA class II and III for at least 3 months using ACEi or AT1-blockers as mandatory therapy; had to have a satisfactory ECG reading with an LVEF ≤ 0.35 or LVEDD ≥ 60 mm in combination with a fractional shortening of $\leq 20\%$ - Number: treatment group (131); control group (124) - Mean age $\pm$ SD (years): treatment group (56.1 ± 10.7); control group (57.7 ± 10.2) - Sex (M/F): treatment group (114/17); control group (105/19) - CKD stage: not reported - DM: treatment group (18%); control group (25%) - Exclusion criteria: myocarditis, hypertrophic or restrictive cardiomyopathy; valvular disorders, AV-block II or III; inability to perform walk testing; major events within the last three months before recruitment, such as MI, PTCA, NSTEMI or CABG; sinus bradycardia < 60 BPM; supine SBP < 110/mm Hg; heart transplant, pacemakers or implantable cardioverter-defibrillator implants
Interventions	Treatment group - Carvedilol: 25 mg orally Control group - Betaxolol: 20 mg orally
Outcomes	ECG assessments of LVEF

BETACAR 1999 (Continued)

- Evaluation of the incidence of major CV adverse events
- Combined risk of hospitalisation and/or death for CV reason
- Exercise performance (6-min walk test).
- NYHA class
- QoL using MLW Heart Failure questionnaire

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| Notes | <ul style="list-style-type: none"> • Funding: Sanofi-Synthelabo • Authors did not report screening information |
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% of lost to follow-up; not all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in data management

BLAST-AHF 2015

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|--------------|--|
| Methods | <ul style="list-style-type: none"> • Study design: double-blind, placebo-controlled, phase II B, dose ranging RCT • Study duration: December 2013 to February 2016 (was paused between November 2014 and May 2015) • Duration of follow-up: 6 months |
| Participants | <ul style="list-style-type: none"> • Countries: 12 (Argentina, Bulgaria, Canada, Czech Republic, Germany, Hungary, Israel, Poland, Romania, Russia, Slovakia, USA) • Setting: multicentre (> 70 sites) • Inclusion criteria: history of HF who presented to the hospital with acute HF, as evidenced by elevated natriuretic peptides (BNP > 400 pg/mL or NT-proBNP > 1600 pg/mL) (for patients with BMI > 30 kg/m²: BNP > 200 pg/mL or NT-proBNP > 800 pg/mL and for patients with rate-controlled persistent or permanent atrial fibrillation: BNP > 600 pg/mL or NT-proBNP > 2400 pg/mL) and at least two physical HF signs including congestion on chest radiograph, rales, oedema, and/or elevated jugular venous pressure; SBP ≥ 120 mm Hg and ≤ 200mm Hg; eGFR 20 to 75 mL/min/1.73 m² • Number: treatment group 1 (129); treatment group 2 (183); treatment group 3 (126); control group (183) |

BLAST-AHF 2015 (Continued)

- Mean age $\pm$ SD (years): treatment group 1 (70.1 ± 10.48); treatment group 2 (69.8 ± 9.03); treatment group 3 (70.8 ± 9.31); control group (71.1 ± 9.39)
- Sex (M/F): treatment group 1 (78/50); treatment group 2 (113/69); treatment group 3 (78/47); control group (115/68)
- CKD stage (eGFR; mean, range): treatment group 1 (53.79, 41.18 to 69.50); treatment group 2 (53.96, 40.16 to 63.44); treatment group 3 (53.62, 41.90 to 64.50); control group (53.37, 42.24 to 67.39)
- DM: treatment group 1 (41.4%); treatment group 2 (42.9%); treatment group 3 (47.2%); control group (46.4%)
- Exclusion criteria: use of ARB within 7 days prior, IV inotropes or vasopressors within 2 hours prior, or IV nitrates within 1 hour prior to randomisation (patients receiving nitroglycerin ≤ 0.1 mg/kg/hour for screening SBP ≥ 150 mm Hg were eligible)

Interventions	Treatment group 1 • TRV027: 1 mg/hour Treatment group 2 • TRV027: 5 mg/hour Treatment group 3 • TRV027: 25 mg/hour Control group • Placebo
Outcomes	• Time from baseline to death through day 30 • Time from baseline to HF re-hospitalisation through day 30 • The first assessment time point following worsening HF through day 5 • Change in dyspnoea VAS score calculated as the AUC representing the change from baseline over time from baseline through day 5 • Length of initial hospital stay (in days) from baseline • VAS AUC to day 5 • The change in core laboratory-measured NT-proBNP from baseline to 48 hours • All-cause mortality through day 180 • The incidence of treatment-emergent adverse events and serious adverse events • Changes in vital signs including the incidences of asymptomatic and symptomatic hypotension • Significant changes in laboratory values • Changes in high sensitivity troponin-T and cystatin-C through 48 hours to assess for end-organ protection or prevention of injury
Notes	• Funding: Trevena, Inc • Authors did not report screening information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive randomisation system
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported

BLAST-AHF 2015 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Independent reviews by the Data Safety Monitoring Board and Steering Committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in study design and conduct

CAPRICORN 2001

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: not reported - Duration of follow-up: 1.3 years (mean)
Participants	- Countries: 17 - Setting: multicentre (163 sites) - Inclusion criteria: ≥ 18 years with a stable, definite MI occurring 3 to 21 days before randomisation - Number: treatment group (975), control group (984) - Mean age, range (years): treatment group (63, 29 to 88); control group (63, 25 to 90) - Sex (M/F): 1440/519 - CKD stage: not reported - DM: 22.3% - Exclusion criteria: continued requirement for IV inotropic therapy or uncontrolled HF; ongoing or expected need for beta-blockade; complicating clinical conditions including unstable angina, uncorrected significant valve disease, hypotension < 90 mm Hg, bradycardia < 60 BPM, uncontrolled hypertension, unstable IDDM, significant pulmonary, hepatic or kidney impairment; ongoing therapy with inhaled beta-2 agonists or steroids, rate-limiting calcium channel blockers, anti-arrhythmics except amiodarone, immuno-suppressive agents; expectation of death from other illness during the course of the study; pregnancy, continuing lactation or planned pregnancy; inability or unwillingness to give informed consent
Interventions	Treatment group - Carvedilol: maximum dose of 25 mg twice/day Control group - Placebo
Outcomes	- Death (any cause) or CV hospitalisation - Death (any cause) - Sudden death - Hospitalisation for HF - CV death - Hospitalisations (any cause)

CAPRICORN 2001 (Continued)

- CV hospitalisations
- Unstable ischaemic events
- Non-fatal CV events

- Notes
- Funding: not reported
 - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done by an automated system.
Allocation concealment (selection bias)	Low risk	Participants randomised using an automated process
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% withdrew from study (reasons not described)
Selective reporting (reporting bias)	Low risk	Design paper previously published. All prespecified outcomes presented
Other bias	Unclear risk	Target sample size was revised on the basis of the new co-primary endpoint of death (any cause) or CV hospital admission. Details of sponsor involvement not described

CARMEN 2001

- Methods
- Study design: double-blind, parallel-group RCT
 - Study duration: not reported
 - Duration of follow-up: 18 months
- Participants
- Countries: 13 European countries
 - Setting: multicentre (54 sites)
 - Inclusion criteria: stable mild CHF, with at least a 2-month history of symptoms and a LVEF < 40% were eligible if they were on stable CHF medication and free from CV hospitalisations for at least 2 weeks prior to randomisation
 - Number: treatment group 1 (191); treatment group 2 (190); control group (191)
 - Mean age (years): treatment group 1 (61.9); treatment group 2 (62.9); control group (62.1)
 - Sex (M): treatment group 1 (77%), treatment group 2 (84%); control group (81%)
 - CKD stage (SCr): treatment group 1 (1.873 ± 0.412); treatment group 2 (1.927 ± 0.427); control group (1.873 ± 0.409)
 - DM: treatment group 1 (15%); treatment group 2 (12%); control group (16%)

CARMEN 2001 (Continued)

- Exclusion criteria: patients with confounding factors, e.g. recent or planned coronary revascularization; contraindications for beta-blocker therapy; ongoing ACEi was stopped between 2 and 14 days and ARB, alpha-blockers and beta-blockers were stopped 4 weeks before randomisation

Interventions	Treatment group 1 - Carvedilol: 3.125 to 50 mg Treatment group 2 - Enalapril: 2.5 to 10 mg Control group - Carvedilol and enalapril
Outcomes	- Death classified as CV (sub-categories: sudden cardiac death, worsening of CHF, acute MI or other fatal CV events) or non-CV - Hospitalisations were classified as CV (sub-categories: worsening of CHF, or other reasons) or non-CV - CHF medication changes
Notes	- Funding: Roche - Authors report the number of patients screened, but no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	The drug code was kept at the independent randomisation centre only to be released after completion of all study-related activities or in case of an emergency
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An endpoint committee of three experienced cardiologists, blinded to treatment, reviewed all events involving death, hospitalisations or CHF medication changes
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all patients randomised were included in the final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

CASINO 2004

Methods	- Study design: double-blind, double-dummy, placebo-control parallel-group RCT - Study duration: not reported
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CASINO 2004 (Continued)

	Duration of follow-up: 6 months
Participants	- Country: Greece - Setting: multicentre (number of sites not reported) - Inclusion criteria: decompensated low output CHF (LVEF < 35%) - Number: treatment group 1 (75); treatment group 2 (75); control group (77) - Mean age ± SD (years): not reported - Sex (M/F): not reported - CKD stage: not reported - DM: not reported - Exclusion criteria: not reported
Interventions	Treatment group 1 - Levosimendan (IV) Treatment group 2 - Dobutamine (IV) Control group - Placebo (IV)
Outcomes	The composite of death or rehospitalisation due to HF deterioration during the follow-up, was the primary endpoint
Notes	- Funding: not reported - Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

CHARM-Added 2003

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: March to November 1999 (enrolment) - Duration of follow-up: 3.5 years
Participants	- Countries: 26 - Setting: multicentre (number of sites not reported); outpatient - Inclusion criteria: ≥ 18 years with symptomatic HF (NYHA Class II–IV) of at least 4 weeks' duration; LVEF $\leq 40\%$, on ACEi for at least 30 days - Number: treatment group (1276); control group (1272) - Mean age $\pm$ SD (years): treatment group (64.0 ± 10.7); control group (64.1 ± 11.3) - Sex (M/F): treatment group (1006/270); control group (1000/272) - CKD stage: not defined (excluded patients with SCr ≥ 265 mmol/L) - DM: 29.7% - Exclusion criteria: SCr ≥ 265 mmol/L; serum potassium ≥ 5.5 mmol/L or a history of marked ACEi-induced hyperkalaemia resulting in either a serum potassium ≥ 6.0 mmol/L or a life-threatening adverse event; known bilateral renal artery stenosis; current symptomatic hypotension; persistent systolic or diastolic hypertension; stroke, acute MI, 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 non-cardiac disease (e.g. cancer) that is likely to significantly shorten life expectancy to less than 2 years
Interventions	Treatment group - Candesartan: 32 mg once/day Control group - Placebo
Outcomes	- CV death or unplanned admission to hospital for the management of worsening CHF - CV death, admission to hospital for CHF or non-fatal MI - CV death, admission to hospital for CHF, non-fatal MI, or non-fatal stroke - CV death, admission to hospital for CHF, non-fatal MI, non-fatal stroke, or coronary revascularization; death (any cause) or admission to hospital for CHF; and development of new diabetes
Notes	- Funding: study sponsored by AstraZeneca - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	The assignment code being held by an independent centre and the data safety monitoring board.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

CHARM-Added 2003 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of patients lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in the analysis

CHARM-Alternative 2003

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: March 1999 to March 2001 (enrolment) - Duration of follow-up: follow-up was concluded on March 2003; 33.7 months (median)
Participants	- Countries: 26 - Setting: multicentre (number of sites not reported); outpatient - Inclusion criteria: symptomatic HF (NYHA Class II–IV) of at least 4 weeks' duration, LVEF $\leq$ 40%, and intolerance to ACEi - Number: treatment group (1013), placebo (1015) - Mean age $\pm$ SD (years): treatment group (66.3 $\pm$ 11.0); control group (66.8 $\pm$ 10.5) - Sex (M/F): treatment group (691/322); control group (691/324) - CKD stage: not defined (excluded patients with SCr $\geq$ 265mmol/L) - DM: treatment group (27.4%); control group (26.6%) - Exclusion criteria: SCr $\geq$ 265 mmol/L; serum potassium $\geq$ 5.5 mmol/L or a history of marked ACEi-induced hyperkalaemia resulting in either a serum potassium $\geq$ 6.0 mmol/L or a life-threatening adverse event; known bilateral renal artery stenosis; current symptomatic hypotension; persistent systolic or diastolic hypertension; stroke, acute MI, 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 non-cardiac disease (e.g. cancer) that is likely to significantly shorten life expectancy to less than 2 years.
Interventions	Treatment group - Candesartan: 32 mg once/day Control group - Placebo
Outcomes	- CV death or unplanned admission to hospital for the management of worsening CHF - CV death, admission to hospital for CHF or non-fatal MI - CV death, admission to hospital for CHF, non-fatal MI, or non-fatal stroke - CV death, admission to hospital for CHF, non-fatal MI, non-fatal stroke, or coronary revascularization; death (any cause) or admission to hospital for CHF; and development of new diabetes
Notes	- Funding: AstraZeneca R&D - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
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CHARM-Alternative 2003 (Continued)

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	The assignment code being held by an independent centre and the data safety monitoring board.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up with no differences between groups; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in the analysis

CHARM-Preserved 2003

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: March 1999 to July 2000 (enrolment) - Duration of follow-up: 36.6 months (median)
Participants	- Countries: 26 - Setting: multicentre (number of sites not reported); outpatient - Inclusion criteria: symptomatic HF (NYHA Class II–IV) of at least 4 weeks' duration, LVEF > 40%, and not taking ACEi (pre-amendment) - Number: treatment group (1514); control group (1509) - Mean age $\pm$ SD (years): treatment group (67.2 ± 11.1); control group (67.1 ± 11.1) - Sex (M/F): treatment group (920/594); control group (891/618) - CKD stage: not defined (excluded patients with SCr ≥ 265 mmol/L) - DM: treatment group (28.7%); control group (28.0%) - Exclusion criteria: SCr ≥ 265 mmol/L; serum potassium ≥ 5.5 mmol/L or a history of marked ACEi-induced hyperkalaemia resulting in either a serum potassium ≥ 6.0 mmol/L or a life-threatening adverse event; known bilateral renal artery stenosis; current symptomatic hypotension; persistent systolic or diastolic hypertension; stroke, acute MI, 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 non-cardiac disease (e.g. cancer) that is likely to significantly shorten life expectancy to less than 2 years
Interventions	Treatment group - Candesartan: 32 mg once/day Control group - Placebo

CHARM-Preserved 2003 (Continued)

Outcomes	- CV death or unplanned admission to hospital for the management of worsening CHF - CV death, admission to hospital for CHF or non-fatal MI - CV death, admission to hospital for CHF, non-fatal MI, or non-fatal stroke - CV death, admission to hospital for CHF, non-fatal MI, non-fatal stroke, or coronary revascularization; death (any cause) or admission to hospital for CHF; and development of new diabetes.
Notes	- Funding: AstraZeneca R&D - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	The assignment code being held by an independent centre and the data safety monitoring board
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of patients lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in the analysis

CIBIS I 1994

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: March 1989 to August 1992 - Duration of follow-up: last follow-up visits took place between December 1992 and February 1993; 22.8 months (median)
Participants	- Countries: Europe - Setting: multicentre (number of sites not reported) - Inclusion criteria: CHF with or without sinus rhythm, and dyspnoea or fatigue corresponding to NYHA functional class III or IV; had to be ambulatory and not awaiting cardiac transplantation; mandatory background medication was diuretic and vasodilator therapy. LVEF (isotopic or angiographic performed within 4 weeks before randomisation) had to be < 40% - Number: treatment group (320); control group (321) - Mean age $\pm$ SD (years): treatment group (60.1 $\pm$ 1.2); control group (59.2 $\pm$ 1.1) - Sex (M/F): treatment group (264/56); control group (265/56) - CKD stage: not reported but SCr > 300 μmol/L was an exclusion criterion

CIBIS I 1994 (Continued)

- DM: not reported
- Exclusion criteria: included HF due to hypertrophic or restrictive cardiomyopathy with predominant left ventricular diastolic dysfunction; HF secondary to mitral or aortic valve disease that was not surgically repaired or had been surgically repaired for less than 6 months; patient with coronary heart disease awaiting bypass surgery or a recent history of MI (less than 3 months); patients already on a heart transplantation waiting list; nonambulatory patient with disabling permanent dyspnoea at rest; insulin-dependent diabetes; asthma; renal insufficiency (SCr > 300 µmol/L); hypothyroidism or hyperthyroidism; life expectancy was shortened by a severe illness such as a malignant disease; resting heart rate < 65 BPM; SBP <100 mm Hg or >160 mm Hg immediately before randomisation

Interventions	Treatment group • Bisoprolol: 1.25 to 5 mg/day Control group • Placebo
Outcomes	• Death • Tolerability of bisoprolol and analysis of all critical events
Notes	• Funding: Merck • Authors did not report screening information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally controlled by computerized interrogation and stratified by centre
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	To avoid any influence on non-death end points, all critical events were blinded as well as independently analysed and adjudicated on by the Critical Events Committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

CIBIS II 1997

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: not reported
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CIBIS II 1997 (Continued)

	Duration of follow-up: 1.3 years (mean)
Participants	- Countries: 18 European countries - Setting: multicentre (number of sites not reported); outpatient - Inclusion criteria: CHF (NYHA class III or IV, and LVEF $\leq$ 35%) - Total number of study participants (CKD cohort): 849 (32.1% of total cohort); treatment group (434); control group (415) - Median age, IQR (years) (CKD cohort): not reported - Sex (M/F) (CKD cohort): not reported - CKD stage (CKD cohort): eGFR $<$ 60 but not with kidney failure (excluded if SCr $>$ 300 mmol/L) - DM (CKD cohort): not reported - Exclusion criteria: uncontrolled hypertension; MI or unstable angina pectoris in the previous 3 months; PTCA or CABG in the previous 6 months; previous or scheduled heart transplant; atrioventricular block greater than first degree without a chronically implanted pacemaker; resting heart rate $>$ 60 BPM; SBP at rest $<$ 100 mm Hg; kidney failure (SCr $>$ 300 mmol/L); reversible obstructive lung disease; pre-existing or planned therapy with beta-adrenoreceptor blockers
Interventions	Treatment group - Bisoprolol: started at 1.25 mg/day, increased successively as per protocol (max of 10 mg/day) Control group - Placebo
Outcomes	- Death (any cause) - Hospitalisations (any cause) - CV death - HF hospitalisations - Combined endpoint (CV death or CV hospital admissions) - Permanent treatment withdrawals
Notes	- Secondary analysis - Funding: This study was sponsored by E Merck, Darmstadt - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by computer system
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias)	High risk	$>$ 10% lost to follow-up

CIBIS II 1997 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented
Other bias	High risk	Sponsor representation on the study committee

CIBIS III 2006

Methods	- Study design: investigator-initiated, multicentre, prospective, open-label, 2-parallel, blinded end point evaluation RCT - Study duration: October 2002 and May 2005 - Duration of follow-up: 18 months
Participants	- Countries: 18 Europe countries - Setting: multicentre (number of sites not reported); outpatient - Inclusion criteria: ≥ 65 years with mild to moderate CHF (NYHA class II or III, LVEF $\leq 35\%$), not taking ACEi, beta-blockers, or ARB - Number: treatment group 1 (505); treatment group 2 (505) - Mean age $\pm$ SD (years): treatment group 1 (72.4 ± 5.8); treatment group 2 (72.5 ± 5.7) - Sex (M/F): 689/321 - CKD: 18.0% - Baseline SCr: treatment group 1 (99.6 ± 26.1); treatment group 2 (101.9 ± 26.9) - DM: 20.6% - Exclusion criteria: treatment with an ACEi, ARB, or a beta-blocker for > 7 days during the 3 months before randomisation; acute coronary syndrome within 3 months before randomisation; PCI or coronary bypass surgery planned or performed within 3 months before randomisation; stroke within 1 month or with permanent neurological sequelae within 6 months before randomisation; heart rate at rest < 60 BPM without a functioning pacemaker; supine SBP < 100 mm Hg at rest; important electrolyte disturbances; SCr ≥ 220 mol/L; atrioventricular block greater than first degree without a functioning pacemaker; and obstructive lung disease contraindicating bisoprolol treatment
Interventions	Treatment group 1 - Bisoprolol first - Bisoprolol: 10 mg once/day for 6 months followed by combination of bisoprolol and enalapril for 6 to 24 months Treatment group 2 - Enalapril first - Enalapril: 10 mg twice/day for 6 months followed by combination of bisoprolol and enalapril for 6 to 24 months
Outcomes	- Combined primary end point of death (any cause) or hospitalisation - CV death - CV hospitalisation - Safety
Notes	- Funding: supported by Merck KGaA, Darmstadt, Germany - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
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CIBIS III 2006 (Continued)

Random sequence generation (selection bias)	Low risk	Random numbers produced by a dynamic balancing algorithm
Allocation concealment (selection bias)	Low risk	Treatment was allocated by telephone from the statistical centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded end point evaluation
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% withdrew from study
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	Sponsor involved in study conduct

Cice 1999a

Methods	- Study design: parallel, double-blind, placebo-controlled RCT - Study duration: April to December 1997 (recruitment) - Duration of follow-up: 3 months
Participants	- Country: Italy - Setting: single centre - Inclusion criteria: maintenance HD patients with diastolic HF and normal systolic function (ejection fraction > 40%) - Number: treatment group (24); control group (24) - Mean age $\pm$ SD: 46 $\pm$ 5 years - Sex (M/F): 29/19 - CKD stage: uraemic HD patients (5D) - DM: not reported - Exclusion criteria: ischaemic heart disease; valvular disease; inadequate ECG window; atrial fibrillation; contraindication to calcium channel blockers
Interventions	Treatment group - Diltiazem: 60 mg twice/day Control group - Placebo
Outcomes	Surrogates of cardiac function: LVMI, ejection fraction, BP, hypotensive episodes
Notes	Funding: not reported

Cice 1999a (Continued)

- Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Primary outcome not prespecified
Other bias	Unclear risk	Insufficient information to permit judgement

Cice 2001

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: February 1996 to December 1998 (recruitment) • Duration of follow-up: 12 months
Participants	• Country: Italy • Setting: not reported • Inclusion criteria: uraemia on periodic HD with dilated cardiomyopathy; all patients were symptomatic for HF (NYHA class II to III) for at least one year with LVEF < 35% • Number: treatment group (58); control group (56) • Mean age $\pm$ SD (years): treatment group (54.9 $\pm$ 8.1); control group (55.2 $\pm$ 7.1) • Sex (M/F): 69/45 • CKD stage: uraemic periodic HD patients • DM: not reported • Exclusion criteria: current NYHA functional class IV; heart rate < 50 BPM; sick sinus syndrome; first degree atrioventricular block with a PQ interval > 0.24 sec; second or third-degree heart block (unless controlled by a pacemaker); documented episodes of sustained ventricular tachycardia (> 30 sec, > 120 BPM); SBP < 90 mm Hg; stroke; acute MI; unstable angina; coronary angioplasty or aortocoronary bypass surgery in the 3 previous months; uncorrected valvular heart disease; active myocarditis; obstructive and restrictive cardiomyopathy; current treatment with verapamil, alpha/beta adrenergic agonists or antagonists; chronic obstructive airways disease; hepatic disease (serum transaminase > 3 times normal); drug or alcohol abuse; or any other life-threatening noncardiac disease
Interventions	Treatment group

Cice 2001 (Continued)

- Carvedilol: 25 mg twice/day or to the highest dose tolerated

Control group

- Placebo

Outcomes	• Changes in LVEDV, LVESV, and LVEF at 1, 6 and 12 months after randomisation • Changes in symptoms of HF 6 and 12 months after the randomisation • Death (any cause) • Hospitalisation for HF • CV death • Hospitalisation (any cause) • Composite endpoint (CV death plus acute non-fatal MI)
Notes	• Funding: not reported • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Cice 2010

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: January 1999 to January 2003 (enrolment) • Duration of follow-up: 3 years
Participants	• Country: Italy • Setting: multicentre (30 sites); outpatient • Inclusion criteria: chronic, congestive HF (NYHA class II and III, LVEF $\leq$ 40%); on ACEi; and CKD (on HD) • Number: treatment group (165); control group (167)

Cice 2010 (Continued)

- Mean age $\pm$ SD (years): treatment (62.7 ± 14.2); control group (62.7 ± 14.6)
- Sex (M/F): 179/153
- CKD stage: HD
- DM: 28.9%
- Exclusion criteria: hypotension during dialysis; atrial fibrillation; Intolerant to low dose of telmisartan

Interventions	Treatment group • Telmisartan: drug dosage was titrated to a target dose of 80 mg/day • ACEi Control group • Placebo • ACEi
Outcomes	• Death (any cause) • CV death • Hospitalisation for decompensated HF • Acute non-fatal MI • Combined endpoint (CV death in addition to acute non-fatal MI) • CV hospital admission • Nonfatal stroke • Coronary revascularization • Permanent premature treatment withdrawals • Hypotension • Plasma potassium
Notes	• Funding: sponsored by the University of Campania • Details on number screened unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocated through a computer-generated assignment program
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow-up; unclear if outcome data is presented on all patients randomised
Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented

Cice 2010 (Continued)

Other bias	Low risk	The study appears to be free of other sources of bias
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COMET 2003

Methods	- Study design: multicentre, double-blind, parallel RCT - Study duration: December 1996 to January 1999 (recruitment) - Duration of follow-up: 58 months (mean)
Participants	- Countries: 15 European countries - Setting: multicentre (341 sites) - Inclusion criteria: CHF (NYHA II–IV), previous admission for a CV reason, an ejection fraction of less than 0.35, and to have been treated optimally with diuretics and ACEi unless not tolerated - Number: treatment group 1 (1511); treatment group 2 (1518) - Mean age $\pm$ SD (years): treatment group 1 (61.6 $\pm$ 11.3); treatment group 2 (62.3 $\pm$ 11.4) - Sex (M/F): treatment group 1 (1200/311); treatment group 2 (1217/301) - CKD stage: not reported - DM: treatment group 1 (24%); treatment group 2 (24%) - Exclusion criteria: a recent change of treatment (introduction of a new class of drug for HF or treatment with oral -adrenergic or -adrenergic receptor blockers within the 2 weeks before randomisation); requirement for IV inotropic therapy; current treatment with calcium channel blockers (of the diltiazem or verapamil class), amiodarone (> 200 mg per day) or class-I anti-arrhythmic drugs, or administration of any investigational drug within the preceding 30 days; unstable angina, MI, coronary revascularization, or stroke within the previous 2 months; uncontrolled hypertension (SBP > 170 mm Hg or DBP > 105 mm Hg); haemodynamically significant valvular disease; symptomatic and sustained ventricular arrhythmias within the past 2 months not adequately treated with anti-arrhythmic drugs or implantation of an automatic defibrillator; pregnancy, women with childbearing potential on inadequate contraception; known drug or alcohol misuse; poor compliance with treatment or any other serious systemic disease that might complicate management and reduce life expectancy; contraindication to use of blockers, such as resting heart rate of fewer than 60 BPM, sick sinus syndrome, bifascicular block, second or third degree atrioventricular block unless treated with a pacemaker, sitting SBP < 85 mm Hg; history of asthma or chronic obstructive pulmonary disease, peripheral arterial disease with symptoms at rest, or unstable insulin-dependent DM
Interventions	Treatment group 1 - Carvedilol: target dose 25 mg twice/day Treatment group 2 - Metoprolol tartrate: target dose 50 mg twice/day
Outcomes	- Death (any cause) - Composite endpoint of death (any cause) or admission (any cause)
Notes	- Funding: day to day operations were managed initially by Boehringer Mannheim and later by F Hoffmann La Roche - Authors do not report the number of patients screened or reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement

COMET 2003 (Continued)

Allocation concealment (selection bias)	Low risk	Investigators at each site were supplied with numbered treatment kits and instructed to take the lowest numbered kit available for each new patient
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The blinded endpoint committee consisted of three cardiologists who assigned mode-of-death categorisations
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis.
Selective reporting (reporting bias)	Low risk	The study protocol is available. A primary endpoint was added to the protocol while the study was in progress due to findings reported from two related studies; however, this was without any knowledge of any interim results or treatment assignments
Other bias	High risk	Day to day operations were managed initially by Boehringer Mannheim and later by F Hoffmann La Roche

CONSENSUS 1987

Methods	- Study design: double-blind, placebo-controlled, parallel RCT - Study duration: April 1985 to December 1986 - Duration of follow-up: 12 months
Participants	- Countries: Finland, Norway, Sweden - Setting: multicentre (35 sites) - Inclusion criteria: severe congestive HF (NYHA functional class IV) - Number: treatment group (127); control group (126) - Mean age (years): treatment group (71); control group (70) - Sex (M): treatment group (70%); control group (71%) - CKD stage (mean SCr): treatment group (132 µmol/L); control group (124 µmol/L) - DM: treatment group (24%), control group (21%) - Exclusion criteria: acute pulmonary oedema; haemodynamically important aortic or mitral valve stenosis; MI within the previous two months; unstable angina; planned cardiac surgery; right HF due to pulmonary disease; SCr > 300 µmol/L
Interventions	Treatment group - Enalapril: target dose 20 mg twice/day Control group - Placebo
Outcomes	- Death (any cause) (6 months) and cause of death - Death (any cause) (12 months) - Overall death (during entire study period)
Notes	Funding: This study was supported by a grant from Merck Sharp and Dohme Research Laboratories

CONSENSUS 1987 (Continued)

- Authors do not report the number of patients screened or reasons for screen failure
- The study was terminated early due to an increased risk of death with placebo administration identified during an interim analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation of treatment
Allocation concealment (selection bias)	Unclear risk	Unclear if the fixed size of the block (2) was known to investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The cause of death was classified by two investigators independently
Incomplete outcome data (attrition bias) All outcomes	Low risk	The data were analysed according to the intention-to-treat principle; < 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	High risk	Sponsor was involved in the statistical analysis; study was stopped early without a formal stopping rule

COPERNICUS 2001

Methods	• Study design: large-scale, prospective, double-blind, placebo-controlled RCT • Study duration: October 1997 to March 2000 (stopped early) • Duration of follow-up: 10.4 months (mean)
Participants	• Countries: 21 • Setting: multicentre (334 sites); outpatient • Inclusion criteria: severe CHF as a result of ischaemic or non-ischaemic cardiomyopathy • Number: treatment group (1156); control group (1133) • Mean age: years ($\pm$ SD): treatment group (63.2 ± 11.4); control group (63.4 ± 11.5) • Sex (M): treatment group (79%); control group (80%) • CKD stage (mean SCr (μmol/L): treatment group (134 ± 37); control group (134 ± 36) • DM: not reported • Exclusion criteria: HF caused by uncorrected primary valvular disease or a reversible form of cardiomyopathy; received or were likely to receive a cardiac transplant; severe primary pulmonary, kidney, or hepatic disease; contraindication to beta-blocker therapy
Interventions	Treatment group • Carvedilol: target dose of 25 mg twice/day

COPERNICUS 2001 (Continued)

	Control group
	Placebo
Outcomes	- Death (any cause) - Combined risk of death or hospitalisation for any reason - Adverse effects
Notes	Funding: "Supported by grants from Roche Pharmaceuticals and GlaxoSmithKline. The trial was designed, executed, and analyzed by a steering committee, an end-points committee, a biostatistics center, and a data and safety monitoring board, all of whom operated independently of the sponsors"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; authors utilised an intention-to-treat design
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

CORONA 2005

Methods	- Study design: RCT - Study duration: September 2003 to April 2005. The study was stopped, as planned, on the date that 1422 primary events were anticipated (May 2007) - Duration of follow-up: 32.8 months (median)
Participants	- Countries: 19 European countries, Russia, South Africa - Setting: multicentre (371 sites) - Inclusion criteria: chronic NYHA class II, III, or IV HF of Ischaemic cause (as reported by investigators) and an ejection fraction of no more than 40% (no more than 35% in patients in NYHA class II) - Number: treatment group (2514); control group (2497) - Mean age $\pm$ SD (years): treatment group (73 ± 7.1); control group (73 ± 7.0) - Sex (M/F): treatment group (593/1921); control group (587/1910) - CKD stage (eGFR): treatment group (58 ± 15); control group (58 ± 15)

CORONA 2005 (Continued)

- % DM: treatment group (30); control group (29)
- Exclusion criteria: previous statin-induced myopathy or hypersensitivity reaction; decompensated HF or a need for inotropic therapy; MI within the past 6 months; unstable angina or stroke within the past 3 months; PCI, CABG, or the implantation of a cardioverter defibrillator or biventricular pacemaker within the past 3 months or a planned implantation of such a device; previous or planned heart transplantation; clinically significant, uncorrected primary valvular heart disease or a malfunctioning prosthetic valve; hypertrophic cardiomyopathy; acute endomyocarditis or myocarditis, pericardial disease, or systemic disease (e.g. amyloidosis); acute or chronic liver disease; levels of alanine aminotransferase or thyrotropin of more than 2 times the upper limit of the normal range; a SCr > 2.5 mg/dL (221 µmol/L); chronic muscle disease or an unexplained creatine kinase level of more than 2.5 times the upper limit of the normal range; previous treatment with cyclosporine; any other condition that would substantially reduce life expectancy or limit compliance with the protocol; or the receipt of less than 80% of dispensed placebo tablets during the run-in period

Interventions	Treatment group • Rosuvastatin: 10 mg/day Control group • Placebo
Outcomes	• Death from CV causes, nonfatal MI, or nonfatal stroke • Death (any cause), any coronary event, death from CV causes, and the number of hospitalisations
Notes	• Funding: AstraZeneca • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised interactive Web-based response system
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The data were analysed at the Statistical Data Analysis Center at the University of Wisconsin, Madison, independently of the sponsor, according to a predefined statistical analysis plan"
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor participated in study design and analysis

DAD-HF II 2014

Methods	- Study design: single blind RCT - Study duration: July 2009 to August 2012 - Duration of follow-up: 36 months
Participants	- Country: Greece - Setting: multicentre (4 sites) - Inclusion criteria: admitted for dyspnoea on minimal exertion or rest dyspnoea with an oxygen saturation < 90% on admission arterial blood gas, and had one or more of the following: a) signs of congestion (third heart sound or pulmonary rales > 1/3 or lower extremity/sacral oedema >1+ on examination, b) interstitial congestion or pleural effusion on chest X-ray, and c) serum BNP > 400 pg/mL or NT-proBNP > 1500 pg/mL - Number: treatment group 1 (50); treatment group 2 (56); control group (55) - Median age, IQR (years): treatment group 1 (77, 68 to 81); treatment group 2 (78, 65 to 82); control group (78, 67 to 82) - Sex (M/F): treatment group 1 (25/25); treatment group 2 (29/27); control group (33/22) - CKD stage (eGFR, mean, range; mL/min): treatment group 1 (53.1, 40.3 to 68.3); treatment group 2 (48.7, 36.4 to 70.5); control group (60.6, 43.8 to 73.4) - DM: treatment group 1 (48%); treatment group 2 (41%); control group (56%) - Exclusion criteria: SCr > 200 µmol/L or GFR <30 mL/min/1.73 m²; SBP < 90 mm Hg; severe valvular disease; known adverse reactions to furosemide or dopamine; complex congenital heart disease; anticipated need for IV contrast use; suspected or confirmed acute coronary syndrome on admission; scheduled cardiac surgery within 6 months
Interventions	Treatment group 1 - High-dose furosemide: 20 mg/hour Treatment group 2 - Low-dose furosemide: 5 mg/hour - low dose dopamine: 5 µg/kg/min Control group - Low-dose furosemide: 5 mg/hour
Outcomes	60-day and one-year post-discharge death (any cause) and recurrent hospitalizations for HF - In-hospital outcomes studied included dyspnoea relief, worsening kidney function during the first 24 hours and at SCr peak during hospitalisations, changes in dyspnoea, and length of hospital stay
Notes	- Funding: The study was not sponsored by industry support and was funded locally at participating sites - Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias)	High risk	Single-blind

DAD-HF II 2014 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators locally at the participating sites adjudicated all outcomes events and adverse events
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	< 10 % of lost to follow-up; insufficient information to permit judgement on intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

de Graeff 1989

Methods	- Study design: open, parallel design RCT - Study duration: not reported - Duration of follow-up: 3 months
Participants	- Country: The Netherlands - Setting: single centre - Inclusion criteria: severe restriction of physical activity or symptoms of dyspnoea or fatigue at rest for more than 3 months (NYHA functional class III-IV), despite adequate treatment with salt restriction, diuretics and digoxin - Number: treatment group (7); control group (6) - Mean age $\pm$ SD: 64 $\pm$ 3 years - Sex (M/F): 12/1 - CKD stage: not reported but CrCl < 30 mL/min was an exclusion criterion - DM: not reported - Exclusion criteria: acute MI or unstable angina pectoris within the preceding 6 weeks; SBP $\leq$ 90 mm Hg; severe valvular disease; CrCl < 30 mL/min
Interventions	Treatment group - Ramipril (oral): 5 to 10 mg twice/day Control group - Captopril (oral): 12.5 to 50 mg 3 times/day
Outcomes	- Death - Worsening HF - Adverse events
Notes	- Funding: not reported - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
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de Graeff 1989 (Continued)

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; insufficient information to permit judgement on intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

DIAMOND 1999

Methods	- Study design: double-blind, placebo- controlled RCT - Study duration: not reported - Duration of follow-up: 18 months
Participants	- Country: Denmark - Setting: multicentre (34 sites); outpatient - Inclusion criteria: hospitalised with worsening congestive HF - Total number of study participants (CKD cohort): 755 (49.7% of total cohort); treatment group (383); control group (372) - Mean age, range (years) (CKD cohort): not reported - Sex (M/F) (CKD cohort): not reported - CKD stage (CKD cohort): eGFR: 20 to 52.85 - DM (CKD cohort): not reported - Exclusion criteria: acute MI within 7 days of screening; heart rate < 50 BPM during walking; sinoatrial block or second- or third-degree atrioventricular block that was not treated with a pacemaker; history of drug-induced proarrhythmia; corrected QT interval exceeding 460 ms; DBP > 115 mm Hg or a SBP < 80 mm Hg; serum potassium < 3.6 mmol/L or > 5.5 mmol/L; recent use of class I or III anti-arrhythmic drugs; CrCl < 20 mL/min; serious liver dysfunction, acute myocarditis, planned cardiac surgery or angioplasty, aortic stenosis, cardiac surgery within the preceding four weeks; implantable cardioverter-defibrillator
Interventions	Treatment group - Dofetilide: twice/day for 18 months. Dose as per protocol Control group - Placebo

DIAMOND 1999 (Continued)

Outcomes	• Death (any cause) • CV death • Death from arrhythmia • Death from cardiac causes or successful resuscitation after cardiac arrest • Arrhythmias requiring treatment, worsening congestive HF • MI • Composite endpoint (first event of death, stroke, or arterial embolism)
Notes	• Funding: supported by a grant from Pfizer Central Research, Sandwich, United Kingdom • Authors report the number of patients screened, but no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	Rationale and design paper published
Other bias	Unclear risk	Insufficient information to permit judgement

DIG 1996

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: February 1991 to August 1993 (enrolment) • Duration of follow-up: 5 years
Participants	• Countries: Canada, USA • Setting: multicentre (320 sites); outpatient • Inclusion criteria: HF (LVEF $\leq$ 45%); and sinus rhythm • Total number of study participants (CKD cohort): 3157 (46.4% of total cohort); numbers per group not reported • Median age (years) (CKD cohort): eGFR < 30 (72); eGFR 30 to 60 (68) • Sex (M/F) (CKD cohort): 2263/894 • CKD stage (CKD cohort): eGFR < 60 but SCr $\leq$ 3.0 mg/dL

DIG 1996 (Continued)

- DM (CKD cohort): 74%
- Exclusion criteria: < 21 years; baseline LVEF not available; MI, cardiac surgery, or PTCA within 4 weeks; unstable or refractory angina < 1 month; II-III AV block without a pacemaker; atrial fibrillation (with or without pacemaker) or atrial flutter; cor pulmonale; constrictive pericarditis (such patients are eligible after surgery); acute myocarditis; hypertrophic cardiomyopathy; amyloid cardiomyopathy; complex congenital heart disease; pre-excitation syndromes; current treatment with IV inotropic agents; potassium < 3.2 mmol/L or > 5.5 mmol/L; need for cardiac surgery or PTCA in the near future; on heart transplant list; sick sinus syndrome without pacemaker; recognizable noncardiac causes of CHF; significant renal insufficiency (SCr > 3.0 mg/dL) or severe liver disease; any noncardiac disease that shortens life expectancy to less than 3 years; unlikely to comply with the protocol requirements for follow-up and drug adherence

Interventions	Treatment group • Digoxin: dose determined by investigator as per protocol • Standard therapy Control group • Placebo • Standard therapy
Outcomes	• Death (any cause) • CV death • Death to worsening HF • Hospitalisation for worsening HF • Hospitalisation for other causes • Composite endpoint (CV death or hospitalisation for HF)
Notes	• Funding: National Heart, Lung, and Blood Institute and the Department of Veterans Affairs • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% patients lost to follow-up; final analyses did not include total number of patients randomised
Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented

DIG 1996 (Continued)

Other bias Unclear risk Insufficient information to permit judgement

ELITE 1995

Methods	- Study design: prospective double-blind, parallel, captopril-controlled RCT - Study duration: May 1994 to July 1995; and follow-up was completed in June 1996 - Duration of follow-up: 11 months
Participants	- Countries: USA, Europe, South America - Setting: multicentre (125 sites) - Inclusion criteria: symptomatic HF (NYHA II–IV), decreased LVEF $\leq 40\%$, and no history of prior ACEi therapy - Number: treatment group (370); control group (352) - Mean age $\pm$ SD (years): treatment group (73 ± 6.1); control group (74 ± 5.8) - Sex (M/F): treatment group (248/122); control group (234/118) - CKD stage: not reported but SCr ≥ 221 mol/L (2.5 mg/dL) was an exclusion criterion - DM: treatment group (89%); control group (94%) - Exclusion criteria: SBP < 90 mm Hg or uncontrolled hypertension (DBP > 95 mm Hg); significant obstructive valvular disease or symptomatic ventricular or supraventricular arrhythmia; constrictive pericarditis or active myocarditis; cardiac surgery likely during study period or angioplasty within previous 72 hours; bypass surgery within 2 weeks, or implantable cardioverter defibrillator within 2 weeks; acute MI in previous 72 hours, unstable angina (requiring admission) within 3 months, or angina (requiring 5 glyceryl trinitrate tablets/week) within 6 weeks; stroke or transient Ischaemic attack in previous 3 months; digitalis toxicity; uncontrolled diabetes; chronic cough of any aetiology; untreated thyrotoxicosis or hypothyroidism; renal-artery stenosis; angio-oedema of any aetiology; haematuria of unknown aetiology; condition that would contraindicate a vasodilator; unlikely survival for length of study or risk to patient; SCr ≥ 221 mol/L (2.5 mg/dL); potassium < 3.5 or > 5.5 mmol/L; magnesium < 0.7 mmol/L; transaminases $>$ twice upper limit of normal; Hb < 10 g/dL or HCT $< 30\%$, WCC $< 3000 \times 10^6$/L, or platelets $< 100 \times 10^9$/L; another investigational drug in previous 4 weeks, inability to give informed consent, potentially noncompliant (e.g. alcohol or drug abuse); previous treatment with losartan or other angiotensin II antagonist
Interventions	Treatment group - Captopril: 6.25 mg titrated 25 to 50 mg, 3 times/day - Losartan placebo Control group - Losartan: 12.5 mg titrated to 25 to 50 mg, once/day - Captopril placebo
Outcomes	- Safety measure of kidney dysfunction, defined as an increase in SCr ≥ 26.5 μmol/L (≥ 0.3 mg/dL) from baseline (last measurement before randomisation) that was confirmed by a repeat measurement 5 to 14 days later, during continued treatment - Death (any cause) and hospital admission for HF were also prespecified endpoints - Composite of death and/or admission for HF was added as the secondary endpoint by protocol amendment on completion of patient participation in the study before unbinding - Admission to hospital for MI or unstable angina, worsening of HF (NYHA functional classification), withdrawal from the study due to study drug intolerance, and changes in neurohormonal profile
Notes	- Funding: Merck Research Laboratories - Authors did not report screening information

ELITE 1995 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised patients were stratified by age. Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All deaths (including cause of death) and hospital admissions were adjudicated on by an independent Clinical Endpoint Adjudication Committee, blinded to study treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Study was administered and coordinated by the sponsor

ELITE II 2000

Methods	- Study design: double-blind, randomised, controlled RCT - Study duration: June 1997 to May 1998 (enrolment) - Duration of follow-up: 555 days (median)
Participants	- Countries: 46 - Setting: multicentre (289 sites) - Inclusion criteria: aged ≥ 60 years (required that 85% be aged > 65 years); NYHA class II–IV HF; LVEF $\leq 40\%$ - Number: treatment group (1578); control group (1574) - Mean age $\pm$ SD (years): treatment group (71.4 ± 6.7); control group (71.5 ± 6.9) - Sex (M/F): treatment group (1102/475); control group (1083/491) - CKD stage: not reported (but excluded if SCr $> 220 \mu\text{mol/L}$) - DM: 24% - Exclusion criteria: intolerance of ACEi or ARB; SBP < 90 mm Hg; DBP > 95 mm Hg; haemodynamically important stenotic valvular heart disease; active myocarditis or pericarditis; automatic implanted cardioverter defibrillators; coronary angioplasty within 1 week of enrolment; CABG, acute MI, or unstable angina pectoris within 2 weeks of enrolment; cerebrovascular accident or transient ischaemic attack within 6 weeks of enrolment; documented or suspected significant renal artery stenosis; haematuria; and SCr $> 220 \mu\text{mol/L}$
Interventions	Treatment group Losartan: 50 mg once/day Control group

ELITE II 2000 (Continued)

- Captopril: 50 mg 3 times/day

Outcomes	• Death (any cause) (primary) • Composite of sudden cardiac death or resuscitated cardiac arrest • Hospital admission (any cause and cause-specific CV admissions) • Composite variables (assessed by time to first event) of death (any cause) or hospital admissions (any cause)
Notes	• Funding: This study was funded by Merck Research Laboratories • Authors do not report the number of patients screened or reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but not information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Results were reviewed and classified, according to prespecified criteria, by an independent clinical endpoint classification committee, unaware of treatment status
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported
Other bias	Low risk	The study appears to be free of other sources of bias

EMPHASIS-HF 2010

Methods	• Study design: double-blind, placebo- controlled RCT • Study duration: March 2006 to May 2010 (enrolment) • Duration of follow-up: 21 months (median)
Participants	• Countries: 29 • Setting: multicentre (278 sites); outpatients • Inclusion criteria: HF (NYHA class II, LVEF $\leq$ 30%) and on ACEi and/or ARBs and beta-blockers • Total number of study participants (CKD cohort): 912 (33.3% of total cohort); treatment group (439); control group (473) • Mean age $\pm$ SD (years) (CKD cohort): not reported • Sex (M/F) (CKD cohort): not reported • CKD stage (CKD cohort): eGFR: 30 to 60 mL/min/1.73 m² • DM (CKD cohort): not reported

EMPHASIS-HF 2010 (Continued)

- Exclusion criteria: Acute MI; NYHA class III or IV HF; Serum potassium level >5.0 mmol/L; eGFR < 30 mL/min/1.73 m²; need for a potassium-sparing diuretic; any other clinically significant, coexisting condition

Interventions	Treatment group • Eplerenone: up to 50 mg/day as per protocol in addition to recommended therapy Control group • Placebo in addition to recommended therapy
Outcomes	• Composite of CV death or hospitalisation for HF • Hospitalisation for HF or death (any cause) • Death (any cause) • CV death • Hospitalisation (any cause) • Hospitalisation for HF • Hyperkalaemia • Hypotension
Notes	• Funding: Pfizer • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by automated computer system
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	Study is registered, protocol paper published
Other bias	Unclear risk	Insufficient information to permit judgement

Erb 2014

Methods	• Study design: double-blind, single-centre, prospective, placebo-controlled RCT • Study duration: March 2008 to December 2009
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Erb 2014 (Continued)

	Duration of follow-up: 19 months
Participants	- Country: Germany - Setting: single centre - Inclusion criteria: ischaemic cardiomyopathy scheduled for elective CABG surgery with or without valve surgery, with LVEF $\leq 30\%$ (diagnosed by preoperative ECG or fluoroscopy during coronary catheterization) - Number: treatment group (19); control group (18) - Mean age $\pm$ SD (years): treatment group (69.5 ± 11.5); control group (63.4 ± 7.8) - Sex (M/F): treatment group (13/4); control group (15/1) - CKD stage: not reported - DM: treatment group (41%); control group (50%) - Exclusion criteria: pregnancy and/or breast feeding; liver insufficiency Child–Pugh class B or C or Model for End-stage Liver Disease > 17; disease or recent operation (< 2 months prior) of the oesophagus or upper airway; neurological or psychiatric disorder; DM treated with sulphonylurea drugs; HIV infection; hepatitis B or C infection; alcohol abuse.
Interventions	Treatment group - Levosimendan: 12.5 mg Control group - Placebo
Outcomes	- SOFA scores (ranging between 4 and 24) on postoperative days 0–3 - Haemodynamic parameters - Need for vasoactive medication - Need for HD - ICU length of stay 30-day and 6-month survival - HRQoL at 6 months post-operation
Notes	- Funding: none - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	High risk	$< 10\%$ of lost to follow-up; final analyses did not included total number of patients randomised

Erb 2014 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

EVEREST 2005

Methods	- Study design: event-driven, double-blind, placebo-controlled RCT - Study duration: October 2003 to February 2006 (enrolment) - Duration of follow-up: 9.9 months (median)
Participants	- Countries: multiple (North America, South America, Europe) - Setting: multicentre (359 sites); outpatient - Inclusion criteria: hospitalised for worsening HF with evidence of systemic congestion and reduced LVEF - Total number of study participants (CKD cohort): 1646 (39.8% of total cohort); treatment group (827); control group (819) - Mean age $\pm$ SD (years) (CKD cohort): not reported - Sex (M/F) (CKD cohort): not reported - CKD stage (CKD cohort): SCr 1.3 to 3.5 mg/dL - DM (CKD cohort): not reported - Exclusion criteria: cardiac surgery within 60 days of enrolment; cardiac mechanical support, biventricular pacemaker placement within the last 60 days; comorbid conditions with an expected survival of < 6 months; Acute MI at the time of hospitalisation; haemodynamically significant uncorrected primary cardiac valvular disease; refractory end-stage HF; haemofiltration or dialysis; supine SBP < 90 mm Hg; SCr level > 3.5 mg/dL (309 μmol/L); serum potassium > 5.5 mEq/L; Hb level < 9 g/dL
Interventions	Treatment group - Tolvaptan: 30 mg once/day for a minimum of 60 days Control group - Placebo
Outcomes	- Death (any cause) - CV death - Hospitalisation for HF - Combined endpoint (CV death or subsequent hospitalisation for worsening HF) - Hyperkalaemia - Hypotension - Changes in dyspnoea, body weight, and oedema - QoL
Notes	- Funding: Otsuka Inc funded the EVEREST study under the guidance of the EVEREST steering committee. The data collection and management for this study was by Otsuka; analysis was by University of Wisconsin Statistical Data Analysis Center and Otsuka; and administrative and material support was by Otsuka - Authors report the number of patients screened, but no further details

Risk of bias

EVEREST 2005 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	Study is registered, protocol paper published
Other bias	High risk	Study sponsor (Otsuka) responsible for data collection and management, participated in the data analysis, and provided administrative and material support

EXACT-HF 2013

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: May 2010 to June 2013 - Duration of follow-up: 6 months
Participants	- Countries: USA, Canada - Setting: multicentre (38 sites) - Inclusion criteria: symptomatic HF due to LVEF $\leq$ 40% and elevated serum uric acid ($\geq$ 9.5 mg/dL); have at least 1 additional high-risk marker, including an acute HF event (hospitalisation or emergency department visit) within 12 months, severe LV dysfunction (LVEF $\leq$ 25%), or an elevated natriuretic peptide level (BMP >250 pg/mL or NT-proBNP > 1500 pg/mL) - Number: treatment group (128); control group (125) - Median age, IQR (years): treatment group (63, 54 to 74); control group (63, 52 to 71) - Sex (M/F): treatment group (110/86); control group (98/78) - CKD stage (eGFR): treatment group (50.9, 40.4 to 66.4); control group (53.7, 39.8 to 70.2) - DM: treatment group (57%); control group (52%) - Exclusion criteria: eGFR < 20 mL/min
Interventions	Treatment group - Allopurinol: 300 to 600 mg/day Control group - Placebo

EXACT-HF 2013 (Continued)

Outcomes	• Composite clinical end point that classified a subject's clinical status as improved, worsened, or unchanged at 24 weeks, as previously described. This classification follows sequential rules based on: death; hospitalisation, emergency department visit or emergent clinic visit for worsening HF; medication change for worsening HF (e.g., addition of a new drug class or an increase in diuretic dose by at least 50% for >1 week); and Patient Global Assessment using a 7-point scale • 12 and 24 weeks included changes in QoL assessed by the Kansas City Cardiomyopathy Questionnaire and submaximal exercise capacity assessed by 6-minute walk test • ECG measures of LV remodelling including LV volumes, mass, and ejection fraction measured in a core laboratory (Mayo Clinic), biomarker including uric acid, NT-proBNP, cystatin C, and myeloperoxidase measured in a core laboratory (University of Vermont), and time to first HF hospitalisation (as determined by the investigator) and time to all-cause death or hospitalisation
Notes	• Funding: National Institutes of Health: NHLBI; the National Center for Advancing Translational Sciences; and the National Institute on Minority Health and Health Disparities.\ • Authors did not report screening information.\

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Permuted block randomisation scheme stratified by clinical site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Fuchs 1995

Methods	• Study design: prospective, double-blind RCT • Study duration: not reported • Duration of follow-up: 3 months
Participants	• Country: Germany • Setting: multicentre (11 sites) • Inclusion criteria: CHF, NYHA (NYHA) class III or IV • Number: treatment group (19); control group (10) • Mean age $\pm$ SD (years): not reported

Fuchs 1995 (Continued)

- Sex (M/F): treatment group (14/5); control group (9/1)
- CKD stage: not reported
- DM: not reported
- Exclusion criteria: arterial hypotension; exercise tolerance limited by symptoms due to conditions other than CHF (such as angina pectoris, intermittent claudication, or dyspnoea as a result of pulmonary disease); other relevant cardiac disease

Interventions	Treatment group • Delapril (oral): 7.5 or 15 to 30 mg, twice/day Control group • Captopril (oral): 12.5 or 25 to 50 mg, twice/day
Outcomes	• Changes in this classification involving exercise work, haemodynamic variables (mean pulmonary arterial pressure, pulmonary capillary wedge pressure, mean right arterial pressure, and cardiac output), as well as changes in left ventricular diameters (end-diastolic and end-systolic), Kostuk's classification (X-thorax), clinical signs and symptoms, and investigator's assessment of overall effect (general state and symptomatic effect) • Adverse events
Notes	• Funding: Takeda Pharma GmbH • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Placebo tablets for this double-dummy study were taste to Delapril and Captopril
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% lost to follow-up; not all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

FUSION I 2004

Methods	• Study design: multicentre, open-label, pilot RCT
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FUSION I 2004 (Continued)

- Study duration: December 2001 to February 2003
- Duration of follow-up: 3 months of treatment with an additional 4 weeks of follow-up

Participants	• Country: USA • Setting: multicentre (46 sites) • Inclusion criteria: HF classified as NYHA class III or IV for ≥ 60 days before randomisation' had a 6-minute walk test result of < 400 m, and had ≥ 2 hospital admissions (or unscheduled outpatient visits requiring IV vasoactive treatment) for acutely decompensated HF within the preceding 12 months • Number: treatment group 1 (72); treatment group 2 (69); control group (69) • Mean age $\pm$ SD (years): treatment group 1 (67 ± 12); treatment group 2 (68 ± 14); control group (67 ± 12) • Sex (M/F): treatment group 1 (49/23); treatment group 2 (46/23); control group (51/18) • CKD stage (SCr, mg/dL) treatment group 1 (1.8 ± 0.71); treatment group 2 (1.8 ± 0.69); control group (1.8 ± 0.70) • DM: treatment group 1 (57%); treatment group 2 (49%); control group (45%) • Exclusion criteria: SBP < 90 mm Hg; undergone placement of a biventricular pacemaker in the preceding 60 days; undergone placement of an implantable cardioverter-defibrillator in the preceding 30 days; receiving long-term dialysis or were likely to require dialysis during the 4-month study period; evidence of acute MI within the preceding 30 days; unable to complete a 6-minute walk test; received or were awaiting an organ transplantation
Interventions	Treatment group 1 • Nesiritide: 0.005 g/kg/min Treatment group 2 • Nesiritide: 0.01 g/kg/min Control group • Usual care
Outcomes	• To assess the safety and tolerability of different Nesiritide doses administered as serial outpatient infusions • Safety and tolerability were measured through an investigator's reporting of adverse events; serious adverse events, discontinuations of study infusions, laboratory assessments, and vital signs. Serious adverse events were those that led to hospitalisation, prolonged hospitalisation, or death • Surrogate measures with mechanistic implications included measures of serum aldosterone, serum endothelin-1, and serial measurements of ventricular function by using ejection fractions derived from ECG
Notes	• Funding: Scios, Inc • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

FUSION I 2004 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

FUSION II 2008

Methods	- Study design: phase IIB, prospective, parallel, double-blind RCT - Study duration: April 2004 to June 2006. Follow-up ended in December 2006 - Duration of follow-up: 3 months
Participants	- Countries: North, Central, and South America, Australia, Russia, India, and the Pacific Rim - Setting: multicentre (190 sites) - Inclusion criteria: 2 HF hospitalisations or the equivalent within 12 months, with the most recent within the prior 60 days; LVEF < 40% within 24 weeks; investigator documentation of consistent NYHA class III or IV symptoms during the previous 60 days; estimated CrCl < 60 mL/min calculated by the Cockcroft-Gault equation; 24-hour urine collection was also required for NYHA class III patients - Number: treatment group 1 (307); treatment group 2 (306); control group 1 (153); control group 2 (154) - Mean age $\pm$ SD (years): not reported per individual group - Sex (M/F): not reported per individual group - CKD stage: eGFR < 60 mL/min - DM: not reported per individual group - Exclusion criteria: SBP < 90 mm Hg; dependence on (or inability to discontinue) intermittent or continuous IV vasoactive medications; > 2 outpatient infusions of vasoactive therapy within 30 days without a hospitalisation; biventricular pacemaker within 45 days or a single- or dual-chamber pacemaker; implantable cardioverter-defibrillator within 15 days; cardiogenic shock or volume depletion; chronic dialysis
Interventions	Treatment group 1 - Nesiritide: 2 g/kg bolus, followed by an infusion of 0.01 g/kg, once/week Treatment group 2 - Nesiritide: 2 g/kg bolus, followed by an infusion of 0.01 g/kg, twice/week Control group 1 - Usual care: once/week Control group 1 - Usual care: twice/week
Outcomes	- Death (any cause) or the first hospitalisation for CV or renal causes from randomisation (week 12) - Number of CV and renal hospital admissions; days alive and out of the hospital; and time to CV death (week 12) - QoL

FUSION II 2008 (Continued)

- Worsening kidney function*
- Hypotension

*Unable to estimate the risk ratio of worsening kidney function as the proportion of patients was reported and details on the number of patients included in analysis with creatinine measured not reported

- | | |
|-------|---|
| Notes | <ul style="list-style-type: none"> • Funding: Scios, Inc • Authors did not report screening information |
|-------|---|

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of an interactive voice response system
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All deaths and hospitalizations were adjudicated by a blinded clinical events committee that used predefined criteria to classify events
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	High risk	Outcomes reported in treatment groups combined and control group combined
Other bias	Unclear risk	Insufficient information to permit judgement

Giles 1989

- | | |
|--------------|--|
| Methods | <ul style="list-style-type: none"> • Study design: parallel, double-blind RCT • Study duration: not reported • Duration of follow-up: 3 months |
| Participants | <ul style="list-style-type: none"> • Country: USA • Setting: multicentre (16 sites) • Inclusion criteria: NYHA class II, III or IV and had remained symptomatic despite therapy with digoxin and diuretics • Number: treatment group (94); control group (95) • Mean age (years): treatment group (61.3); control group (59.1) (SD not reported) • Sex (M/F): treatment group (71/23); control group (77/18) • CKD stage: not reported • DM: treatment group (not reported); control group (2.1%) • Exclusion criteria: history of captopril intolerance; recent unstable angina; MI or cerebrovascular accident; clinically important kidney, hepatic or hematologic disorders; hyperkalaemia or hypokalaemia; |

Giles 1989 (Continued)

predominant cor pulmonale and haemodynamically significant aortic stenosis; SBP < 80 mm Hg; evidence of digitalis toxicity; receiving other investigational therapy; abusers of alcohol or recreational drugs

Interventions	Treatment group - Lisinopril (oral): 5 to 20 mg once/day Control group - Captopril (oral): 12.5 to 50 mg 3 times/day
Outcomes	- Functional assessment and QoL - NYHA functional class (determined by the investigator throughout the study) - Patient's global evaluation of response (patient assessment) - Yale Scale dyspnoea/fatigue index - Radiologic tests - Cardiothoracic ratio as measured on posteroanterior chest roentgenogram - LVEF by gated radionuclide scan - Congestive HF symptoms: orthopnoea, paroxysmal nocturnal dyspnoea - Congestive HF signs: rales, oedema, third heart sound, jugular venous distension, weight and heart rate
Notes	- Funding: Merck Sharp & Dohme Research Laboratories - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	An independent data and safety monitoring board was established to oversee the safety
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

GISSI-HF 2004

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: August 2002 to February 2005 - Duration of follow-up: median of 46.8 months (IQR 36 to 54)
Participants	- Country: Italy - Setting: multicentre (357 sites) - Inclusion criteria: clinical evidence of HF of any cause that was classified according to the European Society of Cardiology guidelines as NYHA class II–IV, provided that they had their LVEF measured within 3 months before enrolment; when LVEF > 40%, the patient had to have been admitted at least once to hospital for HF in the preceding year - Number: treatment group (3529); control group (3517) - Mean age $\pm$ SD (years): treatment group (67 ± 11); control group (67 ± 11) - Sex (M/F): treatment group (2717/777); control group (2742/739) - CKD stage: not reported - DM: treatment group (28.4%); control group (28.2%) - Exclusion criteria: specific indication or contraindication to n-3 PUFA; known hypersensitivity to study treatments; presence of any non-cardiac comorbidity (e.g. cancer) that was unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomisation; acute coronary syndrome or revascularization procedure within the preceding 1 month; planned cardiac surgery, expected to be done within 3 months after randomisation; significant liver disease; pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant
Interventions	Treatment group - n-3 PUFA: 1 g/day Control group - Placebo
Outcomes	- Time to death, and time to death or admission to hospital for CV reasons - CV death, CV death or admission for any reason, sudden cardiac death, admission for any reason, admission for cardio vascular reasons, admission for HF, MI, and stroke
Notes	- Funding: Società Prodotti Antibiotici (SPA; Italy), Pfizer, Sigma Tau, and AstraZeneca - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised telephone randomisation system
Allocation concealment (selection bias)	Unclear risk	Concealed randomisation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

GISSI-HF 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	Sponsor not involved in the analysis

HEAAL 2008

Methods	- Study design: event-driven, double-blind RCT - Study duration: November 2001 to March 2005 (enrolment) - Duration of follow-up: 4.7 years (median)
Participants	- Country: 30 - Setting: multicentre (255 sites); outpatient - Inclusion criteria: HF (NYHA class II-IV, LVEF ≤ 40%); stable CV medical therapy for at least 2 weeks; and known intolerance to ACEi - Total number of study participants (CKD cohort): 764 (19.9% of total cohort); treatment group (395); control group (369) - Mean age, range (years) (CKD cohort): not reported - Sex (M/F) (CKD cohort): not reported - CKD stage (CKD cohort): eGFR < 60; SCr > 220 µmol/L - DM (CKD cohort): not reported - Exclusion criteria: pregnancy or lactation; known intolerance to ARBs; SBP < 90 mm Hg; haemodynamically significant stenotic valvular heart disease; active myocarditis; active pericarditis; planned heart transplantation within 6 months; coronary angioplasty, CABG surgery, acute MI, unstable angina pectoris, cerebrovascular accident, or transient ischaemic attack within the previous 12 weeks; documented or suspected significant renal artery stenosis; contraindication to a vasodilator; life-limiting disease other than HF; mental or legal incapacitation; drug or alcohol misuse within the previous 2 years; participation in any investigative drug study in the previous 4 weeks; SCr > 220 µmol/L; serum potassium < 3.5 mmol/L or > 5.7 mmol/L; hepatic enzymes of more than 3 times the normal range; Hb < 6.2 mmol/L
Interventions	Treatment group - Losartan: 150 mg/day Control group - Losartan: 50 mg/day
Outcomes	- Composite (death or admission for HF) - Composite (death or CV admission) - Death - Death or all-cause admission - CV death - All-cause admission - CV admission - Admission for HF - Changes in the severity of heart disease (change in NYHA functional class, angioedema) - Hyperkalaemia - Hypotension

HEAAL 2008 (Continued)

- Worsening kidney failure

Notes

- Funding: Merck & Co, Inc. Whitehouse Station, NJ, USA
- Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked and stratified randomisation
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% patients lost to follow up; not all patients randomised included in final analysis (12 excluded for poor data quality)
Selective reporting (reporting bias)	Low risk	Study is registered, protocol paper published
Other bias	High risk	Sponsor involved in statistical analysis

HORIZON-HF 2008

Methods	• Study design: double-blind, placebo-controlled, dose-escalation RCT • Study duration: August 2006 to July 2007 • Duration of follow-up: 11 months
Participants	• Countries: Poland, Romania, Greece • Setting: multicentre (3 cohorts) • Inclusion criteria: LVEF $\leq$ 35%; hospitalised with HF; heart rate (HR) < 110 and > 60 BPM; on standard HF therapy • Number: treatment group 1 (29); treatment group 2 (30); treatment group 3 (30); control group (31) • Mean age $\pm$ SD (years): treatment group 1 (54 $\pm$ 11); treatment group 2 (56 $\pm$ 11); treatment group 3 (54 $\pm$ 11); control group (57 $\pm$ 11) • Sex (M/F): treatment group 1 (26/3); treatment group 2 (26/4); treatment group 3 (28/2); control group (25/6) • CKD stage: not reported but SCr > 3.0 mg/dL was an exclusion criterion • DM: treatment group 1 (31%); treatment group 2 (10%); treatment group 3 (13%); control group (16%) • Exclusion criteria: use of IV inotropes; serum digoxin > 0.5 ng/mL; recent acute coronary syndromes or coronary revascularization; atrial fibrillation; left bundle branch block; implanted electrical devices; SCr > 3.0 mg/dL; severe liver enzyme abnormalities
Interventions	Treatment group

HORIZON-HF 2008 (Continued)

- Istaroxime (IV): 0.5 µg/kg/min

Treatment group

- Istaroxime (IV): 1 µg/kg/min

Treatment group

- Istaroxime (IV): 1.5 µg/kg/min

Control group

- Placebo

Outcomes	- Change in pulmonary capillary wedge pressure compared with placebo after a 6-h continuous infusion - Changes in cardiac index, right atrial pressure, SBP, DBP, HR, and stroke work index - Changes in LVEF, LVEDV, LVESV, diastolic function indexes, neurohormones, kidney function, troponin, pharmacokinetics, safety
Notes	- Funding: Sigma-Tau i.f.r., SpA - Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centrally randomised; insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all participants randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

I-PRESERVE 2008

Methods	- Study design: placebo-controlled RCT - Study duration: June 2002 to April 2005 - Duration of follow-up: 49.5 months (mean)
Participants	Countries: 25

I-PRESERVE 2008 (Continued)

- Setting: multicentre (293 sites)
- Inclusion criteria: ≥ 60 years; HF symptoms and a LVEF $\geq 45\%$. patients hospitalised for HF during the previous 6 months and have current NYHA class II, III, or IV symptoms with corroborative evidence
- Number: treatment group (2067); control group (2061)
- Mean age $\pm$ SD (years): treatment group (72 ± 7); control group (72 ± 7)
- Sex (M/F): treatment group (840/1227); control group (797/1264)
- CKD stage (eGFR): treatment group (72 ± 23); control group (72 ± 22)
- DM: treatment group (28%); control group (27%)
- Exclusion criteria: previous intolerance to ARB; an alternative probable cause of the patient's symptoms (e.g., significant pulmonary disease); any previous LVEF $< 40\%$; a history of acute coronary syndrome, coronary revascularization, or stroke within the previous 3 months; substantial valvular abnormalities; hypertrophic or restrictive cardiomyopathy; pericardial disease; cor pulmonale or other cause of isolated right HF; a SBP < 100 mm Hg or > 160 mm Hg or a DBP > 95 mm Hg despite antihypertensive therapy; other systemic disease limiting life expectancy to < 3 years; substantial laboratory abnormalities (such as a Hb < 11 g/dL, SCr > 2.5 mg/dL (221 μ mol/L), or liver-function abnormalities); characteristics that might interfere with compliance with the study protocol

Interventions	Treatment group • Irbesartan: 75 to 300 mg once/day Control group • Placebo
Outcomes	• Composite of death from any cause or hospitalisation for a protocol-specified CV cause • Death from any cause and hospitalisation for CV causes • Death due to worsening HF or sudden death or hospitalisation due to worsening HF • Change in the total score on the Minnesota Living with HF scale at 6 months • Change in the plasma level of NT-proBNP at 6 months • Death from CV causes, nonfatal MI, or nonfatal stroke • Death from CV causes
Notes	• Funding: supported by Bristol-Myers Squibb and Sanofi-Aventis • Authors report the number of patients screened, but no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomisation schedule was implemented with the use of an interactive voice-response system
Allocation concealment (selection bias)	Unclear risk	The randomisation block size was two and was stratified according to site. Patients were also stratified according to their use of an ACEi at randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Deaths and hospitalizations were adjudicated by members of an independent end-point committee who were unaware of study-group assignments and used prespecified criteria
Incomplete outcome data (attrition bias)	High risk	$> 10\%$ lost to follow-up

I-PRESERVE 2008 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	Sponsor not involved in the analysis

Jia 2015

Methods	- Study design: single-blind RCT - Study duration: not reported - Duration of follow-up: 3 months for survival - 9 day for primary endpoint
Participants	- Country: China - Setting: single centre; inpatient - Inclusion criteria: level III or IV cardiac function, as assessed using the NYHA cardiac functional grading system; 1 or both of the following symptoms: (1) dyspnoea at rest and/or the need for mechanical ventilation to treat ADHF or (2) oliguria that was not the result of hypovolaemia; in addition, selected patients had to have an LVEF that was ≤ 0.35, as shown by 2-dimensional ECG, and BNP > 400 pg/mL - Number: treatment group 1 (30); treatment group 2 (30); treatment group 3 (30); control group (30) - Mean age $\pm$ SD (years): treatment group 1 (65.6 ± 11.6); treatment group 2 (72.2 ± 12.4); treatment group 3 (68.1 ± 12.3), control group (68.0 ± 10.5) - Sex (M/F): treatment group 1 (17/13); treatment group 2 (16/14); treatment group 3 (21/9), control group (16/14) - CKD stage (SCr): treatment group 1 (1.09 ± 0.38); treatment group 2 (1.17 ± 0.47); treatment group 3 (1.36 ± 0.46), control group (1.25 ± 0.58) - DM: treatment group 1 (43.3%); treatment group 2 (36.7%); treatment group 3 (50%), control group (33.3%) - Exclusion criteria: < 18 years; childbearing potential; HF because of restrictive or hypertrophic cardiomyopathy or uncorrected stenotic valvular disease; suffered an acute MI during the previous 14 days or a refractory angina at the time of randomisation; sustained ventricular tachycardia or ventricular fibrillation or 2nd- or 3rd degree atrioventricular block; resting heart rate > 120 BPM or SBP < 85 mm Hg; patients with severe kidney failure (SCr > 450 mmol/L); hepatic failure; cardiac tamponade; adult respiratory distress syndrome; septic shock
Interventions	Treatment group 1 - Levosimendan: $0.1 \mu\text{g/kg/min}$ for 24 hours Treatment group 2 - Nesiritide (IV): 2 mg/kg followed by a continuously injected dose of $0.01 \mu\text{g/kg/min}$ for the next 72 hours Treatment group 3 - Levosimendan - Nesiritide Control group - Placebo
Outcomes	- Dyspnoea, pulmonary congestion, oedema and NYHA functional class - Survival
Notes	Funding: Government

Jia 2015 (Continued)

- Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were unaware of patient treatment allocation at the time of assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised were included in the final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

Kum 2008

Methods	- Study design: RCT - Study duration: not reported - Duration of follow-up: 12 months
Participants	- Country: Hong Kong - Setting: single centre; inpatient - Patients: CHF patients on stable doses of ACEi - Number: treatment group (25); control group (25) - Mean age $\pm$ SD (years): treatment group (66.0 ± 11.3); control group (68.9 ± 9.5) - Sex (M/F): treatment group (19/6); control group (17/8) - CKD stage (SCr): 1.927 ± 0.288 - DM: treatment group (32%) control group (40%) - Exclusion criteria: recent acute coronary syndrome; recent PCI or recent HF decompensation within 3 months of study enrolment; patients with major systemic illness; and patients with malignancy or disease with survival likely < 1 year
Interventions	Treatment group Add-on therapy: irbesartan 300 mg/day Control group

Kum 2008 (Continued)

- Continuation of conventional therapy

Outcomes	Serial clinical and echocardiographic assessment
Notes	- Funding: not reported - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	The patients were aware of the treatment assignment since we did not use placebo tablets for those assigned to conventional therapy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staffs involved in the assessment of these clinical and echocardiographic parameters were blinded of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised were included in the final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

MDC 1993

Methods	- Study design: placebo-controlled parallel RCT - Study duration: September 1986 to July 1991 (enrolment) - Duration of follow-up: 18 months
Participants	- Countries: Europe, North America - Setting: multicentre (33 sites) - Inclusion criteria: aged 16 to 75 years; symptomatic idiopathic dilated cardiomyopathy; ejection fraction < 40% - Number: treatment group (194); control group (189) - Mean age $\pm$ SD (years): treatment group (49 ± 12); control group (49 ± 12) - Sex (M): treatment group (70%); control group (75%) - CKD stage (mean SCr): 101 μmol/L - DM: not reported - Exclusion criteria: treatment with beta-blockers, calcium-channel blockers, inotropic agents (except digitalis), or high doses of tricyclic antidepressant drugs; significant coronary artery disease shown by angiography, clinical or histological signs of ongoing myocarditis; other life-threatening diseases;

MDC 1993 (Continued)

obstructive lung disease requiring beta-2-agonists; excessive alcohol consumption; drug abuse; insulin-dependent diabetes; phaeochromocytoma and thyroid disease

Interventions	Treatment group - Metoprolol: 100 to 150 mg/day Control group - Matched placebo
Outcomes	- Combined primary endpoint (death (any cause) and clinical deterioration to a point at which cardiac transplantation would normally be offered as a treatment option) - Cardiac function, exercise capacity, QoL, and hospital admission or emergency visits for HF treatment
Notes	- Funding: study supported by Astra Hassle AB, Molndal, Sweden, Astra GmbH, Linz, Austria, Astra Chemicals GmbH, Wedel, Germany, Astra Pharmaceutica BV, Rijswijk, Netherlands, Ciba-Geigy Corporation, USA, Swedish Heart Lung Foundation, and Swedish Medical Research Council - Authors reported the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned to groups at each centre according to a computer-generated allocation list
Allocation concealment (selection bias)	Unclear risk	Unclear if the fixed size of the block (4) was known to investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Code-breaking terminology used; however it was unclear if participants or study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All endpoints were reviewed by an endpoint committee (the executive group) unaware of group assignment, who rendered a final classification before the code was broken
Incomplete outcome data (attrition bias) All outcomes	High risk	> 35% in each group were lost to follow-up (didn't experience event and were not under observation at 18 months); the reasons for these losses are not described
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias.

MERIT-HF 1997

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: February 1997 to April 1998 (enrolment) - Duration of follow-up: 1 year (mean)
Participants	- Countries: 13 European countries, USA - Setting: multicentre (313 sites); outpatient

MERIT-HF 1997 (Continued)

- Inclusion criteria: CHF (NYHA class II–IV, EF $\leq$ 40%); stabilized with optimum standard therapy; and 40 to 80 years of age
- Total number of study participants (CKD cohort): 1469 (36.8% of total cohort); treatment group (735); control group (734)
- Mean age $\pm$ SD (years) (CKD cohort): eGFR < 45 (69.6 ± 7.7); eGFR 45 to 60 (67.4 ± 8.4)
- Sex (M/F) (CKD cohort): 1003/466
- CKD stage (CKD cohort): eGFR < 60
- DM (%) (CKD cohort): eGFR < 45 (38); eGFR 45 to 60 (25)
- Exclusion criteria: acute MI or unstable angina within 28 days before randomisation; indication or contraindication for treatment with beta-blockade or drugs with beta-blocking properties such as amiodarone; beta-blockade within 6 weeks before enrolment; HF secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty, or implanted cardioversion defibrillator (expected or performed), or procedures such as CABG or PTCA planned or performed in the past 4 months; atrioventricular block of the second and third degree, unless the patient had an implanted pacemaker and a spontaneous heart rate $\geq$ 68 BPM; unstable decompensated HF (pulmonary oedema, hypoperfusion) or supine SB $<$ 100 mm Hg at enrolment; any other serious disease that might complicate management and follow-up according to the protocol; use of calcium antagonists such as diltiazem or verapamil; use of amiodarone within 6 months before enrolment; poor compliance

Interventions	Treatment group • Metoprolol CR/XL: dose as per protocol once/day Control group • Placebo
Outcomes	• Death (any cause) • CV death • Combined endpoint (death (any cause) in combination with admission to hospital (any cause, time to first event)) • Combined endpoint (death (any cause) and hospitalisation for HF) • Sudden death • Death from worsening HF • Hospitalisation (any cause) • CV hospitalisation • Hypotension
Notes	• Funding: Astra • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice recording system provided investigators with computer-generated assignment
Allocation concealment (selection bias)	Low risk	Randomisation method described that would not allow investigator to know intervention group before eligible participant entered the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study

MERIT-HF 1997 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	< 10% patients lost to follow-up; insufficient information about the final analysis to permit judgement regarding intention-to-treat
Selective reporting (reporting bias)	Low risk	Design and rationale previously published
Other bias	Unclear risk	Insufficient information to permit judgement

MMHFT 1992

Methods	- Study design: double-blind, placebo-controlled, parallel RCT - Study duration: February 1985 and October 1989 (enrolment) - Duration of follow-up: 2.7 years (median)	
Participants	- Country: Germany - Setting: single centre - Inclusion criteria: ≥ 18 years; congestive HF (NYHA functional class I-III on standard treatment) - Number: treatment group (83); control group (87) - Mean age (years): 62.4 - Sex (M/F): 128/42 - CKD stage: not reported (excluded if receiving dialysis for chronic kidney failure) - DM: not reported - Exclusion criteria: HF NYHA Class IV at entry; malignancies or other diseases that greatly affected life expectancy; HD or PD for chronic kidney failure; connective tissue diseases; concomitant immunosuppressive therapy; known renal artery stenosis; gestation and lactation; significant aortic stenosis; significant mitral stenosis; MI within 3 weeks; SBP < 95 mm Hg; uncontrolled hypertension	
Interventions	Treatment group - Captopril: maximum dose 25 mg twice/day) Control group - Matched placebo	
Outcomes	- Death due to HF - Death due to progressive HF - Deterioration of HF to severe HF (NYHA class IV)	
Notes	- Funding: This study was in part supported by a grant from the Squibb von Heyden GmbH, Germany - Authors do not report the number of patients screened or reasons for screen failure	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement

MMHFT 1992 (Continued)

Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All end points were defined and all deaths were classified prior to breaking the code
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients randomised were included in final analysis (intention-to-treat). The authors reported that few patients withdrew from the study; however, the numbers reported in the table are unclear
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias.

MOXCON 2003

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: May 1998 to March 1999 - Duration of follow-up: 12 months
Participants	- Countries: 17 - Setting: multicentre (425 sites) - Inclusion criteria: ≥ 18 years; symptomatic HF (NYHA II, III or IV) - Number: treatment group (990); control group (994) - Mean age $\pm$ SD (years): treatment group (64.1 ± 11.26); control group (64.3 ± 11.08) - Sex (M): treatment group (77.6%); control group (79%) - CKD stage: not reported but reduced kidney function ($\text{SCr} > 2.7 \text{ mg/dL}$) was an exclusion criterion - DM: not reported - Exclusion criteria: MI or coronary reperfusion procedure within 3 months; history of syncope within 3 months; likelihood of cardiac surgery within 6 months; heart block of second degree or greater; angina occurring more than 2 times daily; supine SBP (85 mm Hg); haemodynamically significant valvular or LV outflow tract obstruction; reversible active myocardial disease or severe concomitant disease likely to reduce life expectancy to < 5 years, including reduced kidney function ($\text{SCr} > 2.7 \text{ mg/dL}$)
Interventions	Treatment group - Moxonidine SR therapy Control group - Placebo
Outcomes	- Death (any cause) - Hospitalisations due to worsening HF - CV death - Effect on changes in plasma noradrenaline and BNP on death (any cause)

MOXCON 2003 (Continued)

- Notes
- Funding: sponsored and supported by Eli Lilly and Company and Solvay Pharmaceuticals. Study terminated on the recommendation of the Data Monitoring Board based on death data available at the safety review
 - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Centrally administered Interactive Voice Response System that also was used for drug management
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical End-Point Committee (CEC) to adjudicate events (but no stated if unaware)
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised were included in the final analysis
Selective reporting (reporting bias)	High risk	Not all pre-specific outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

NAPA 2007

- Methods
- Study design: prospective, double-blind, placebo-controlled, exploratory RCT
 - Study duration: March 2004 to May 2005
 - Duration of follow-up: 6 months
- Participants
- Country: USA
 - Setting: multicentre (54 sites)
 - Inclusion criteria: chronic LV dysfunction undergoing CABG, with or without mitral valve replacement/repair, using cardiopulmonary bypass
 - Number: treatment group (152); control group (151)
 - Mean age $\pm$ SD (years): treatment group (63.6 $\pm$ 10.5); control group (64.1 $\pm$ 11.3)
 - Sex (M/F): treatment group (111/30); control group (108/30)
 - CKD stage (eGFR): treatment group (82.0 $\pm$ 30.3); control group (77.6 $\pm$ 28.1)
 - DM: not reported
 - Exclusion criteria: planned aortic valve repair or replacement; requirement for ongoing or chronic dialysis; presence of restrictive or obstructive cardiomyopathy, pericarditis, or pericardial tamponade; documented low cardiac filling pressures; known congenital heart disease; evidence of ongoing infection and pulmonary disease, including chronic obstructive pulmonary disease or asthma, requiring hospital stay within 60 days.

NAPA 2007 (Continued)

Interventions	Treatment group - Nesiritide (IV): fixed dose 0.01 g/kg/min without bolus Control group - Placebo
Outcomes	- Change of SCr - eGFR - Mean pulmonary artery pressure - IV inotropic agent/vasopressor and vasodilator use - urine output 180-day death
Notes	- Funding: sponsored by Scios Inc. (Fremont, California) - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow up; not all patients randomised were included in the final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	investigators received payment from sponsor

OPTIMAAL 2002

Methods	- Study design: investigator-initiated, double-blind parallel RCT - Study duration: February 1998 to February 2002 - Duration of follow-up: 2.7 years (mean)
Participants	- Countries: 7 European countries - Setting: multicentre (329 sites) - Inclusion criteria: acute MI and signs or symptoms of HF during the acute phase - Number: treatment group (2744); control group (2733)

OPTIMAAL 2002 (Continued)

- Mean age $\pm$ SD (years): treatment group (67.6 ± 9.9); control group (67.2 ± 9.8)
- Sex (M/F): treatment group (1969/775); control group (1933/800)
- CKD stage: not reported
- DM: treatment group (17.8%); control group (16.5%)
- Exclusion criteria: supine SBP < 100 mm Hg at the time of randomisation; current receipt of an ACEi or ARB; unstable angina; haemodynamically significant stenotic valvular heart disease; haemodynamically significant dysrhythmia; planned coronary revascularization

Interventions	Treatment group • Losartan: target dose 50 mg/day Control group • Captopril: target dose 50 mg 3 times/day
Outcomes	• CV death • Non-CV death • Sudden cardiac death or resuscitated cardiac arrest • Fatal or non-fatal reinfarction • Fatal or non-fatal stroke
Notes	• Funding: supported by an unconditional grant from Merck, Sharp and Dohme Research Laboratories, West Point, PA, USA • Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation numbers were associated with treatment groups by use of a computer-generated allocation schedule.
Allocation concealment (selection bias)	Low risk	Block randomisation was used at each centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A masked endpoint classification committee classified causes of death and adjudicated selected major morbidity events
Incomplete outcome data (attrition bias) All outcomes	Low risk	$< 10\%$ lost to follow-up; all patients randomised were included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Ozdemir 2007

Methods	- Study design: open-label clinical RCT - Study duration: not reported - Duration of follow-up: 12 weeks
Participants	- Country: Turkey - Setting: not reported - Inclusion criteria: with ischaemic cardiomyopathy and NYHA class II-III HF symptoms, already receiving a beta-blocker and an ACEi - Number: treatment group (51); control group (26) - Mean age $\pm$ SD (years): treatment group (59.8 ± 8.4); control group (61.5 ± 7.0) - Sex (M/F): treatment group (41/10); control group (21/4) - CKD stage: not reported (patients with basal SCr level > 2 mg/dL excluded) - DM: treatment group (29.4%); control group (26.9%) - Exclusion criteria: serum potassium > 5 mEq/L; SCr > 2 mg/dL; SBP < 100 mm Hg; nonischaemic or hypertrophic cardiomyopathy; atrial fibrillation; a history of acute coronary syndrome; revascularization or hospitalisation from HF within the preceding 3 months; NYHA Class IV symptoms; hyper- or hypothyroidism, sustained or nonsustained (> 3 consecutive beats) ventricular tachycardia on Holter; ventricular tachycardia; fibrillation within 48 hours of a previous ST elevation MI; haemodynamically significant valvular disease
Interventions	Treatment group - Losartan: 100 mg/day - Standard therapy Control group - Standard therapy
Outcomes	24-hour ECG Holter findings - Heart rate variability parameters - Heart rate turbulence parameters - Safety
Notes	- Funding: not reported - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study

Ozdemir 2007 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% lost to follow-up; not all randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Pacher 1996

Methods	- Study design: double-blind RCT - Study duration: not reported - Duration of follow-up: 48 weeks
Participants	- Country: Austria - Setting: single centre - Inclusion criteria: severe congestive HF in NYHA functional class III-IV while receiving digitalis, diuretics and low dose ACEi therapy for at least 3 months before study entry - Number: treatment group (42); control group (41) - Mean age $\pm$ SD (years): treatment group (56 ± 17); control group (56 ± 14) - Sex (M/F): treatment group (34/8); control group (35/6) - CKD stage: not reported but SCr level > 2 mg/dL was an exclusion criterion - DM: treatment group (21%); control group (27%) - Exclusion criteria: > 70 years; history of enalapril intolerance; haemodynamically serious valvular disease requiring surgery; recent unstable angina, MI or cerebrovascular accident (during the previous month); severe pulmonary disease; clinically important kidney, hepatic or haematological disorders, hyperkalaemia, hypokalaemia or SCr level > 2 mg/dL or any other disease that might substantially shorten survival or impede participation in a long-term study
Interventions	Treatment group - Low-dose group: 5 mg twice/day enalapril and placebo throughout Control group - High-dose group: started at 5 mg twice/day and titrated up to 40 mg/day of enalapril, in two daily intakes
Outcomes	- Haemodynamic results and exercise variables - Neurohumoral plasma levels - Changes in kidney function - Adverse events
Notes	- Funding: Merck Sharp and Dohme Ltd - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Computer generated allocation schedule (Adherence to random assignment was confirmed by Merck Sharp and Dohme Ltd., which held the only master code)

Pacher 1996 (Continued)

Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not centralized measurements
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor may be involved in data analysis

Packer 1986

Methods	- Study design: RCT - Study duration: not reported - Duration of follow-up: 3 months
Participants	- Country: USA - Setting: multicentre (2 sites); outpatient - Inclusion criteria: severe CHF (LVEF < 30%) with persistent dyspnoea or fatigue at rest/during minimal exertion, despite therapy with digitalis and diuretics - Number: treatment group 1 (21); treatment group 2 (21) - Mean age $\pm$ SD (years): treatment group 1 (59.3 $\pm$ 2.9); treatment group 2 (62.2 $\pm$ 3.0) - Sex (M/F): treatment group 1 (19/2); treatment group 2 (16/5) - CKD stage mean CrCl $\pm$ SD (mL/min): treatment group 1 (46.3 $\pm$ 4.7); treatment group 2 (51.5 $\pm$ 6.4) - DM: not reported - Exclusion criteria: not reported
Interventions	Treatment group 1 - Captopril: 50 mg 3 times/day Treatment group 2 - Enalapril: 20 mg twice/day
Outcomes	- Cardiac function (short term) - Metabolic effects (long term): serum sodium, serum potassium, SCr, BUN, plasma renin activity, CrCl, urinary sodium, urinary potassium, weight
Notes	- Funding: supported by grants from the National Heart, Lung, and Blood Institute - Authors did not report screening information

Risk of bias

Packer 1986 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of patients withdrew from study; not all patients randomised were included in long-term study
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appears to be free of other sources of bias

Palazzuoli 2014

Methods	- Study design: open-label RCT - Study duration: April 2011 to December 2012 (enrolment) - Duration of follow-up: 6 months
Participants	- Country: Italy - Setting: single centre; inpatient - Inclusion criteria: admitted with a diagnosis of ADHF and CKD (SCr >1.4 mg/dL and eGFR < 50 mL/min/1.73 m²) - Number: treatment group (30); control group (28) - Mean age ± SD (years): treatment group (71 ± 7); control group (73 ± 8) - Sex (M/F): treatment group (16/14); control group (15/13) - CKD stage: eGFR < 50 mL/min/1.73 m² but not with ESKD or the need for RRT (dialysis or ultrafiltration) - DM: treatment group (55.2%); control group (61.1%) - Exclusion criteria: received more than 2 IV doses of furosemide or any continuous infusion of furosemide 1 month before randomisation; ESKD or the need for RRT; isolated diastolic dysfunction; recent MI; SBP < 80 mm Hg or with a SCr > 6.0 mg/dL; recent contrast studies (cardiac catheterization, iodate liquid administration); taking nesiritide thiazides or tolvaptan during the in-hospital period
Interventions	Treatment group - Continuous furosemide infusion: started at 80 ± 20 mg/day increased dose as per protocol Control group - Intermittent furosemide bolus: started at 80 ± 20 mg/day increased dose as per protocol
Outcomes	Kidney function (eGFR and creatinine)

Palazzuoli 2014 (Continued)

- Urine output
- Change in BNP levels
- Weight loss, electrolyte balance, length of stay, need for additional treatment
- Composite (death and rehospitalisation for HF)

Notes

- Funding: University of Siena
- Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment randomised using a computer-generated scheme
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% patients lost to follow-up; excluded patients with missing data from analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appears to be free of other sources of bias

PARADIGM-HF 2013

Methods

- Study design: double-blind RCT
- Study duration: December 2009 to November 2012
- Duration of follow-up: 27 months (median)

Participants

- Countries: 47
- Setting: multicentre (1043 sites)
- Inclusion criteria: ≥ 18 years, NYHA class II, III, or IV symptoms, and an ejection fraction $\leq 40\%$
- Number: treatment group (4187); control group (4212)
- Mean age $\pm$ SD (years): treatment group (63.8 ± 11.5); control group (63.8 ± 11.3)
- Sex (M/F): treatment group (3308/879); control group (3259/953)
- CKD stage (SCr): treatment group (1.13 ± 0.3); control group (1.12 ± 0.3)
- DM: treatment group (34.7%); control group (34.6%)
- Exclusion criteria: symptomatic hypotension; SBP < 100 mm Hg at screening or 95 mm Hg at randomisation; eGFR < 30 mL/min/1.73 m² at screening or at randomisation or a decrease in the eGFR of more than 25% (which was amended to 35%) between screening and randomisation; serum potassium $>$

PARADIGM-HF 2013 (Continued)

5.2 mmol/L at screening (or > 5.4 mmol/L at randomisation); history of angioedema or unacceptable side effects during receipt of ACEi or ARBs

Interventions	Treatment group • LCZ696: 200 mg twice/day Control group • Enalapril:10 mg twice/day
Outcomes	• Composite of death from CV causes or a first hospitalisation for HF • Time to death from any cause • Change in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire • Time to a new onset of atrial fibrillation • Time to the first occurrence of a decline in kidney function
Notes	• Funding: Supported by Novartis • Details on number screened unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomisation system
Allocation concealment (selection bias)	Unclear risk	Concealed study-group assignments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adjudication of these outcomes was carried out in a blinded fashion by a clinical-end-points committee according to prespecified criteria
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised were included in the final analysis
Selective reporting (reporting bias)	Low risk	Protocol published and all prespecified outcomes presented
Other bias	High risk	Sponsor involved in the protocol development and data acquisition/ analysis

PEP-CHF 1999

Methods	• Study design: double-blind RCT • Study duration: 2000 to 2003 • Duration of follow-up: 2.1 years (median)
Participants	• Countries: 8 (Bulgaria, Czech Republic, Hungary, Ireland, Poland, Russia, Slovakia, UK) • Setting: multicentre (53 sites)

PEP-CHF 1999 (Continued)

- Inclusion criteria ≥ 70 years; treated with diuretics for a clinical diagnosis of CHF due to LV diastolic dysfunction; CV hospitalisation within the previous 6 months
- Number: treatment group (424); control group (426)
- Median age, IQR (years): treatment group (75, 72 to 79); control group (75, 72 to 79)
- Sex (M/F): treatment group (195/229); control group (183/243)
- CKD stage (SCr, median, IQR): treatment group (1.098, 0.95 to 1.255); control group (1.074, 0.916 to 1.244)
- DM: treatment group (21%); control group (20%)
- Exclusion criteria: wall motion index < 1.4 , roughly equivalent to an LVEF of 40%; haemodynamically significant valve disease; stroke within the previous month; sitting SBP < 100 mm Hg, SCr > 200 $\mu\text{mol/L}$ or potassium > 5.4 mmol/L; history of ACEi intolerance or use of an ACEi or ARB within the previous week; potassium-sparing diuretics (other than low-dose spironolactone), or potassium supplements

Interventions	Treatment group • Perindopril: 2 mg/d Control group • Placebo
Outcomes	• Composite of death (any cause) or unplanned HF related hospitalisation • CV death • Worsening HF requiring hospitalisation or an increase in diuretic treatment • Hospital bed-days for CV reasons • Hospital bed-days for any reason • Change in NYHA class between baseline and 1 year
Notes	• Funding: "Servier funded the trial and provided site monitors for source data verification. The sponsor had access to the database and participated in the analysis under the supervision of an independent statistician (NF). The Steering Committee wrote the manuscript. Servier representatives commented on it prior to submission. The authors received remuneration and research grants from Servier for the conduct of this study" • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	In blocks of four within treatment centres to placebo or perindopril through a centrally administered process, concealed from the study investigators. The study medication was provided in externally indistinguishable tablets.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Potential qualifying events were independently classified by MT and JGFC, blind to treatment allocation (but both sponsored by Servier)
Incomplete outcome data (attrition bias)	Low risk	$< 10\%$ lost to follow-up; all patients randomised were included in the final analysis

PEP-CHF 1999 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Sponsor involved in data analysis and provided remuneration for authors

Pita-Fernandez 2015

Methods	- Study design: open-label RCT - Study duration: January to July 2009 (enrolment) - Duration of follow-up: 1 year
Participants	- Country: Spain - Setting: single centre; outpatient - Inclusion criteria: admitted to hospital for HF; ≥ 50 years; Hb < 12 mg/dL; CKD (eGFR < 60 mL/min/1.73 m²); receiving treatment with angiotensin inhibitors - Number: treatment group (30); control group (17) - Mean age $\pm$ SD (years): treatment group (78.2 $\pm$ 7.8); control group (74.2 $\pm$ 5.9) - Sex (M/F): treatment group (16/14); control group (11/6) - CKD stage: eGFR < 60 mL/min/1.73 m² (not on dialysis or ultrafiltration) - DM: treatment group (40%); control group (52.9%) - Exclusion criteria: HF because of acute MI; requiring devices or surgery; pericardial disease; acute bleeding; pulmonary embolism; treatment with erythropoietin, ultrafiltration, or HD; oncology patients
Interventions	Treatment group - Dose of renin-angiotensin system inhibitors taken by the patients in the intervention group on admission was reduced by 50% Control group - Continued to take the same dose of renin-angiotensin system inhibitors they were taking on admission
Outcomes	- Difference in Hb, CrCl, and protein C (3 months) - Survival at 6 to 12 months (used 12-month data for analysis)
Notes	- Funding: none - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Pita-Fernandez 2015 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; all patients randomised included in final survival analysis
Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

PRAISE-II 2003

Methods	- Study design: double-blind RCT - Study duration: December 1995 to January 2000 - Duration of follow-up: 33 months (median)
Participants	- Countries: USA, Canada - Setting: multicentre (number of sites not reported) - Inclusion criteria: NYHA functional class III or IV symptoms of HF due to a non-ischaemic cardiomyopathy - Number: treatment group (827); control group (827) - Mean age $\pm$ SD (years): treatment group (59 ± 14); control group (59 ± 13) - Sex (M/F): treatment group (546/281); control group (546/281) - CKD stage (SCr, mg/mL): treatment group (1.2 ± 0.4); control group (1.3 ± 0.4) - DM: not reported - Exclusion criteria: reversible cause of cardiomyopathy or uncorrected primary valve disease; history of sudden death or sustained ventricular tachycardia or fibrillation within the previous year; receiving an anti-arrhythmic agent known to adversely affect cardiac function or survival; evidence of digitalis toxicity, and/or had a clinical indication for cardiac pacing (but were not paced); severe pulmonary, kidney, or hepatic disease or any disease (other than HF) that might have limited survival, within the previous 3 years; SBP < 85 or ≥ 160 mm Hg and/or DBP ≥ 90 mm Hg; SCr > 3.0 mg/dL and/or potassium < 3.5 or > 5.5 mmol/L; any liver function test result that was > 3 times the upper limit of normal; and/or a white or red cell count > 30% outside of the normal range
Interventions	Treatment group - Amlodipine: 5 to 10 mg/d Control group - Placebo
Outcomes	- Death (any cause) - CV death - Frequency and cause of hospitalisation
Notes	- Funding: supported by a grant from Pfizer, Inc - Authors did not report screening information

Risk of bias

PRAISE-II 2003 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

Pre-RELAX-AHF 2009

Methods	- Study design: placebo-controlled, parallel, dose-finding pilot RCT - Study duration: December 2007 to August 2008 - Duration of follow-up: 6 months
Participants	- Countries: Belgium, Hungary, Israel, Italy, Poland, Romania, Russia, USA - Setting: multicentre (54 sites) - Inclusion criteria: ≥ 18 years within 16 h of presentation for acute HF; preserved or increased blood pressure (SBP > 125 mm Hg at the time of screening) and impaired kidney function (eGFR of 30 to 75) - Number: treatment group 1 (40); treatment group 2 (43); treatment group 3 (39); treatment group 4 (50); control group (62) - Mean age $\pm$ SD (years): treatment group 1 (72.2 ± 11.0); treatment group 2 (71.6 ± 9.2); treatment group 3 (69.2 ± 11.6); treatment group 4 (70.7 ± 11.0); control group (68.4 ± 9.9) - Sex (M/F): treatment group 1 (21/19); treatment group 2 (18/24); treatment group 3 (19/18); treatment group 4 (30/19); control group (40/21) - CKD stage (mean eGFR $\pm$ SD): treatment group 1 (56.5 ± 15.8); treatment group 2 (50.6 ± 14.1); treatment group 3 (53.4 ± 22.0); treatment group 4 (53.4 ± 15.2); control group (53.9 ± 16.8) - DM: treatment group 1 (33%); treatment group 2 (52%); treatment group 3 (32%); treatment group 4 (41%); control group (49%) - Exclusion criteria: receiving IV inotropic agents or IV vasodilators (other than IV nitrates at a dose of 0.1 mg/kg/h if SBP > 150 mm Hg); fever; severe pulmonary disease; significant stenotic valvular disease; acute coronary syndrome within 45 days; troponin concentration more than three times upper limit of normal
Interventions	Treatment group 1 Relaxin: 10 μg/kg/day for 48 hours

Pre-RELAX-AHF 2009 (Continued)

Treatment group 2

- Relaxin 30: µg/kg/day for 48 hours

Treatment group 3

- Relaxin 100: µg/kg/day for 48 hours

Treatment group 4

- Relaxin: 250 µg/kg/day for 48 hours

Control group

- Placebo: for 48 hours

Outcomes	• Worsening HF (day 5) • Hospitalisation for HF • Improved dyspnoea (6, 12, 24 hours)* • Oedema, rales (day 5)* • Hypotension (discontinuation due to reduction in blood pressure) • Hyperkalaemia • Worsening kidney failure** • Death (any cause) (180 days) • CV death (180 days) • Composite endpoint (CV death or readmission to hospital due to HF or kidney failure) *Number of patients with dyspnoea, oedema, or rales at baseline not reported; unable to estimate risk ratio **Authors provide multiple indicators to define worsening kidney function: ≥ 26 µmol/L increase at days 5 and 14 chosen for analysis
Notes	• Funding: Corthera (USA). • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done via a telephone-based interactive voice response system
Allocation concealment (selection bias)	Low risk	Only the study pharmacy and an independent, unblinded statistician were aware of the contents of the kits allocated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information on lost-to-follow-up to permit judgement. Data analysed using a modified intention-to-treat analysis

Pre-RELAX-AHF 2009 (Continued)

Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	Sponsor involved in study conduct

PRIME-II 1997

Methods	- Study design: placebo-controlled RCT - Study duration: September 1992 to August 1995 - Duration of follow-up: 2 years	
Participants	- Countries: 13 European countries - Setting: multicentre (192 sites) - Inclusion criteria: HF (LVEF $\leq$ 35%) before randomisation - Number: treatment group (953); control group (953) - Mean age $\pm$ SD (years): treatment group (64.6 $\pm$ 9.6); control group (64.8 $\pm$ 9.5) - Sex (M/F): treatment group (783/170); control group (749/204) - CKD stage: not reported - DM: treatment group (20.9%); control group (20.5%) - Exclusion criteria: obstructive valve disease; obstructive or restrictive cardiomyopathy; any potentially transient cause of HF (e.g. acute myocarditis); MI during the previous 3 months; unstable angina; uncontrolled arrhythmias; current need for IV inotropic support; intolerance of dopamine or ibopamine; concomitant use of medication known to interact with these drugs (e.g. metoclopramide, levodopa); pregnancy or lactation; inadequate contraception in women of childbearing age; administration of another investigational drug within the previous 30 days	
Interventions	Treatment group - Ibopamine: 100 mg 3 times/day Control group - Placebo	
Outcomes	- Death (any cause) - Cause of death - Need for cardiac transplantation - Number of and reason for hospital admissions - QoL - Symptom scores - Reasons for withdrawal from study medication	
Notes	- Funding: the study was sponsored by the Zambon Group, Milan, Italy - Authors did not report screening information	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation schedule

PRIME-II 1997 (Continued)

Allocation concealment (selection bias)	Low risk	Pharmacy of each participating centre held individual sealed envelopes that corresponded to the drug kits allocated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data were handled under masked conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	High risk	Sponsor involved in study conduct

PROFILE 2002

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: August 1991 to April 1993 - Duration of follow-up: mean of 302 ± 142 days
Participants	- Countries: Canada; USA; Scandinavia - Setting: multicentre (number of sites not reported) - Inclusion criteria: symptomatic HF of NYHA class III and IV, LVEF ≤ 35% by radionuclide ventriculography or ECG; treatment with digitalis, diuretics, and ACEi ≥ 60 days; ability to provide informed consent. Use of beta-blocking agents was at the discretion of the attending physician. - Number: treatment group (1170); control group (1175) - Mean age ± SD (years): treatment group (65.6 ± 10.8); control group (65.3 ± 10.7) - Sex (M/F): treatment group (941/234); control group (910/260) - CKD stage (SCR, mg/dL): treatment group (1.4 ± 0.4); control group (1.4 ± 0.4) - DM: not reported - Exclusion criteria: restrictive cardiomyopathy; primary valvular heart disease; consideration for heart transplantation; history of acute MI; coronary bypass surgery or other cardiac surgery ≤ 60 days; symptom-limiting, unstable, or moderate (> 3 attacks/week) angina; history of symptomatic ventricular arrhythmias; ongoing therapy with type 1 anti-arrhythmic agents, calcium channel blockers or hydralazine; inhaled beta-agonists more than once/ week; oral or intravenous non-digitalis inotropes < 1 week before baseline measurements; hepatic enzymes > 2 times the upper limit of normal; SCR ≥ 3.0 mg/dL; severe pulmonary or other disease that might limit survival
Interventions	Treatment group - Flosequinan Control group - Placebo
Outcomes	Death

PROFILE 2002 (Continued)

- Notes
- Funding: Boots Pharmaceuticals
 - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	An independent committee classified deaths as resulting from low-output state, sudden death, or other causes
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

PROMISE 1989

Methods	• Study design: placebo-controlled RCT • Study duration: January 1989 to October 1990 • Duration of follow-up: 6.1 months (median)
Participants	• Countries: Canada, USA • Setting: multicentre (119 centres); outpatient • Inclusion criteria: HF (presence of dyspnoea or fatigue with LVEF $\leq$ 35%, NYHA class III or IV); and on standard therapy (digoxin, diuretics, and ACEi) • Total number of study participants (CKD cohort): 539 (49.5% of total cohort); treatment group (271); control group (268) • Mean age $\pm$ SD (years) (CKD cohort): not reported • Sex (M/F) (CKD cohort): not reported • CKD stage (CKD cohort): SCr >1.3 mg/dL (not severe kidney disease) • DM (CKD cohort): not reported • Exclusion criteria: HF due to obstructive valvular disease, active myocarditis, hypertrophic or amyloid cardiomyopathy, uncorrected thyroid disease, or a malfunctioning artificial heart valve; history of a serious symptomatic ventricular arrhythmia; angina pectoris; MI within previous 3 months; severe primary pulmonary, kidney, or hepatic disease; SBP < 85 mm Hg; serum potassium < 3.5 mmol/L; need for beta-adrenergic blockers, Calcium-channel blockers, disopyramide, flecainide, encainide, levodopa, dopamine, or dobutamine

PROMISE 1989 (Continued)

Interventions	Treatment group - Milrinone (oral): 10 mg 4 times/day, modified as per protocol Control group - Placebo
Outcomes	- Death (any cause) - Hospitalisation (any cause) - CV death - Functional capacity - Adverse effects (hypotension)
Notes	- Funding: Sterling, Inc - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	Study is registered, all prespecified outcomes presented
Other bias	Unclear risk	Insufficient information to permit judgement

PROTECT 2008

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: May 2007 and January 2009 (randomisation) - Duration of follow-up: 6 months
Participants	- Countries: North America, Europe, Israel, Argentina - Setting: multicentre (173 sites); inpatient

PROTECT 2008 (Continued)

- Inclusion criteria: history of HF of at least 14 days duration for which diuretic therapy has been pre-scribed; hospitalised for acute HF syndrome requiring IV diuretic therapy; impaired kidney function (estimated CrCl of 20 to 80 mL/min)
- Number: treatment group (1356); control group (677)
- Mean age $\pm$ SD (years): treatment group (70.2 ± 11.7); control group (70.2 ± 11.5)
- Sex (M): treatment group (67.3%); control group (66.8%)
- CKD stage (mean CrCl $\pm$ SD (mL/min)): treatment group (50.4 ± 20.0); control group (51.0 ± 20.5)
- DM: treatment group (45.2%); control group (45.8%)
- Exclusion criteria: acute contrast induced nephropathy; ongoing or planned IV therapy for HF with positive inotropic agents, vasopressors, vasodilators, or mechanical support with the exception of IV nitrates; BNP < 500 pg/mL or NT-proBNP < 2000 pg/mL; ongoing or planned treatment with ultrafiltration, haemofiltration, or dialysis; severe pulmonary disease; significant stenotic valvular disease; heart transplant recipient or admitted for cardiac transplantation; clinical evidence of acute coronary syndrome in the 2 weeks prior to screening; HF due to significant arrhythmias; acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy; known hepatic impairment; non-cardiac pulmonary oedema, including suspected sepsis; allergy to soybean oil or eggs; history of seizure; stroke within 2 years; history of or current brain tumour of any aetiology; brain surgery within 2 years; encephalitis/meningitis within 2 years; history of penetrating head trauma; closed head injury with loss of consciousness (LOC) over 30 min within 2 years; history of, or at risk for, alcohol withdrawal seizures; advanced Alzheimer's disease; advanced multiple sclerosis; Hb < 8 g/dL, HCT < 25%, or the need for a blood transfusion; previous exposure to KW-3902 (study drug)

Interventions	Treatment group • Rolofylline: 30 mg, 4-hour IV infusion/day for 3 days Control group • Placebo: 4-hour IV infusion/day for 3 days
Outcomes	• Treatment success, treatment failure, or no change in the patient's clinical condition (defined according to survival, heart-failure status, and changes in kidney function) • Post-treatment development of persistent renal impairment • Death (any cause) (7 days, 180 days)* • Readmission for HF during the first 7 days** • Composite endpoint (60-day rate of death or readmission for CV or renal causes) * Used death during first 7 days in analysis ** Unable to estimate effect measure as the number at risk not provided
Notes	• Funding: NovaCardia • Secondary study (primary analysis did not monitor outcomes > 3 months) • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation schedule
Allocation concealment (selection bias)	Low risk	Assigned through a central randomisation system
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

PROTECT 2008 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were adjudicated by an independent clinical events committee that was unaware of treatment assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified outcomes that are of interest in this review have been reported
Other bias	High risk	Sponsor involved in study conduct

RALES 1995

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: March 1995 to August 1998 - Duration of follow-up: 24 months (mean)	
Participants	- Countries: 15 - Setting: multicentre (195 sites); outpatient - Patients with HF (NYHA class III-IV and LVEF ≤ 35%); and on an ACEi and loop diuretics - Total number of study participants (CKD cohort): 792 (47.6% of total cohort); numbers per group not reported - Mean age ± SD (years) (CKD cohort): 70.0 ± 9.4 years - Sex (M) (CKD cohort): 69.4% - CKD stage (CKD cohort): eGFR < 60 (but SCr ≤ 2.5 mg/dL) - DM (CKD cohort): 26.2% - Exclusion criteria: primary valvular disease; congenital heart disease; unstable angina; liver failure; listing for cardiac transplant, active cancer, or any other life-threatening disease; SCr > 2.5 mg/dL; potassium > 5 mmol/L	
Interventions	Treatment group - Spironolactone: 25 mg once/day, up-titrated as per protocol Control group - Placebo	
Outcomes	- Death (any cause) - Death or HF hospitalisation - Hyperkalaemia - Worsening kidney function - Improved NYHA class, dyspnoea, oedema	
Notes	- Funding: Supported by a grant from Searle, Skokie, Ill - Authors did not report screening information	

Risk of bias

Bias	Authors' judgement	Support for judgement
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RALES 1995 (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% patients lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

REACH UP 2010

Methods	- Study design: double-blind, placebo-controlled pilot RCT - Study duration: August 2007 to January 2009 - Duration of follow-up: 180 days (3 days treatment)
Participants	- Countries: international (countries not reported) - Setting: multicentre (21 sites) - Inclusion criteria: ADHF, volume overload, and recent kidney deterioration - Number: treatment group (36); control group (40) - Mean age $\pm$ SD (years): treatment group (71 ± 12); control group (65 ± 11) - Sex (M): treatment group (69%); control group (70%) - CKD stage (CrCl): treatment group (47 ± 17); control group (48 ± 17) - DM: treatment group (47%); control group (40%) - Exclusion criteria: administration of IV vasodilators within 6 hours of randomisation (with the exclusion of nitrates); administration of any vasopressor or inotropic drug within 72 hours (with the exception of dopamine or dobutamine at doses $\leq 5 \mu\text{g/kg/min}$ or milrinone at a dose $\leq 0.25 \mu\text{g/kg/min}$); administration of IV radiographic contrast within 14 days of randomisation or planned during the hospitalisation; ongoing or planned therapy with mechanical circulatory support, ventilatory support (including biphasic positive airway pressure or continuous positive airway pressure, ultrafiltration, haemofiltration, or dialysis; rapidly progressive acute kidney failure defined as an increase in SCr $\geq 0.7 \text{ mg/dL}$ in a 24-hour period; evidence of acute tubular necrosis, postobstructive nephropathy or other causes of acute kidney injury unrelated to HF or its treatment; severe pulmonary or hepatic dysfunction (bilirubin $> 3 \text{ mg/dL}$ or albumin $< 2.8 \text{ mg/dL}$); anaemia (Hb $< 8 \text{ g/dL}$ or HCT $< 25\%$); and acute coronary syndrome within 2 weeks
Interventions	Treatment group Rolofylline: 30 mg once/day as a 4-hour continuous IV infusion Control group

REACH UP 2010 (Continued)

- Placebo

Outcomes	• Death or readmission for HF or WRF through 30 days after randomisation worsening symptoms and/or signs of HF to day 7 • Worsening kidney function to day 7
Notes	• Funding: Funded by NovaCardia (Merck) • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random assignment of treatment to allocation numbers
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study personnel were blind to the treatment until after the completion of the study, and the study database was locked
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	All investigators received payment from sponsor

RELAX-AHF 2012

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: October 2009 to February 2011 • Duration of follow-up: 180 days
Participants	• Countries: 11 • Setting: multicentre (96 sites) • Inclusion criteria: admitted to hospital for acute HF and CKD (eGFR < 60) • Number: treatment group (581); control group (580) • Mean age ± SD (years): treatment group (71.6 ± 11.7); control group (72.5 ± 10.8) • Sex (M): treatment group (63%); control group (62%) • CKD stage: eGFR < 60 • DM: treatment group (48%); control group (47%) • Exclusion criteria: treatment with other IV HF drugs (except IV nitrate ≤ 0.1 mg/kg/hour in patients with SBP at screening of > 150 mm Hg) or mechanical support within 2 hours before screening; signs of active infection; known significant pulmonary or valvular disease; acute HF due to significant arrhythmia

RELAX-AHF 2012 (Continued)

mias; acute coronary syndrome diagnosed within 45 days; troponin concentration 3 times or more higher than the level diagnostic of MI

Interventions	Treatment group - Serelaxin: 30 µg/kg/day Control group - Placebo
Outcomes	- Change in patient-reported dyspnoea from baseline to day 5* - Signs and symptoms of congestion at day 2 (rales/oedema)* - Worsening HF (14 days) - Death (any cause) (30 days) - CV death (180 days) - Readmissions for HF - Composite endpoint (all-cause or CV death or readmissions to hospital for HF or kidney failure) - Adverse events related to renal impairment - Hypotension (day 5) *Unable to estimate risk of worsening dyspnoea, rales, or oedema as baseline measures not provided
Notes	- Funding: supported by Corthera, Inc., a Novartis affiliate company - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation scheme; central interactive voice response system to request assignment of study drug
Allocation concealment (selection bias)	Low risk	Identical masked kits. The randomisation scheme and the kit list consisting of kit numbers randomly assigned to treatment were generated by an independent supplier
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel involved in the operations of the study or with any potential site contact, such as medical monitors, remained masked to treatment assignments from the time of randomisation until after the day 180 database lock
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented and protocol published
Other bias	High risk	Sponsor involved in study conduct

RENO-DEFEND 1 2011

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: February 2009 to October 2009 (terminated early) - Duration of follow-up: 180 days
Participants	- Countries: North and South America, Eastern and Western Europe - Setting: multicentre (200 sites) - Inclusion criteria: hospitalised with acute decompensated HF and kidney dysfunction (eGFR 20 to 80 mL/min) - Number: treatment group 1 (9); treatment group 2 (9); treatment group 3 (10); treatment group 4 (9); control group (9) - Mean age (years): treatment group 1 (73); treatment group 2 (71); treatment group 3 (69.7); treatment group 4 (75.9); control group (74.3) - Sex (M/F): treatment group 1 (50%); treatment group 2 (55.6%); treatment group 3 (80%); treatment group 4 (55.6%); control group (66.7%) - CKD stage (eGFR): 20 to 80 mL/min - DM: not reported - Exclusion criteria: low-output syndrome; SBP < 95 mm Hg at the time of randomisation; significant stenotic valvular disease; clinical evidence of acute coronary syndromes in the 2 weeks before screening; MI or haemodynamically destabilizing significant arrhythmias; acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy; known risk for seizures and/or an increased risk for seizures as determined by the investigator; ongoing or planned treatment with ultrafiltration, haemofiltration, or dialysis; history of acute contrast-induced nephropathy or received IV contrast dye within 2 weeks before day 1 or were expected to receive IV contrast during the treatment period of the study
Interventions	Treatment group 1 - Selective A1 Adenosine Receptor Antagonist (SLV320): 1.25 mg twice/day Treatment group 2 - SLV320: 3.75 mg twice/day Treatment group 3 - SLV320: 07.5 mg twice/day Treatment group 4 - SLV320: 15 mg twice/day Control group - Placebo
Outcomes	- Change in SCr from baseline to Day 14 - Dyspnoea, rales, oedema (day 3)* - eGFR (day 60) - Change in BNP - Subject Global Clinical Assessment Score (day 60) - Urine osmolality (day 4) - Serum osmolality (day 60) - Composite (death or CV/renal hospitalisation): day 60, day 180 - Death (any cause) - All-cause hospitalisation *Data on symptoms of congestion not provided.

RENO-DEFEND 1 2011 (Continued)

- Notes
- Study was terminated early, due to safety concerns
 - Funding: The study was sponsored and funded by Solvay Pharmaceuticals (Abbott Laboratories)
 - Details on screening not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, methods not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	Data on all outcomes provided.
Other bias	High risk	Sponsor may be involved in data analysis

Risler 1991

Methods	• Study design: cross-over RCT • Study duration: not reported • Duration of follow-up: 6 months
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: HF (NYHA class III-IV) • Number: 8 • Mean age $\pm$ SD: 56 $\pm$ 3 years • Sex (M/F): 6/2 • CKD stage (eGFR): 82 $\pm$ 20 mL/min/1.73 m² • DM: 25% • Exclusion criteria: not reported
Interventions	Treatment group • Lisinopril: 5 mg/day Control group

Risler 1991 (Continued)

- Captopril: 12.5 mg 3 times/day

Outcomes	• CV function • Kidney function • Adverse side effects
Notes	• Funding: not reported • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

ROSE AHF 2013

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: September 2010 to March 2013 (enrolment) • Duration of follow-up: 180 days
Participants	• Countries: Canada, USA • Setting: multicentre (26 sites); inpatient • Inclusion criteria: hospitalised with acute HF and kidney dysfunction (eGFR 15 to 60) • Number: treatment group 1 (122); treatment group 2 (119); control group (119) • Median age, IQR (years): treatment group 1 (71, 63 to 80); treatment group 2 (69, 59 to 79); control group (70, 62 to 78) • Sex (M): treatment group 1 (69%); treatment group 2 (76%); control group (75%) • CKD stage (eGFR): 15 to 60 mL/min/1.73 m² (not on RRT) • DM: treatment group 1 (58%); treatment group 2 (56%); control group (52%) • Exclusion criteria: received IV vasoactive treatment or ultra-filtration therapy for HF since initial presentation; anticipated need for IV vasoactive treatment or ultra-filtration for HF during this hospital-

ROSE AHF 2013 (Continued)

isation; SBP < 90 mm Hg; Hb < 9 g/dL; RRT; history of renal artery stenosis > 50%; haemodynamically significant arrhythmias including ventricular tachycardia or defibrillator shock within 4 weeks; acute coronary syndrome within 4 weeks; active myocarditis; hypertrophic obstructive cardiomyopathy; greater than moderate stenotic valvular disease; restrictive or constrictive cardiomyopathy; complex congenital heart disease; constrictive pericarditis; non-cardiac pulmonary oedema; clinical evidence of digoxin toxicity; need for mechanical haemodynamic support; Sepsis' Terminal illness (other than HF) with expected survival of less than 1 year

Interventions	Treatment group 1 - Dopamine: 2 µg/kg/min for 72 hours Treatment group 2 - Nesiritide: 0.005 µg/kg/min for 72 hours Control group - Placebo
Outcomes	72-hour cumulative urinary volume - Change in cystatin-C from randomisation to 72 hours - Other decongestion or kidney function endpoints (24, 48, 72 hours) - Symptom relief endpoints (global well-being, dyspnoea, worsening HF) (72 hours)* - Hypotension - Change in NT-proBNP - Rehospitalisation (60 days) - Death (72 hours, 60 days and 180 days) (used 180 days in analysis) - Composite endpoint (death or rehospitalisation or unscheduled visit for HF) *Dyspnoea reported as the area under the curve for a VAS, unable to determine baseline risk
Notes	- Funding: Sponsored by the National Heart, Lung, and Blood Institute - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the randomisation process to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; unclear how many patients analysed in survival analysis for 180 day death and not all patients randomised were evaluated for hypotension, but these were secondary outcomes of the study

ROSE AHF 2013 (Continued)

Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

SADKO-CHF 2005

Methods	- Study design: RCT - Study duration: not reported - Duration of follow-up: 6 months
Participants	- Country: Russia - Setting: not reported - Inclusion criteria: NYHA class II-III CHF due to ischaemic heart disease, dilated cardiomyopathy or de-compensated hypertensive heart and ejection fraction < 40% - Number: treatment group 1 (28); treatment group 2 (26); treatment group 3 (26) - Median age (IQR) (years): not reported - Sex (M/F): not reported - CKD stage: not reported % DM: not reported - Exclusion criteria: not reported
Interventions	Treatment group 1 - Quinapril: 13 mg/day Treatment group 2 - Valsartan: 121 mg/day Treatment group 3 - Quinapril: 12 mg/day - Valsartan: 78 mg/day
Outcomes	- Clinical state - QoL - ECG 6 min walk test - Holter ECG monitoring with measurements of parameters of heart rate variability - Determination of neurohormones in peripheral blood
Notes	- Funding: unclear - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

SADKO-CHF 2005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Low risk	Insufficient information to permit judgement

SAVE 1991

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: January 1987 to January 1992 - Duration of follow-up: 2 years
Participants	- Countries: Canada, USA - Setting: multicentre (45 sites); outpatient - Inclusion criteria: acute MI; left ventricular dysfunction; symptoms or NYHA not reported - Total number of study participants (CKD cohort): 719 (32.2% of total cohort); treatment group (359); control group (360) - Mean age $\pm$ SD (years) (CKD cohort): eGFR < 45 (67.1 ± 8.0); eGFR 45 to 59 (63.1 ± 8.7) - Sex (M/F) (CKD cohort): 555/164 - CKD stage (CKD cohort): eGFR < 60 (but SCr $\leq$ 2.5 mg/dL) - DM (CKD cohort): 27% - Exclusion criteria: contraindication to ACEi; need to treat symptomatic congestive HF/systemic hypertension; SCr > 2.5 mg/dL; other conditions limiting survival; unstable course after infarction (HF resistant to diuretics)
Interventions	Treatment group - Captopril: target dose 25 mg 3 times/day, adjusted as per protocol Control group - Placebo
Outcomes	- Death (any cause) - CV death - Development of HF or recurrent fatal or nonfatal MI - Combination outcome of CV death and morbidity - Hospitalisation for HF
Notes	- Funding: Supported by a grant from the Bristol-Myers Squibb Institute for Pharmaceutical Research (who was not involved in the acquisition or management of data) - Authors did not report screening information

SAVE 1991 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer-generated assignment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Low risk	Study sponsor (Bristol-Myers Squibb) was not involved in the acquisition or management of data

SENIORS 2002

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: September 2000 to November 2003 - Duration of follow-up: 30 months
Participants	- Countries: Czech Republic, France, Germany, Hungary, Italy, Netherlands, Romania, Spain, Ukraine, UK - Setting: multicentre (160 sites); outpatient - Patients with CHF (hospital admission within previous 12 months for congestive HF OR LVEF $\leq$ 35%); and $\geq$ 70 years of age - Total number of study participants (CKD cohort): 704 (33.1% of total cohort); treatment group (348); control group (356) - Mean age $\pm$ SD (years) (CKD cohort): treatment group (77.3 $\pm$ 5.0); control group (77.4 $\pm$ 5.1) - Sex (M/F) (CKD cohort): 417/287 - CKD stage (CKD cohort): eGFR < 55.5 (but SCr < 250 mmol/L) - DM (CKD cohort): 28.9% - Exclusion criteria: new drug therapy for HF in the 6 weeks prior to randomisation; any change in CV drug therapy in the 2 weeks prior to randomisation; HF due primarily to uncorrected valvular heart disease; contraindication or previous intolerance to beta-blockers (e.g. heart rate < 60 BPM or SBP < 90 mm Hg); current use of beta-blockers, significant hepatic or kidney dysfunction; cerebrovascular accidents within the previous 3 months; being on a wait list for PCI or cardiac surgery or other major medical conditions that may have reduced survival during the period of the study
Interventions	Treatment group

SENIORS 2002 (Continued)

- Nebivolol: target dose 10 mg once/day, as per protocol

Control group

- Placebo

Outcomes	• Composite of death (any cause) or CV hospital admission • Death (any cause) • Hospital admissions (any cause) • CV hospital admissions • CV death • Worsening kidney function • Hypotension • Dyspnoea
Notes	• Funding: The study was supported by Menarini Ricerche SpA • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation
Allocation concealment (selection bias)	Low risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% patients lost to follow-up; not all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented
Other bias	High risk	Study protocol was developed by an independent Steering Committee in collaboration with the sponsor (Menarini Ricerche SpA)

SHIFT 2010

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: September 2006 to March 2010 • Duration of follow-up: 30 months
Participants	• Countries: 37 • Setting: multicentre (677 sites); outpatient

SHIFT 2010 (Continued)

- Inclusion criteria: HF (LVEF $\leq$ 35%); hospital admission for worsening HF within the previous 12 months; sinus rhythm; and resting heart rate of $\geq$ 70 BPM
- Total number of study participants (CKD cohort): 1579 (24.1% of total cohort); treatment group (780); control group (799)
- Mean age $\pm$ SD (years) (CKD cohort): 66.7 $\pm$ 9.6
- Sex (M/F) (CKD cohort): 989/590
- CKD stage (CKD cohort): eGFR $<$ 60
- DM (CKD cohort): 38.0%
- Exclusion criteria: recent ($<$ 2 months) MI; ventricular or atrioventricular pacing operative for 40% or more of the day; atrial fibrillation or flutter; symptomatic hypotension

*A baseline creatinine measurement and at least one follow-up visit was available for 6160/6558 patients to determine CKD status

Interventions	Treatment group • Ivabradine: 7.5 mg twice/day, as per protocol Control group • Placebo
Outcomes	• CV death or hospital admission for worsening HF • Death (any cause) • CV death • Death from HF • Hospital admission (any cause) • Hospital admission for worsening HF • Any CV hospital admission or hospital admission for non-fatal MI • Worsening kidney function • Hyperkalaemia • QoL
Notes	• Funding: Servier, France (responsible for data management and final data analyses) • Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by computer-generated allocation schedule
Allocation concealment (selection bias)	Low risk	Allocation sequence was generated through a validated software
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding

SHIFT 2010 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% patients lost to follow-up; not all patients randomised included in analysis
Selective reporting (reporting bias)	Low risk	Study registered, all prespecified outcomes presented
Other bias	High risk	The sponsor was responsible for data management and final data analyses

Skvortsov 2007

Methods	- Study design: RCT - Study duration: not reported - Duration of follow-up: 12 months
Participants	- Country: Russia - Setting: not reported - Inclusion criteria: CHF (NYHA class II-III and LVEF < 35%); SCr < 150 µmol/L and blood potassium < 5 mmol/L - Number: treatment group (19); control group (30) - Mean age ± SD (years): treatment group (54.6 ± 8.24); (control group (50.0 ± 11.12) - Sex (M/F): 44/5 - CKD stage: SCr < 150 µmol/L - DM: not reported - Exclusion criteria: Not reported
Interventions	Treatment group - Spironolactone: 25 to 75 mg/day Control group - Control
Outcomes	- Clinical-functional status - LV remodelling parameters - Safety
Notes	- Funding: not reported - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement

Skvortsov 2007 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% withdrew from study; not all patients randomised were included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

SOLVD (Prevention) 1992

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: July 1986 to May 1990 - Duration of follow-up: 37.4 months (mean)
Participants	- Countries: USA, Canada, Belgium - Setting: multicentre (83 sites) - Inclusion criteria: heart disease with ejection fractions ≤ 0.35; not receiving diuretics, digoxin, or vasodilators for the treatment of HF - Number: treatment group (2111); control group (2117) - Mean age (years): treatment group (59.1); control group (59.1) - Sex (M): treatment group (88.5%); control group (88.6%) - CKD stage (SCr): treatment group (1.2 mg/dL); control group (1.2 mg/dL) - DM: treatment group (15.4%); control group (15.1%) - Exclusion criteria: > 80 years; haemodynamically serious valvular disease requiring surgery; unstable angina pectoris (or requiring revascularization procedures); MI during the previous month; severe pulmonary disease; SCr > 2 mg/dL; any other disease that might shorten survival/impepe participation
Interventions	Treatment group - Enalapril: 2.5 to 10 mg twice/day Control group - Placebo
Outcomes	- Death - Hospitalisations - Development of HF
Notes	- Funding: Government & Merck - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
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SOLVD (Prevention) 1992 (Continued)

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Independent Data & Safety Monitoring Board (not specified if it was aware about the treatments)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	< 10% lost to follow up; insufficient information on analysis to permit judgement on intention-to-treat.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears free from other bias

SOLVD (Treatment) 1992

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: June 1986 to January 1991 (enrolment) - Duration of follow-up: 41.4 months (mean)
Participants	- Countries: Belgium, Canada, USA - Setting: multicentre (83 sites) - Inclusion criteria: heart disease with ejection fractions ≤ 0.35; taking drugs other than ACEi as conventional therapy for congestive HF - Total number of study participants (CKD cohort): 1036 (40.3% of total cohort); treatment group (498); control group (538) - Mean age $\pm$ SD (years) (CKD cohort): treatment group (64.1 ± 8.3); control group (64.5 ± 7.6) - Sex (M/F) (CKD cohort): 782/254 - CKD stage (CKD cohort): eGFR < 60 (but SCr < 2 mg/dL) - DM (CKD cohort): treatment group (30%); control group (29%) - Exclusion criteria: >80 years; haemodynamically serious valvular disease requiring surgery; unstable angina pectoris (or requiring revascularization procedures); MI during the previous month; severe pulmonary disease; SCr > 2 mg/dL; any other disease that might shorten survival/impede participation *Baseline SCr data were available for 2502/2569 participants to determine CKD status.
Interventions	Treatment group - Enalapril: 2.5 to 20 mg/day as per protocol Control group - Placebo
Outcomes	Death (any cause)

SOLVD (Treatment) 1992 (Continued)

- Cause-specific death (cardiac)
- All-cause and cause-specific (cardiac) hospitalisation
- Composite endpoint (death (any cause) or hospitalisation for HF)
- Worsening kidney function

Notes

- Funding: supported under contracts from the National Heart, Lung, and Blood Institute and by a gift from Merck Sharp and Dohme, which had no part in the design, conduct, or monitoring of the study or in the analysis, interpretation, or reporting of the results
- Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Pharmacy provided with sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% patients lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	Protocol available, all prespecified outcomes presented
Other bias	Low risk	The study appears to be free of other sources of bias

SPICE 2000

Methods	• Study design: double-blind RCT • Study duration: October 1996 to June 1997 • Duration of follow-up: 12 weeks
Participants	• Countries: 7 • Setting: multicentre (number of sites not reported) • Inclusion criteria: LVEF < 35%, CHF (NYHA class II through IV), and intolerance of ACEi • Number: treatment group (179) control group (91) • Median age, IQR (years): treatment group (66, 58 to 74); control group (65, 58 to 73) • Sex (M): treatment group (65.9%); control group (74.7%) • CKD stage: eGFR not defined but SCr level $\geq 220 \mu\text{mol/L}$ (2.5 mg/dL) was an exclusion criterion • DM: treatment group (20.1%); control group (16.5%)

SPICE 2000 (Continued)

- Exclusion criteria: currently taking an ACEi, SCr $\geq$ 220 μ mol/L (2.5 mg/dL); potassium > 5.5 mmol/L (5.5 mg/dL); history of serious hyperkalaemia induced by use of an ACEi; use of potassium-sparing diuretics; known renal arterial stenosis; kidney transplantation

Interventions	Treatment group • Candesartan: 4 to 16 mg Control group • Placebo
Outcomes	• Drug tolerability • Assessment of NYHA class, physical examination, laboratory tests • 6-minute walk test • QoL assessment • Compliance assessment • Evaluation for adverse events
Notes	• Funding: Astra-Merck • Details on number screened unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	Some of the authors are employees of Astra-Merck

Statsenko 2007

Methods	• Study design: open prospective RCT • Study duration: not reported • Duration of follow-up: 16 weeks
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Statsenko 2007 (Continued)

Participants	- Country: Russia - Setting: not reported - Inclusion criteria: aged 45 to 70 years; CHF (NYHA class II-III); T2DM - Number: treatment group (30); control group (30) - Mean age $\pm$ SD (years): treatment group (62.9 ± 1.66); control group (62.8 ± 1.43) - Sex (M/F): 28/32 - CKD stage (baseline eGFR): treatment group (82.2); control group (87.1) - DM: 100% - Exclusion criteria: not reported
Interventions	Treatment group - Mildronate: 1 g/day - Standard therapy Control group - Standard therapy
Outcomes	- Cardio-haemodynamic indices - Kidney function - QoL
Notes	- Funding: not reported - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

SWORD 1995

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: 2.3 years of recruitment - Duration of follow-up: 148 days (mean)
Participants	- Countries: multinational (number not reported) - Setting: multicentre (546 sites), outpatients - Inclusion criteria: LVEF $\leq 40\%$ and either a recent (6 to 42 days) MI or symptomatic HF with a remote (> 42 days) MI - Number: treatment group (1549); control group (1572) - Mean age $\pm$ SD (years): treatment group (60.4 ± 10.1); control group (59.9 ± 9.8) - Sex (M): treatment group (86%); control group (86%) - CKD stage: not defined but CrCl < 50 mL/min was an exclusion criterion - DM: not reported - Exclusion criteria: unstable angina pectoris; class IV HF; history of life-threatening arrhythmia (sustained ventricular tachycardia/fibrillation or cardiac arrest) unrelated to an MI; history of sick sinus syndrome or high-grade atrioventricular block untreated by a permanent pacemaker; history of recent (within 14 days) coronary angioplasty or CABG; electrolyte abnormalities (serum potassium < 4.0 mmol/L or magnesium < 0.75 mmol/L); CrCl < 50 mL/min, corrected QT > 460 ms; use of concomitant anti-arrhythmic drugs (except beta-adrenergic blockers, calcium-channel blockers, or digoxin) or drugs that prolong the QT interval
Interventions	Treatment group - d-Sotalol: 100 mg increased to 200 mg twice/day, if tolerated Control group - Placebo
Outcomes	- Death (any cause) - Cardiac death - CV death, presumed arrhythmic death, non-fatal severe arrhythmic events, hospital admission for CV causes, and combinations of these endpoints
Notes	- Funding: Supported by a grant from Bristol-Myers Squibb - Study terminated - Authors did not report screening information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Group sequential design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	The data for interim analyses were unblinded by an independent third party

SWORD 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Termination recommended by interim analysis
Selective reporting (reporting bias)	Low risk	Study rationale and design previously published; all prespecified outcomes presented
Other bias	High risk	Sponsor involved in study design and management

Taheri CAPD 2012

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: February to September 2008 - Duration of follow-up: 6 months
Participants	- Country: Iran - Setting: single centre; outpatient - Inclusion criteria: HF (NYHA class III and IV, LVEF $\leq$ 45%); CKD (on CAPD); on ACEi or ARB; serum potassium $\leq$ 5.5 mEq/L - Number: treatment group (9); control group (9) - Mean age $\pm$ SD (years): treatment group (50.7 $\pm$ 17.4); control group (57.2 $\pm$ 13.1) - Sex (M/F): treatment group (5/4); control group (5/4) - CKD stage: on CAPD - DM: 52.6% - Exclusion criteria: not reported
Interventions	Treatment group - Spironolactone: 25 mg every other day Control group - Placebo
Outcomes	- Serum potassium (hyperkalaemia) - Serum Hb - Ejection fraction - Death (6 months)
Notes	- Funding: supported by a grant from the Isfahan Kidney Research Center, Isfahan University of Medical Sciences and ethics committee of Isfahan School of Medicine - Authors report the number of patients screened, but no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available

Taheri CAPD 2012 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow up; not all patients randomised were included in final analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Unclear how study was powered

Taheri HD 2009

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: 2005 - Duration of follow-up: 6 months
Participants	- Country: Iran - Setting: single centre; outpatient - Inclusion criteria: HF (NYHA class III and IV, LVEF $\leq$ 45%); CKD (on HD); on ACEi or ARB and erythropoietin; and serum potassium $\leq$ 5.5 mmol/L - Number: treatment group (8); control group (8) - Mean age $\pm$ SD (years): treatment group (59.5 $\pm$ 6.5); control group (56.8 $\pm$ 9.3) - Sex (M/F): treatment group (5/3); control group (6/2) - CKD stage: HD - DM: treatment group (62.5%); control group (62.5%) - Exclusion criteria: not reported
Interventions	Treatment group - Spironolactone: 25 mg after each dialysis session for 6 months Control group - Placebo
Outcomes	- Serum potassium (hyperkalaemia) - Ejection fraction, left ventricular mass - Death (any cause) (6 months) - Hospitalisations for HF (6 months)* *Total number of hospitalisations reported, not the number of patients hospitalised; unable to estimate risk ratio
Notes	- Funding: not reported - Authors did not report screening information

Taheri HD 2009 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost to follow up; not all patients randomised were included in final analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Unclear how study was powered

Toblli 2007

Methods	- Study design: pilot, double-blind, placebo-controlled RCT - Study duration: not reported - Duration of follow-up: 6 months
Participants	- Country: Argentina - Setting: single centre; outpatient office - Inclusion criteria: Hb < 12.5 g/dL for men and 11.5 g/dL for women, serum ferritin < 100ng/ml and/or with transferrin saturation ≤ 20%; CrCl ≤ 90 mL/min, and LVEF ≤ 35% - Number: treatment group (20); control group (20) - Mean age ± SD (years): treatment group (74 ± 8) control group (76 ± 7) - Sex (M/F): not reported (adult patients of both genders) - CKD stage (CrCl, mL/min): treatment group (37.7 ± 10.2; control group (39.8 ± 10.1) - DM: not reported - Exclusion criteria: HD therapy; anaemia not due to iron deficiency available for erythropoiesis; NYHA functional class I; history of allergy to the iron supplements; acute bacterial infections, parasitism known in the 4 previous weeks, and neoplasm; chronic digestive diseases; hypothyroidism; congenital cardiopathies; receiving iron supplements in the 4 previous weeks; receiving rhEPO in the 4 previous weeks; history of hospitalisation during the 4 weeks before enrolment into the study were excluded from the study
Interventions	Treatment group Iron sucrose complex: 200 mg/week Control group

Toblli 2007 (Continued)

- Isotonic saline solution: 200 mg/week

Outcomes	• Minnesota Living with HF Questionnaire • 6-min walk test • Biochemical measures and echocardiography evaluation
Notes	• Funding: none • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Exercise capacity was quantified using a 6MW test with physicians blinded to the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears free from other bias

TOPCAT 2014

Methods	• Study design: phase 3, double-blind, placebo-controlled RCT • Study duration: August 2006 to January 2012 • Duration of follow-up: 3.3 years (mean)
Participants	• Countries: 6 (USA, Canada, Brazil, Argentina, Russia, Georgia) • Setting: multicentre (188 sites) • Inclusion criteria: symptomatic HF and a LVEF $\geq$ 45% • Number: treatment group (1722); control group (1723) • Median age, IQR range (years): treatment group: (68.7, 61 to 76.4); control group (68.7, 60.7 to 75.5) • Sex (M/F): treatment group (834/888); control group (836/887) • CKD stage (median eGFR, IQR): treatment group: (65.3, 53.9 to 79.2); control group (65.5, 53.5 to 79.1) • DM: not reported • Exclusion criteria: severe systemic illness with a life expectancy of less than 3 years; severe kidney dysfunction (eGFR of < 30 mL/min/1.73 m² or SCr $\geq$ 2.5 mg/dL); specific coexisting conditions, medications, or acute events

TOPCAT 2014 (Continued)

Interventions	Treatment group • Spironolactone; 15 to 45 mg/day Control group • Placebo
Outcomes	• Composite of death from CV causes, aborted cardiac arrest • Hospitalisation for the management of HF • Death from any cause • Hospitalisation for any cause • Hyperkalaemia • Hypokalaemia • Elevated SCr level
Notes	• Funding: National Heart, Lung, and Blood Institute • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified according to whether the patient met the criterion for previous hospitalisation or BNP elevation
Allocation concealment (selection bias)	Unclear risk	Permuted blocks
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical end-point committee at Brigham and Women's Hospital according to prespecified criteria; members of the committee were unaware of the study-drug assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears free from other bias

TRACE 1994

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: May 1990 and June 1992 (enrolment) • Duration of follow-up: 4 years
Participants	• Country: Denmark • Setting: multicentre (27 sites)

TRACE 1994 (Continued)

- Inclusion criteria: hospitalised with MI; ejection fraction $\leq 35\%$; symptoms or NYHA not reported
- Number: treatment group (876); control group (873)
- Mean age (years): treatment group (67.7); control group (67.3)
- Sex (M): treatment group (72%); control group (71%)
- CKD stage: not reported
- DM: treatment group (13%); control group (14%)
- Exclusion criteria: absolute or relative contraindication to ACEi or a definite need for ACEi; severe, uncontrolled DM; hyponatraemia (< 125 mmol sodium/L); elevated SCr level (2.3 mg/dL); pregnancy or lactation; acute pulmonary embolism; vascular collagen disease; non-ischaemic obstructive heart disease; unstable angina pectoris requiring immediate invasive therapy; severe liver disease; neutropenia; concurrent immunosuppressive or antineoplastic therapy; drug or alcohol abuse; or treatment with another investigational drug

Interventions	Treatment group • Trandolapril: 1 mg once/day Control group • Matching placebo
Outcomes	• Death (any cause) • Death from a CV cause • Sudden death • Progression to severe HF (defined as the first of the following events: hospital admission for HF, death due to progressive HF, or HF necessitating the administration of open-label ACEi) • Recurrent infarction (fatal or nonfatal) • Change in the wall-motion index
Notes	• Funding: Supported by grants from Roussel-Uclaf and Knoll • Authors report the number of patients screened and reasons for screen failure (in protocol paper)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated assignment scheme with randomisation in blocks of four and stratification according to the centre and the degree of left ventricular dysfunction
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	$< 10\%$ lost to follow-up; all patients randomised included in final analysis

TRACE 1994 (Continued)

Selective reporting (reporting bias)	Low risk	Study rationale and design previously published
Other bias	High risk	Sponsor involved in study conduct

ULTIMATE-HFrEF 2013

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: not reported - Duration of follow-up: 12 weeks
Participants	- Country: Korea - Setting: single centre; outpatient - Inclusion criteria: ≥ 18 years; established clinical diagnosis of chronic systolic HF with NYHA class II-IV symptoms currently and $LVEF \leq 40\%$ - Number: treatment group (21); control group (20) - Mean age $\pm$ SD (years): treatment group (62.1 ± 12.3); control group (65.2 ± 11.5) - Sex (M/F): treatment group (12/8); control group (16/5) - CKD stage: not reported (eGFR < 30 excluded) - DM: not reported - Exclusion criteria: $FEV_1 < 80\%$ of predicted value or $FEV_1/FVC < 70\%$ on spirometry at screening; other valve diseases greater than mild stenosis and/or regurgitation; neuromuscular, orthopaedic, or other non-cardiac conditions that prevent completion of a maximal exercise testing; infiltrative/ inflammatory myocardial or pericardial disease; primary pulmonary arteriopathy; current use of nitrate preparations therapy or other PDE5 inhibitors (i.e. sildenafil, vardenafil, tadalafil) or cytochrome P450 3A4 (CYP3A4) inhibitors (ketoconazole, itraconazole, erythromycin); severe hypotension (SBP < 90 mm Hg or DBP < 50 mm Hg) or uncontrolled hypertension (SBP > 180 mm Hg or DBP > 100 mm Hg); non-cardiac illness with estimated life expectancy less than 1 year at the time of study entry, based on the judgment of the attending physician; known severe kidney dysfunction (GFR < 30 mL/min/1.73 m² by MDRD equation); known severe liver disease (ALT or AST level > 3 times the upper normal limit, alkaline phosphatase or total bilirubin > 2 times the upper normal limit); actively involved in any physical training program for at least 6 months before study entry; listed for heart transplantation
Interventions	Treatment group - Udenafil: 100 mg twice/day Control group - Placebo
Outcomes	- VO₂ max - LVEF - Serum BNP - Change of ventilator efficiency - Change in NYHA class - Change of pulmonary artery systolic pressure - Change of symptomatic status - Safety - Death (any cause), cardiac death, and HF-related admission and their composite (12 week)
Notes	Funding: study is funded by the Korea Healthcare Technology Research and Development Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea; and Dong-A Pharmaceutical Co., Ltd

ULTIMATE-HFrEF 2013 (Continued)

- Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, interviewers with predefined questionnaires, sonographers, technicians performing cardiopulmonary exercise test, and investigators were all blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% withdrew from study
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other bias

US-Carvedilol 1996

Methods	• Study design: double-blind, placebo-controlled, stratified RCT • Study duration: April 1993 to February 1995 • Duration of follow-up: 6 months (12 months for those with mild HF)
Participants	• Country: USA • Setting: multicentre (65 sites) • Inclusion criteria: symptoms of HF for at least 3 months and ejection fraction ≤ 0.35 despite at least 2 months of treatment. • Number: treatment group (696); control group (398) • Mean age $\pm$ SD (years): treatment group (57.91 ± 2.2); control group (58.1 ± 12.3) • Sex (M/F): treatment group (534/162); control group (304/94) • CKD stage: not reported (but excluded if clinically important kidney disease) • % DM: not reported • Exclusion criteria: major CV event or had undergone a major surgical procedure within 3 months of entry into the study; uncorrected, primary valvular disease; active myocarditis; sustained ventricular tachycardia or advanced heart block not controlled by anti-arrhythmic intervention or a pacemaker; SBP > 160 or < 85 mm Hg or DBP > 100 mm Hg; a heart rate < 68 BPM; clinically important hepatic or kidney disease; any condition other than HF that could limit exercise or survival; or receiving calcium-channel blockers, alpha- or beta-adrenergic agonists or antagonists, or class IC or III anti-arrhythmic agents

US-Carvedilol 1996 (Continued)

Interventions	Treatment group - Carvedilol: target dose 25 to 50 mg twice/day Control group - Placebo
Outcomes	- Death (any cause) - CV morbidity - Safety outcomes
Notes	- Funding: Supported by grants from SmithKline Beecham Pharmaceuticals and Boehringer–Mannheim Therapeutics - Authors do not report the number of patients screened or reasons for screen failure, but they do provide the failure rate for the open-label, run-in period - Study terminated early as advised by the Data and Safety Monitoring Board as a significant effect of carvedilol on survival was identified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All deaths were classified by investigators who had no knowledge of the patients' treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised were included in analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published results include all expected outcomes
Other bias	High risk	The study was stopped early on the recommendation of the Data and Safety Monitoring Board. No formal stopping rules were pre-specified

V-HEFT I 1986

Methods	- Study design: placebo-controlled RCT - Study duration: March 1980 to December 1985 - Duration of follow-up (mean): 2.3 years
Participants	Country: USA

V-HEFT I 1986 (Continued)

- Setting: multicentre (11 sites)
- Inclusion criteria: men aged 18 to 75 years with chronic congestive HF (cardiac dilatation or LV functional impairment in association with reduced exercise tolerance)
- Number: treatment group 1 (183); treatment group 2 (186); control group (273)
- Mean age (years): treatment group 1 (58.3); treatment group 2 (58.3); control group (8.5)
- Sex (M): 100%
- CKD stage: not reported
- DM: treatment group 1 (18.7%); treatment group 2 (17.2%); control group (24.5%)
- Exclusion criteria: if exercise tolerance was limited by chest pain rather than breathlessness and fatigue; MI within the previous 3 months; or substantial obstructive valvular disease or considerable obstructive myocardial disease, chronic pulmonary disease, or other disease likely to limit five-year survival; require long-acting nitrates for angina, calcium antagonists, beta-blockers, or antihypertensive drugs other than diuretics

Interventions	Treatment group 1 • Prazosin: 20 mg/day Treatment group 2 • Hydralazine: 300 mg/day • Isosorbide dinitrate: 160 mg/day Control group • Placebo
Outcomes	• Death (any cause) • Haemodynamic response
Notes	• Funding: Supported by the Cooperative Studies Program of the Medical Research Service, Veterans Administration Central Office, Washington, D.C. • Authors do not report the number of patients screened or reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Low risk	Drug kits were labelled with a coded number. When assigning a patient to a treatment group, an investigator called the coordinating centre to learn which coded number would be given to that patient
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised were included in the analysis

V-HEFT I 1986 (Continued)

Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

V-HEFT II 1991

Methods	- Study design: double-blind RCT - Study duration: March 1986 to September 1990 (recruitment) - Duration of follow-up: 2.5 years (average)	
Participants	- Country: USA - Setting: multicentre (13 sites) - Inclusion criteria: men aged 18 to 75 years with CHF (cardiac dysfunction in association with reduced exercise tolerance) - Number: treatment group (401); control group (403) - Mean age (years): treatment group (60.5); control group (60.6) - Sex (M): 100% - CKD stage: not reported - DM: treatment group (19.9%); control group (20.8%) - Exclusion criteria: MI or cardiac surgery within the previous 3 months; angina pectoris limiting exercise or requiring long-term medical therapy; serious obstructive valvular disease; obstructive lung disease, or other diseases likely to limit life expectancy	
Interventions	Treatment group - Hydralazine: 300 mg/day - Isosorbide dinitrate: 160 mg/day Control group - Enalapril: 20 mg/day	
Outcomes	- Death (any cause) - CV death - Haemodynamic effects - Ejection fraction - Exercise tolerance - Hospitalisation - Side effects	
Notes	- Funding: Supported by the Cooperative Studies Program of the Medical Research Service, Department of Veterans Affairs Central Office, Washington, D.C. - Authors report the number of patients screened and reasons for screen failure.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement

V-HEFT II 1991 (Continued)

Allocation concealment (selection bias)	Low risk	The randomisation scheme was centrally controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All deaths were reviewed blindly
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% were lost to follow-up; all patients randomised were analysed
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

V-HEFT III 1996

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: December 1991 to December 1994 (recruitment) - Duration of follow-up: 3 to 39 months
Participants	- Country: USA - Setting: multicentre (24 sites) - Inclusion criteria: males aged > 18 years with a history and physical findings of congestive HF including limitation of exercise tolerance due to dyspnoea and/or fatigue, plus documentation of LV enlargement and/or dysfunction with exhibited reduction of peak exercise performance - Number: treatment group (224); control group (226) - Mean age (years): treatment group (63); control group (64) - Sex (M): 100% - CKD stage: not reported (excluded if SCr $\geq$ 3.0 mg/dL) - DM: treatment group (26%); control group (34%) - Exclusion criteria: clinically important kidney, hepatic, or haematologic disorders (SCr $\geq$ 3.0 mg/dL, serum potassium < 3.5 or > 5.5 mEq/L, or abnormal liver enzymes $\geq$ 2 times the upper limit of normal); chronic anaemia (HCT < 30%); severe chronic obstructive bronchopulmonary disease, which limits exercise or requires steroids or chronic bronchodilator therapy; inability to perform an exercise test or walk on a treadmill, or need to stop exercise for conditions other than HF; symptomatic hypotension; aortic stenosis, mitral stenosis, or hypertrophic cardiomyopathy; severe aortic or mitral valvular regurgitation; severe hypertension requiring therapy in addition to diuretics and enalapril; haemodynamically significant pericardial disease; angina pectoris severe enough to require long-acting nitrate therapy or frequent administration of sublingual nitroglycerin (> 4 tablets/week); acute MI, coronary artery bypass graft surgery, or angioplasty within 3 months of screening; a cerebrovascular accident within the past 6 months; symptomatic or life-threatening arrhythmias that are not medically controlled or require the use of an automatic implanted cardioverter-defibrillator; allergy or intolerance to calcium antagonists or converting enzyme inhibitors; treatment required with calcium antagonists, beta-blockers, long-acting nitrates, or other vasodilators (except ACEi); treatment with an investigational drug within 4 weeks before study entry; and significant comorbidity which, in the investigator's opinion, makes survival for the duration of the study unlikely or would otherwise interfere with adherence to the protocol

V-HEFT III 1996 (Continued)

Interventions	Treatment group - Felodipine: target 5 mg twice/day Control group - Placebo
Outcomes	- Exercise capacity - Ejection fraction - QoL - Neurohormones - Hospitalisations - Adverse events - Death - Haemodynamic effects
Notes	- Funding: Sharp and Dohme Research Laboratories were responsible for providing the case report forms, assigning the felodipine ER allocation numbers, providing drug supplies, and monitoring the study centres to ensure adherence to the protocol. Effective January 1994, Astra Merck Inc. became the sole V-HeFT III sponsor - Authors report the number of patients screened and reasons for screen failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Low risk	Only the statistical coordinating centre had direct access to the randomisation codes. Each centre's pharmacy was provided with sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Methods for main outcome assessment (exercise capacity) not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias.

Val-HeFT 1999

Methods	Study design: double-blind, placebo-controlled RCT
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Val-HeFT 1999 (Continued)

	- Study duration: March 1997 to October 2000 - Duration of follow-up: 35 months
Participants	- Countries: 16 - Setting: multicentre (302 sites); outpatient - Inclusion criteria: HF (NYHA class II-IV, LVEF < 40%, clinically stable); receiving fixed-dose drug regimen (ACEi, diuretics, digoxin, or beta-blockers) for at least 2 weeks - Total number of study participants (CKD cohort*): 2916 (58.2% of total cohort); treatment group (1476); control group (1440) - Mean age $\pm$ SD (years) (CKD cohort): not reported - Sex (M) (CKD cohort): not reported - CKD stage (CKD cohort): eGFR < 60 (but creatinine $\leq$ 2.5 mg/dL) - DM (CKD cohort): not reported - Exclusion criteria: right HF caused by pulmonary disease; acute MI; cardiac surgery or PTCA within the past 3 months; prior cardiac transplant and patients listed for cardiac transplant; coronary artery disease likely to require intervention; unstable angina; sustained ventricular tachycardia with syncope; episodes within the past 3 months that is untreated; haemodynamically significant valve disease; hypertrophic cardiomyopathy; cerebral vascular accidents within the past 3 months; clinically important kidney (SCr level > 2.5 mg/dL), hepatic, or haematological disorders; malignancies likely to limit 5-year survival; any disease with a life expectancy less than 5 years; contraindication to ARB *Of the 5010 patients randomised, 5002 patients had baseline eGFR values and 4958 patients had urinalysis at baseline. CKD was reported in 2916 patients (defined as an eGFR < 60). The subgroup analysis used in this review, reported data for 2916 CKD patients (1476 in the treatment group and 1440 in the control group)
Interventions	Treatment group - Valsartan: 160 mg twice/day, up-titrated as per protocol Control group - Placebo
Outcomes	- Death (any cause) - Composite (death, sudden death events with resuscitation, hospitalisations for CHF, administration for at least a 4-hour duration of intravenous inotropic or vasodilating agents for worsening HF) - All-cause hospitalisations - Changes from baseline in NYHA functional class - Signs and symptoms of CHF - Ejection fraction - LV internal diastolic diameter - Hypotension - QoL scores - Neurohormone levels
Notes	- Funding: Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement

Val-HeFT 1999 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information about the randomisation process to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measurement unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% patients lost to follow up; not all patients randomised were included in final analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Sponsor (Novartis) performed site monitoring, data collection, and data analysis

VALIANT 2000

Methods	- Study design: double-blind RCT - Study duration: December 1998 to June 2001 - Duration of follow-up: 24.7 months (median)
Participants	- Countries: 24 - Setting: multicentre (931 sites) - Inclusion criteria: acute MI (between 0.5 and 10 days previously) that was complicated by clinical or radiologic signs of HF, evidence of left ventricular systolic dysfunction - Number: treatment group 1 (4909); treatment group 2 (4885); control group (4909) - Mean age $\pm$ SD (years): treatment group 1 (65.0 ± 11.8); treatment group 2 (64.6 ± 11.9); control group (64.9 ± 11.8) - Sex (M/F): treatment group 1 (3365/1544); treatment group 2 (3395/1490); control group (3373/1536) - CKD stage (SCr, mg/dL): treatment group 1 (1.1 ± 0.3); treatment group 2 (1.1 ± 0.3); control group (1.1 ± 0.4) - DM: treatment group 1 (23.1%); treatment group 2 (23.5%); control group (22.8%) - Exclusion criteria: previous intolerance or contraindication to an ACEi or ARB; clinically significant valvular disease; another disease known to limit life expectancy severely; absence of written informed consent
Interventions	Treatment group 1 - Valsartan: 20 to 80 mg twice/day Treatment group 2 - Valsartan: 20 to 40 mg twice/day - Captopril: 6.25 to 25 mg 3 times/day Control group - Captopril: 6.25 to 25 mg 3 times/day

VALIANT 2000 (Continued)

Outcomes	Death from any cause
Notes	- Funding: Supported by a grant from Novartis Pharmaceuticals - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated, interactive voice-response system was used for randomisation
Allocation concealment (selection bias)	Unclear risk	Until the data base was locked, only the data and safety monitoring board and an independent drug-distribution group maintained the code used for treatment-group assignments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All prespecified end points were adjudicated by a clinical end-point committee that was unaware of the treatment group assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	High risk	All analyses were performed at the Duke Clinical Research Institute and were verified by the sponsor. The manuscript was prepared by the academic researchers, who made the publication decisions, and was reviewed by the sponsor

van den Broek 1995

Methods	- Study design: double-blind RCT - Study duration: not reported - Duration of follow-up: 12 weeks
Participants	- Country: Netherlands - Setting: not reported - Inclusion criteria: history of congestive HF (NYHA class II-III), LVEF $\leq$ 40%, peak oxygen consumption $\leq$ 20 mL/min/kg - Number: treatment group 1 (9); treatment group 2 (11) - Mean age $\pm$ SD (years): treatment group 1 (55 $\pm$ 4); treatment group 2 (62 $\pm$ 2) - Sex (M/F): treatment group 1 (7/2); treatment group 2 (5/4) - CKD stage: not reported - DM: not reported

van den Broek 1995 (Continued)

- Exclusion criteria: acute MI, coronary bypass surgery <3 months prior to study, unstable angina pectoris, systolic BP <100 mmHg and/or diastolic BP <60 mmHg, chronic obstructive pulmonary disease, claudication, or any other limitation of measuring peak oxygen consumption

Interventions	Treatment group 1 • Spirapril: 6 mg/day Treatment group 2 • Captopril: 12.5 mg, 3 times/day
Outcomes	• MAP • Calf blood flow • Calf vascular resistance • Hepatic blood flow • Serum ACE activity • Exercise time • VO₂ max • Renal plasma flow • GFR and filtration fraction • Adverse effects
Notes	• Funding: not reported • Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	10% withdrew from study; not all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

VERITAS 1 2005

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: April 2003 through January 2005 - Duration of follow-up: 6 months
Participants	- Countries: Australia, Europe, Israel, North America - Setting: multicentre (53 sites); inpatient - Inclusion criteria: aged >18 years and admitted to hospital with acute HF within the previous 24 hours and persistence of dyspnoea at rest - Number: treatment group (368); control group (367) - Mean age $\pm$ SD (years): treatment group (70 ± 13); control group (70 ± 12) - Sex (M/F): treatment group (220/147); control group (222/139) - CKD stage (mean SCr $\pm$ SD, mg/dL): treatment group (1.4 ± 0.46); control group (1.3 ± 0.45) (37.6% of total sample had medical history of renal impairment) - DM: treatment group (45%); control group (46%) - Exclusion criteria: cardiogenic shock within 48 hours; ST segment elevation MI; ongoing ischaemia or administration of a thrombolytic agent; hypotension (SBP < 100 mm Hg in patients not receiving a vasodilator or < 120 mm Hg in those receiving a vasodilator), anaemia (Hb < 10 g/dL, HCT < 30%), or kidney dysfunction (SCr > 2.5 mg/dL)
Interventions	Treatment group - Tezosentan infusion: 5 mg/h for 30 minutes, followed by 1 mg/h for 24 to 72 hours Control group - Placebo
Outcomes	- Change in dyspnoea (3, 6, and 24 hours) - Death (30 days, 6 months) - Worsening HF at 7 days
Notes	- Funding: The VERITAS studies were funded by Actelion Ltd - Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	High risk	< 10% lost to follow-up (primary outcome); not all patients analysed as randomised

VERITAS 1 2005 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	Sponsor involved in study conduct

VERITAS 2 2005

Methods	- Study design: double-blind, placebo-controlled RCT - Study duration: April 2003 to January 2005 - Duration of follow-up: 6 months	
Participants	- Countries: Australia, Europe, Israel, North America - Setting: multicentre (57 sites); inpatient - Inclusion criteria: aged > 18 years and admitted to hospital with acute HF within the previous 24 hours and persistence of dyspnoea at rest - Number: treatment group (362); control group (351) - Mean age $\pm$ SD (years): treatment group (70 $\pm$ 11); control group (70 $\pm$ 13) - Sex (M/F): treatment group (222/138); control group (191/156) - CKD stage mean SCr $\pm$ SD, mg/dL: treatment group (1.3 $\pm$ 0.43); control group (1.3 $\pm$ 0.42) (35.1% of total sample had medical history of renal impairment) - DM: treatment group (53%); control group (47%) - Exclusion criteria: cardiogenic shock within 48 hours; ST segment elevation MI; ongoing ischaemia or administration of a thrombolytic agent; hypotension (SBP < 100 mm Hg in patients not receiving a vasodilator or < 120 mm Hg in those receiving a vasodilator), anaemia (Hb < 10 g/dL, HCT < 30%), or kidney dysfunction (SCr > 2.5 mg/dL)	
Interventions	Treatment group - Tezosentan infusion: 5 mg/h for 30 minutes, followed by 1 mg/h for 24 to 72 hours Control group - Placebo	
Outcomes	- Change in dyspnoea (3, 6, and 24 hours) - Death (30 days, 6 months) - Worsening HF at 7 days	
Notes	- Funding: The VERITAS studies were funded by Actelion Ltd - Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

VERITAS 2 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% lost to follow-up (primary outcome); not all patients analysed as randomised
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	Sponsor involved in study conduct

Vizzardi 2014

Methods	- Study design: single-blind, placebo-controlled, blinded endpoint, RCT - Study duration: February 2001 to September 2004 - Duration of follow-up: 44 months (mean)
Participants	- Country: Italy - Setting: single centre - Inclusion criteria: NYHA (NYHA) classes I to II HF and LVEF < 40% - Number: treatment group (65); control group (65) - Mean age $\pm$ SD (years): treatment group (61 ± 14.7); control group (65 ± 17.4) - Sex (M/F): not reported - CKD stage (eGFR): treatment group (82.5 ± 27.9); control group (71.3 ± 18.09) - DM: treatment group (15.38%); control group (12.31%) - Exclusion criteria: eGFR < 30 mL/min/ 1.73 m²; serum potassium > 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; IV 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
Interventions	Treatment group - Spironolactone: 25 mg/day Control group - Placebo
Outcomes	- CV death or CV hospitalisations - Death (any cause) - CV death - CV hospitalizations and HF hospitalisations
Notes	Funding: none

Vizzardi 2014 (Continued)

- Authors report the number of patients screened and some other information pertaining to eligibility, but details on screen failures were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The review of medical records and the endpoints adjudication were performed by a committee of 3 cardiologists who were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% lost to follow-up; all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes presented
Other bias	Low risk	The study appears free from other bias

Xamoterol in SHF 1990

Methods	• Study design: double-blind RCT • Study duration: November 1987 to March 1989 (enrolment) • Duration of follow-up: 13 weeks
Participants	• Countries: 10 • Setting: multicentre (66 sites) • Inclusion criteria: NYHA class III-IV despite stable therapy with diuretics and an ACEi • Number: treatment group (327); control group (150) • Mean age $\pm$ SD (years): treatment group (62 ± 10); control group (62 ± 11) • Sex (M/F): not reported • CKD stage: not reported • DM: not reported • Exclusion criteria: women of childbearing potential; MI in the past 8 weeks; pronounced renal impairment (SCr > 250 μmol/L); exercise limitation due to non-cardiac disease; aortic or pulmonary obstructive valvular disease; hypertrophic obstructive cardiomyopathy; receiving concurrent therapy with any drug which has its activity through B-adrenoreceptors; capable of < 1 min of exercise on testing; > 25% variability in baseline exercise duration between the beginning and the end of the run-in period; chest pain as the sole limiting symptom during the exercise test
Interventions	Treatment group • Xamoterol: 200 mg twice/day

Xamoterol in SHF 1990 (Continued)

Control group

- Placebo

Outcomes

- Death
- Symptoms
- Exercise tolerance
- Continuous ambulatory monitoring
- Noradrenaline concentration
- Adverse events

Notes

- Funding: Financial support provided by ICI Pharmaceuticals
- Authors report the number of patients screened, but no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% withdrew from study
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Sponsor involved in study conduct

Yamada 2013

Methods

- Study design: prospective RCT
- Study duration: not reported
- Duration of follow-up: 3 years

Participants

- Country: Japan
- Setting: not reported
- Inclusion criteria: mild to moderate CHF outpatients (NYHA class 1.9 ± 0.6; ischaemic origin: 54%) with LVEF < 40% (28 ± 8%) and SCr < 3.0 mg/d
- Number: treatment group (19); control group (19)
- Mean age ± SD (years): not reported

Yamada 2013 (Continued)

- Sex (M/F): not reported
- CKD stage: SCr < 3.0 mg/d
- DM: not reported
- Exclusion criteria: not reported

Interventions	Treatment group • Atorvastatin: 10 mg/d Control group • Conventional treatment without atorvastatin
Outcomes	• Chronic kidney injury • Interleukin-6 • High-sensitive CRP • Oxidized low-density lipoprotein
Notes	• Funding: not reported • Conference abstract publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Study was described as randomised, allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Yang 2015a

Methods	• Study design: parallel RCT • Study duration: August 2011 to November 2013 (enrolment) • Duration of follow-up: 6 months
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Yang 2015a (Continued)

Participants	- Country: China - Setting: multicentre (10 sites); inpatient - Inclusion criteria: > 60 years and admitted with acute HF (NYHA class III or IV) concurrent with hypertension and DM - Number: treatment group 1 (37); treatment group 2 (35) - Mean age $\pm$ SD (years): treatment group 1 (71.53 ± 11.28); treatment group 2 (70.68 ± 9.34) - Sex (M/F): treatment group 1 (20/17); treatment group 2 (19/16) - CKD stage (mean eGFR $\pm$ SD): treatment group 1 (47.2 ± 4.8); treatment group 2 (45.0 ± 6.2) - DM: 100% - Exclusion criteria: SBP < 100 mm Hg; evidence of cardiogenic shock or other CV disorder contradicting IV administration of a vasodilator; acute coronary syndrome; severe valve stenosis; obstructive hypertrophic cardiomyopathy; restrictive cardiomyopathy or constrictive pericarditis; severe chronic obstructive pulmonary disease; acute phase of some other pulmonary disease; severe liver or kidney (> 2-fold maximum normal value of creatinine) insufficiency; history of allergy to nitroglycerin or urapidil; malignant or psychiatric disease or currently taking other medications or being enrolled in another clinical study
Interventions	Treatment group 1 - Nitroglycerin: 10 mg/min for the initial 6 hours and then adjusted to a maximum rate of 20 mg/min for the remaining administration time (maximum of 140 hours) Treatment group 2 - Urapidil: 50 or 100 mg/min for an initial 6 hours and then adjusted to 300 mg/min for the remaining administration time (maximum of 140 hours)
Outcomes	- Blood pressure - Heart rate - NT-proBNP levels - Red blood cell distribution width - Lipid profiles - Liver function (total bilirubin, ALT and AST) - Kidney function (creatinine, BUN) - Fasting and postprandial plasma glucose - Glycohaemoglobin and echocardiogram results (left atrium, LVEF, left ventricular cardiac output, early diastolic filling to atrial filling velocity ratio of mitral flow, left ventricular end diastolic volume) - HF rehospitalisation (6 months) - CV death (6 months) - Nonfatal MI (6 months) - Malignant arrhythmia (6 months) - Cardiogenic shock (6 months)
Notes	- Funding: the study was supported by grant from the Capital Medical Development Foundation - Authors did not report screening information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Yang 2015a (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	< 10% lost to follow-up; insufficient information to permit judgement on intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Zhao 2010

Methods	- Study design: RCT - Study duration: September 2006 and July 2008 (enrolment) - Duration of follow-up: 3 months
Participants	- Country: China - Setting: single centre; inpatient - Inclusion criteria: admitted for acute MI and acute decompensated HF (left ventricular function between Killip grade II and III), unable to receive, or refusal to accept thrombolytic therapy or primary PCI on admission - Number: treatment group 1 (27); treatment group 2 (28) - Mean age $\pm$ SD (years): treatment group 1 (67.8 ± 7.0); treatment group 2 (66.4 ± 9.3) - Sex (M): treatment group 1 (51.9%); treatment group 2 (50%) - CKD stage (SCr $\pm$ SD): treatment group 1 (109.4 ± 26.6); treatment group 2 (106.8 ± 20.0) - DM: treatment group 1 (11.1%); treatment group 2 (10.7%) - Exclusion criteria: cardiogenic shock: SBP $\leq$ 90 mm Hg for more than 30 min with signs of low peripheral perfusion such as cyanosis or cold extremities; concomitant valvular heart disease, or hypertrophic cardiomyopathy or restrictive cardiomyopathy; coronary bypass surgery in the past month, or PCI in the past 6 months, or thrombolytic therapy in the past 48 hours; presence of contraindications for anticoagulation therapies, such as recent stroke, major surgery, trauma, or cardiac resuscitation for more than 10 min; administration of positive inotropic agents or other vasodilators in the past 24 hours; requirement for mechanical ventilation; severe hepatic (aspartate aminotransferase or alanine aminotransferase elevation of more than 2 times of the normal value) or kidney dysfunction (SCr > 221 μmol/L); unable to give informed written consent
Interventions	Treatment group 1 - Nesiritide: loading dose of 0.5 μg/kg IV for 90 seconds followed by continuous infusion of 0.0075 μg/kg/min for 72 hours Treatment group 2 - Nitroprusside: initial rate of 10 μg/min, dose adjusted based on blood pressure values for 72 hours
Outcomes	Heart rate

Zhao 2010 (Continued)

- Blood pressure
- 24-hour urine volume
- Dyspnoea
- LVEF
- Neurohormonal assessments
- Death
- Severe ventricular arrhythmia
- Worsening of left ventricular function during hospitalisation
- Rehospitalisation due to worsening HF
- Safety (blood sodium, potassium, and creatinine)

- Notes
- Funding: not reported
 - Authors report the number of patients screened, but no further details.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted by one of the investigators by randomly drawing a number from a container
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	< 10% lost to follow-up; not all patients randomised included in final analysis
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

ACEi - angiotensin-converting enzyme inhibitor/s; ADHF - acute decompensated heart failure; ARB - angiotensin receptor blocker/s; AUC - area under the curve; BPM - beats per minute; BNP - brain natriuretic peptide; BUN - blood urea nitrogen; CABG - coronary artery bypass grafting; CHF - chronic heart failure; CKD - chronic kidney disease; CrCl - creatinine clearance; CV - cardiovascular; DBP - diastolic blood pressure; DM - diabetes mellitus; ECG - electrocardiogram; (e)GFR - (estimated) glomerular filtration rate; ESKD - end-stage kidney disease; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; HIV - human immunodeficiency virus; ICU - intensive care unit; IDDM - insulin-dependent diabetes mellitus; IQR - interquartile range; IV - intravenous/ly; JVD - jugular venous distention; LV - left ventricle/ventricular; LEDD - LV end diastolic dimension; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume; MAP - mean arterial pressure; M/F - male/female; MI - myocardial infarction; NSTEMI - non-ST segment elevation myocardial infarction; NYHA - New York Heart Association; NSAID/s - nonsteroidal anti-inflammatory drug/s; Pd - peritoneal dialysis; PCI - percutaneous coronary intervention; PTCA - percutaneous transluminal coronary angioplasty; QoL - quality of life; RCT - randomised controlled trial; rhEPO - recombinant human erythropoietin; RRT renal replacement therapy; SBP - systolic blood pressure; SCr - serum creatinine; SD - standard deviation; SOFA - sequential organ failure assessment; T2DM - type 2 diabetes mellitus; VAS - visual analogue scale; WCC - white cell count

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

Study	Reason for exclusion
AIM-HIGH 2015	Wrong population: not heart failure
ALLHAT & ALHAT-LLT 1996	Wrong population: not heart failure
Alpha Omega 2010	Wrong population: not heart failure
ALTITUDE 2009	Wrong population: not heart failure
ARTS 2012	Study duration/outcome measures < 3 months
ATTEMPT-CVD 2018	Wrong population: not heart failure
BASEL 2005	Wrong intervention: not pharmacological
BLOCADE 2015	Wrong population: not heart failure
BNP-CADS 2007	Study duration/outcome measures < 3 months
CARE 1991	Wrong population: not heart failure
Cice 1997	Wrong population: not heart failure
Cice 1998	Wrong population: not heart failure
Cice 2003	Wrong population: not heart failure
Costanzo 2012	Study duration/outcome measures < 3 months
E-COST 2005	Wrong population: not heart failure
EUROPA 2001	Wrong population: not heart failure
EXAMINE 2011	Wrong population: not heart failure
Feniman De Stefano 2016	Wrong population: not heart failure
GenHAT 2009	Wrong population: not heart failure
Givertz 2007	Study duration/outcome measures < 3 months
Greenbaum 2000	Study duration/outcome measures < 3 months
Hernandez 2000	Wrong population: not heart failure
Higuchi 2014	Wrong population: not heart failure
HIJ-CREATE 2010	Wrong population: not heart failure
HOPE 1996	Wrong population: not heart failure
HOST 2004	Wrong population: not heart failure

Study	Reason for exclusion
Hou 2013	Study duration/outcome measures < 3 months
Issa 2013	Study duration/outcome measures < 3 months
K-STAR 2017	Study duration/outcome measures < 3 months
Kanno 2004	Wrong population: not heart failure
Li 2011d	Wrong population: not heart failure
London 1994	Wrong population: not heart failure
Manche 1999	Study duration/outcome measures < 3 months
Manske 1992	Wrong intervention: not pharmacological
Nagaya 2001	Study duration/outcome measures < 3 months
Nakamura 2002b	Wrong population: not heart failure
Nakamura 2005b	Wrong population: not heart failure
NCT02228408	Wrong population: not heart failure
OAT 2012	Wrong intervention: not pharmacological
OPAL-HK 2015	Wrong population: not heart failure
Owan 2008	Study duration/outcome measures < 3 months
Paoletti 2007	Wrong population: not heart failure
PERFECT 1997	Wrong population: not heart failure
Ponikowski 2010	Study duration/outcome measures < 3 months
SAGE 2004	Wrong population: not heart failure
Schmidt 2008	Wrong population: not heart failure
Smilde 2005	Study duration/outcome measures < 3 months
SPIRO-CKD 2017	Wrong population: not heart failure
Suzuki 2001	Wrong population: not heart failure
TNT 2005	Wrong population: not heart failure
TRILOGY ACS 2010	Wrong population: not heart failure
UK HARP III 2016	Wrong population: not heart failure
UNLOAD 2008	Wrong intervention: not pharmacological
Varriale 1997	Study duration/outcome measures < 3 months

Study	Reason for exclusion
VMAC 2002	Study duration/outcome measures < 3 months
Wang 2004c	Study duration/outcome measures < 3 months
Watanabe 2000	Study duration/outcome measures < 3 months
Xydakis 2004	Wrong population: not heart failure
Yilmaz 2010a	Wrong population: not heart failure

Characteristics of ongoing studies [ordered by study ID]

PARAGON-HF 2018

Trial name or title	Prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker global outcomes in HFpEF
Methods	- Study design: double-blind, parallel group, active-controlled, 2-arm event-driven RCT - Study duration: July 2014 to May 2019 - Duration of follow-up: 57 months
Participants	- Countries: 43 - Setting: multicentre (number of sites not reported) - Inclusion criteria: ≥ 50 years with LVEF $\geq 45\%$ by echo during screening epoch or within 6 months prior to study entry; symptom(s) of HF and requiring treatment with diuretic(s) for HF at least 30 days prior to study entry; current symptom(s) of HF; structural heart disease (left atrial enlargement or left ventricular hypertrophy) documented by echocardiogram; elevated NT-proBNP - Number: 4822* - Mean age $\pm$ SD: 73 ± 8 years - Sex (M/F): (48%/52%) - DM: 43% - Exclusion criteria: any prior measurement of LVEF < 40%; acute coronary syndrome (including MI), cardiac surgery, other major CV surgery within 3 months, or urgent PCI within 3 months or an elective PCI within 30 days prior to entry; Any clinical event within the 6 months prior to entry could have reduced the LVEF (e.g. MI, CABG), unless an echo measurement performed after the event confirms a LVEF $\geq 45\%$; current acute decompensated HF requiring therapy; require treatment with 2 or more of the following: an ACEi, ARB or a renin inhibitor; alternative reason for shortness of breath such as: significant pulmonary disease or severe COPD, Hb <10 g/dL, or (BMI > 40 kg/m²; SBP ≥ 180 mm Hg at entry, or SBP >150 mm Hg and < 180 mm Hg at entry unless the patient is receiving 3 or more antihypertensive drugs, or SBP < 110 mm Hg at entry *5739 entered run-in but only 4822 were randomised
Interventions	Treatment group 1 Valsartan: target dose 160 mg twice/day Treatment group 2 LCZ696: target dose 20 mg twice/day
Outcomes	- Composite endpoint of CV death and total (first and recurrent) HF hospitalisations (57 months) - Change in the clinical summary score from baseline to month 8 by KCCQ (8 months) - Change from baseline to month 8 in NYHA functional class

PARAGON-HF 2018 (Continued)

- Time to first occurrence of a composite renal endpoint (57 months)
- Time to death (any cause) (57 months)

Starting date	July 2014
Contact information	Novartis Pharmaceuticals
Notes	Funding: study sponsored by Novartis

RELAX-AHF-2 2017

Trial name or title	A multicenter, randomised, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of serelaxin when added to standard therapy in acute heart failure patients
Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: June 2013 to February 2017 • Duration of follow-up: 6 months
Participants	• Countries: multiple (34) • Setting: multicentre • Inclusion criteria: ≥ 18 years hospitalised for AHF with anticipated requirement of IV therapy for at least 48 hours, with a SBP ≥ 125 mm Hg and eGFR ≥ 25 and ≤ 75, and remained symptomatic after IV furosemide of at least 40 mg total and who are anticipated to require IV therapy for at least 48 hours • Number: data not published; protocol only • Mean age $\pm$ SD (years): data not published; protocol only • Sex (M/F): data not published; protocol only • CKD stage: data not published; protocol only • DM: data not published; protocol only • Exclusion criteria: dyspnoea primarily due to non-cardiac causes; known history of respiratory disorders requiring the daily use of IV or oral steroids (does not include inhaled steroids)/ need for intubation or the current use of IV or oral steroids for COPD; temperature $> 38.5^{\circ}\text{C}$ (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment; clinical evidence of acute coronary syndrome currently or within 30 days prior to enrolment; AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with sustained ventricular rate < 45 BPM, or atrial fibrillation/flutter with sustained ventricular response of > 130 BPM; patients with severe renal impairment defined as pre-randomisation eGFR < 25 mL/min/1.73 m² and/or those receiving current or planned dialysis or ultrafiltration; patients with HCT $< 25\%$, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding; known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed) or history of cirrhosis with evidence of portal hypertension such as varices; significant, uncorrected, left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis and severe mitral stenosis; severe aortic insufficiency or severe mitral regurgitation for which surgical or percutaneous intervention is indicated; documented, prior to or at the time of randomisation, restrictive amyloid cardiomyopathy, OR acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does NOT include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function)
Interventions	Treatment group • Serelaxin: continuous IV infusion of 30 $\mu\text{g/kg/day}$ for 48 hours Control group

RELAX-AHF-2 2017 (Continued)

	Matching placebo: continuous IV for 48 hours
Outcomes	- Heart failure signs and symptoms (day 60) - Haematology and clinical chemistry tests (day 5) - Adverse events: non-serious (day 5) - Adverse events: serious (day 14) - All deaths and hospitalizations (day 180) - Re-hospitalisation - Worsening heart failure (day 5)
Starting date	October 2013
Contact information	Novartis Pharmaceuticals
Notes	Funding: study sponsored by Novartis Pharmaceuticals

TMAC 2007

Trial name or title	Transplant-Eligible Management of Congestive Heart Failure (TMAC)
Methods	- Study design: prospective, parallel, double-blind, placebo-controlled RCT - Study duration: September 2006 to October 2007 - Duration of follow-up: 6 months
Participants	- Country: USA - Setting: multicentre - Inclusion criteria: awaiting heart transplantation who meet United Network for Organ Sharing status 1B criteria and receive continuous dobutamine or milrinone for at least 3 consecutive days before randomisation. - Number: (data not published; protocol only) - Mean age $\pm$ SD (years): (data not published; protocol only) - Sex (M/F): (data not published; protocol only) - CKD stage: (data not published; protocol only) % DM: (data not published; protocol only) - Exclusion criteria: have SBP < 80 mm Hg for the last 3 measurements within 30 days of randomisation or clinically significant orthostatic hypotension; weigh > 130 kg; have been treated with commercial nesiritide within 3 days before randomisation; have a LVAD or be expected to need one during the 28-day study drug treatment period; have received placement of a bi-V pacer within 6 weeks before randomisation; have an internal cardiac defibrillator implanted within 72 h before randomisation; require chronic HD or PD to treat kidney failure, or had acute dialysis or ultrafiltration within 7 days before randomisation; have been diagnosed with an acute MI within 30 days before randomisation; have received antibiotic treatment (not prophylaxis) within 7 days of randomisation; history of an allergic reaction or sensitivity to commercial nesiritide; be pregnant or nursing; received therapy with another investigational drug or device within 30 days of randomisation; have a history of psychiatric disease or drug or alcohol abuse or poor psychosocial support
Interventions	Treatment group - Nesiritide: 28-day continuous infusion + standard care and continuous IV inotropic therapy Control group - Placebo + standard care and continuous IV inotropic therapy
Outcomes	Days alive without kidney, haemodynamic, or electrical worsening

TMAC 2007 (Continued)

- Changes in pulmonary capillary wedge pressure
- Death (any cause)
- Disease severity using a weighted clinical severity index and scoring system specifically developed for this study
- Changes in pulmonary artery pressure
- Safety outcomes

Starting date	September 2006
Contact information	NCT00338455
Notes	Funding: study sponsored by Scios, Inc.

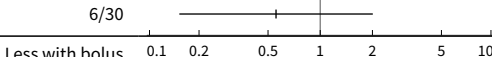
ACEi - angiotensin-converting enzyme inhibitor/s; AHF - acute heart failure; ARB - angiotensin receptor blocker/s; BMI - body mass index; BNP - brain natriuretic peptide; BPM - beats per minute; CABG - coronary artery bypass grafting; COPD - chronic obstructive pulmonary disease; CV - cardiovascular; eGFR - estimated glomerular filtration rate; GI - gastrointestinal; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; HF - heart failure; LVEF - left ventricular ejection fraction; MI - myocardial infarction; NYHA - New York Heart Association; PCI - percutaneous coronary intervention; PD - peritoneal dialysis; pEF - preserved ejection fraction; RCT - randomised controlled trial; SBP - systolic blood pressure

DATA AND ANALYSES

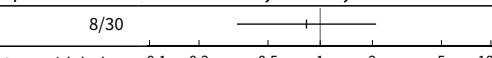
Comparison 1. ACUTE: Diuretic bolus versus continuous infusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Hospitalisation for heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 ACUTE: Diuretic bolus versus continuous infusion, Outcome 1 Cardiovascular death.

Study or subgroup	Bolus n/N	Continuous IV n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Palazzuoli 2014	3/27	6/30		0.56[0.15,2.01]
			Less with bolus	Less with continuous IV

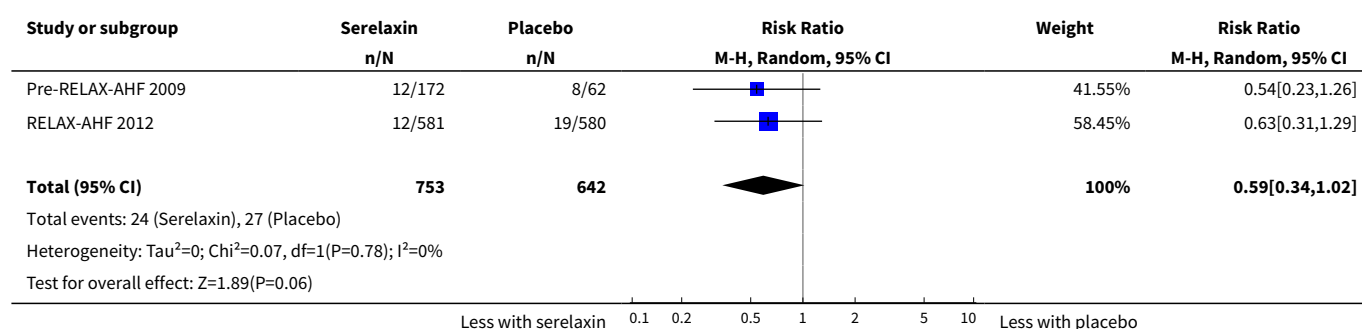
Analysis 1.2. Comparison 1 ACUTE: Diuretic bolus versus continuous infusion, Outcome 2 Hospitalisation for heart failure.

Study or subgroup	Bolus n/N	Continuous IV n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Palazzuoli 2014	6/27	8/30		0.83[0.33,2.1]
			Less with bolus	Less with continuous IV

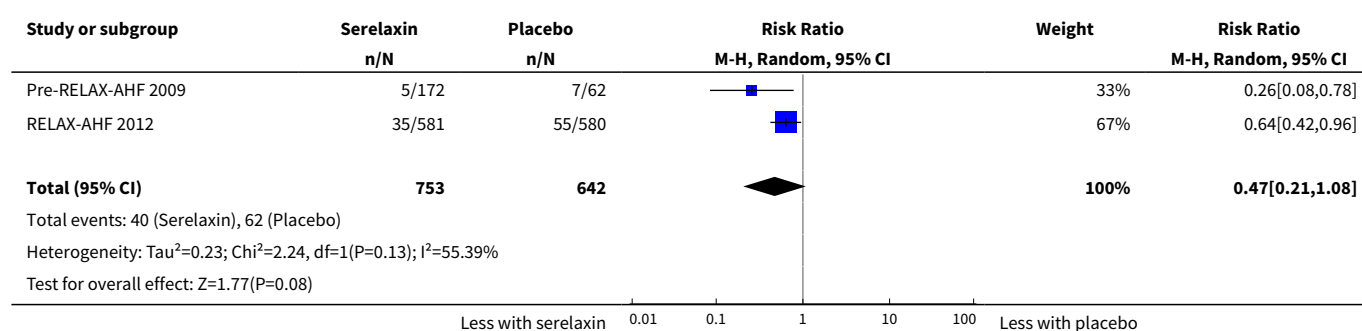
Comparison 2. ACUTE: Serelaxin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	2	1395	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.34, 1.02]
2 Cardiovascular death	2	1395	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.21, 1.08]
3 Worsening heart failure	2	1395	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.54, 0.92]
4 Worsening kidney function	2	1395	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.37, 1.98]
5 Hyperkalaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Hypotension	2	1395	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.81, 1.96]

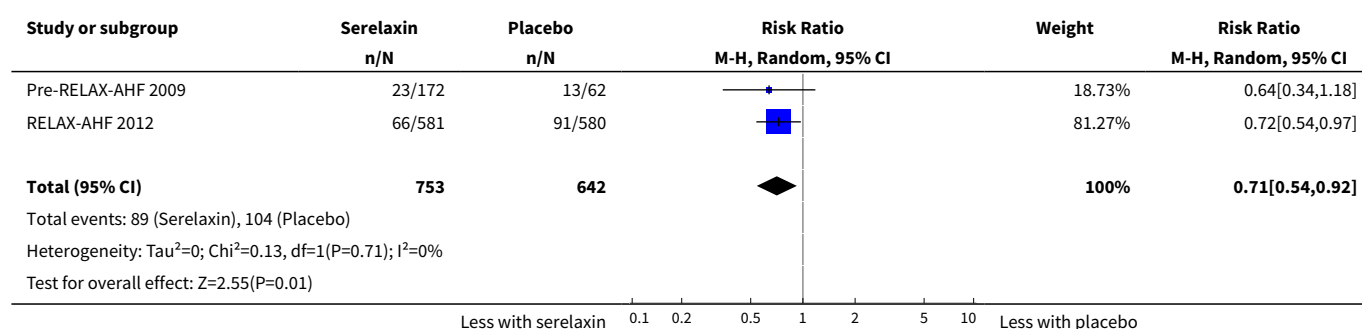
Analysis 2.1. Comparison 2 ACUTE: Serelaxin versus placebo, Outcome 1 Death (any cause).



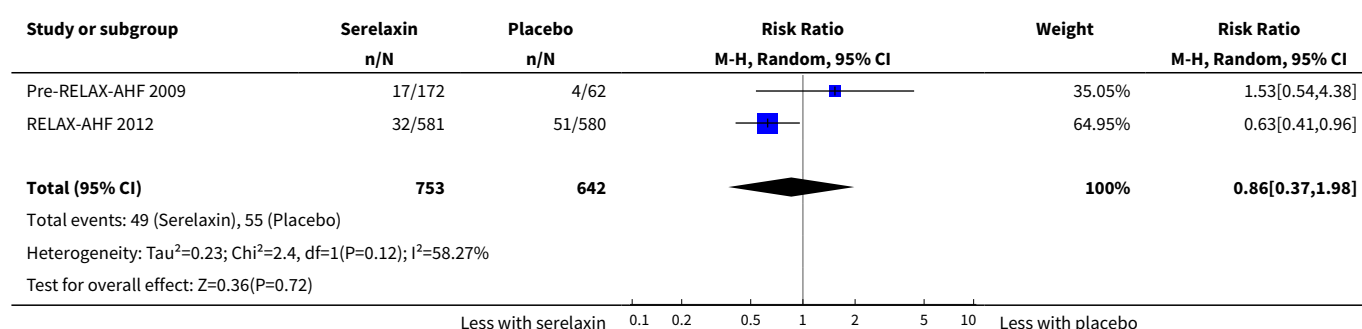
Analysis 2.2. Comparison 2 ACUTE: Serelaxin versus placebo, Outcome 2 Cardiovascular death.



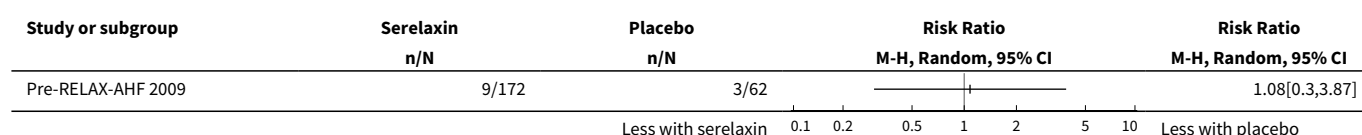
Analysis 2.3. Comparison 2 ACUTE: Serelaxin versus placebo, Outcome 3 Worsening heart failure.



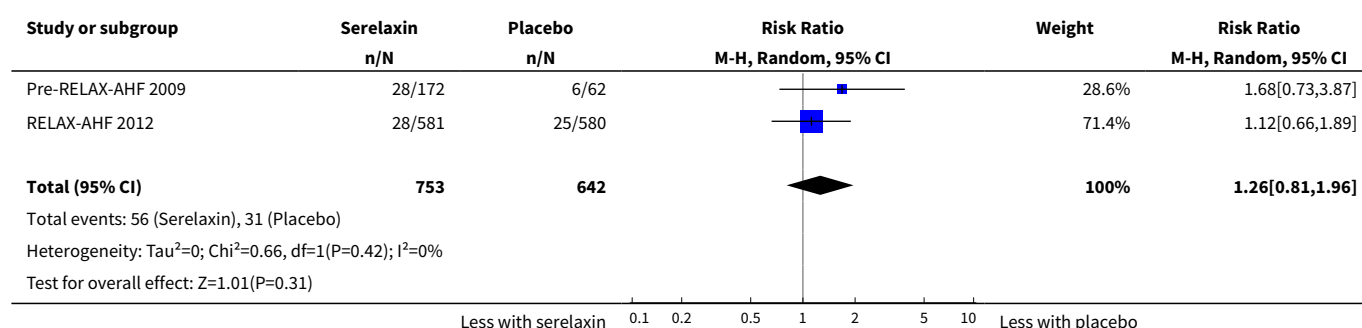
Analysis 2.4. Comparison 2 ACUTE: Serelaxin versus placebo, Outcome 4 Worsening kidney function.



Analysis 2.5. Comparison 2 ACUTE: Serelaxin versus placebo, Outcome 5 Hyperkalaemia.



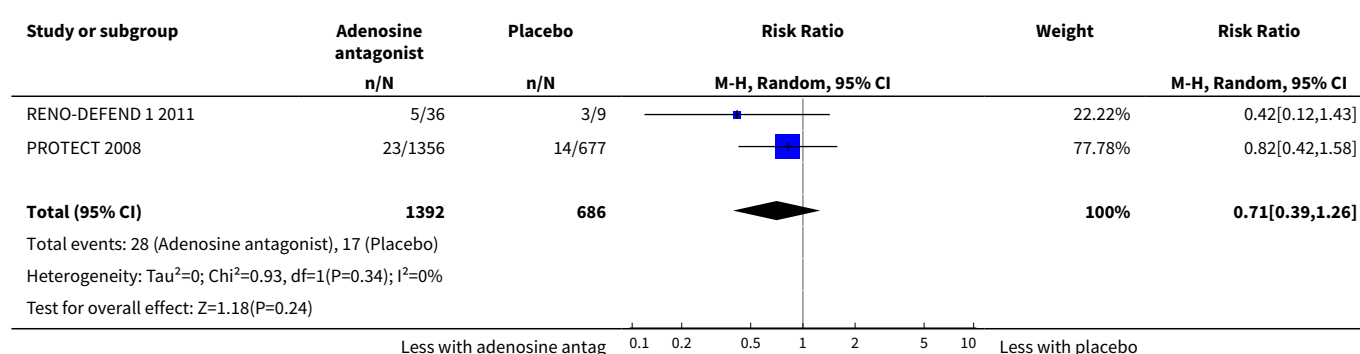
Analysis 2.6. Comparison 2 ACUTE: Serelaxin versus placebo, Outcome 6 Hypotension.



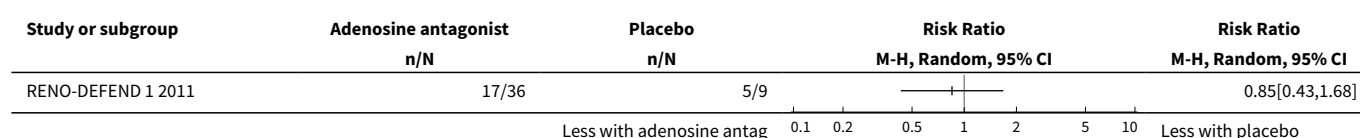
Comparison 3. ACUTE: Adenosine A1-receptor antagonist versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	2	2078	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.39, 1.26]
2 Hospitalisation (any cause)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Worsening heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Worsening kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

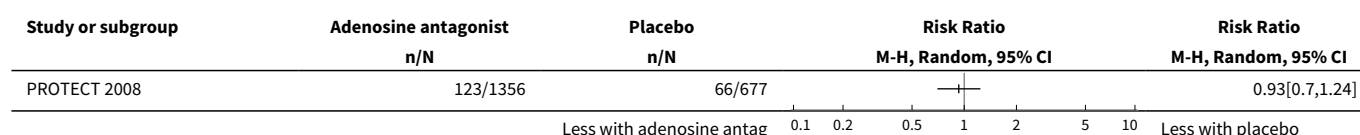
Analysis 3.1. Comparison 3 ACUTE: Adenosine A1-receptor antagonist versus placebo, Outcome 1 Death (any cause).



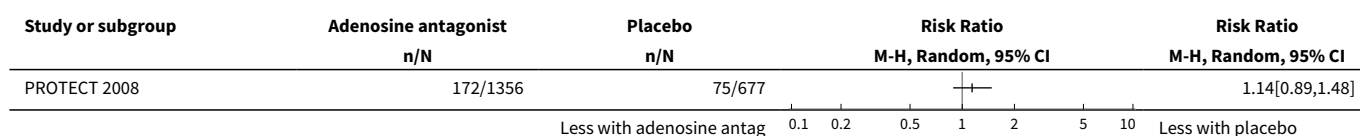
Analysis 3.2. Comparison 3 ACUTE: Adenosine A1-receptor antagonist versus placebo, Outcome 2 Hospitalisation (any cause).



Analysis 3.3. Comparison 3 ACUTE: Adenosine A1-receptor antagonist versus placebo, Outcome 3 Worsening heart failure.



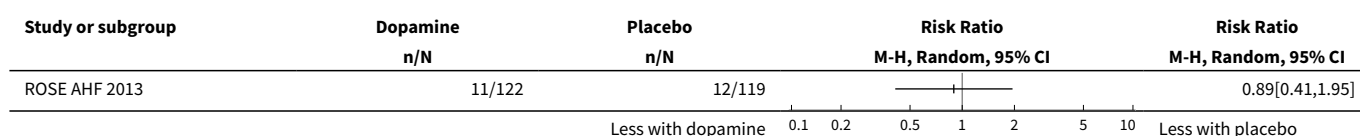
Analysis 3.4. Comparison 3 ACUTE: Adenosine A1-receptor antagonist versus placebo, Outcome 4 Worsening kidney function.



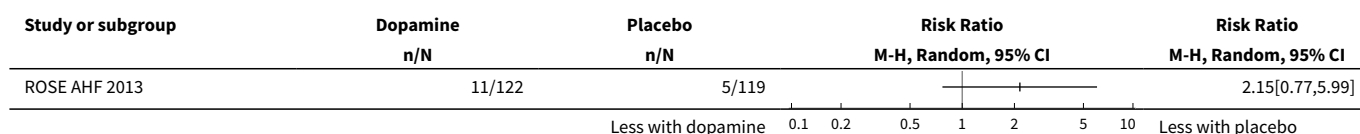
Comparison 4. ACUTE: Dopamine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Worsening heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Hypotension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

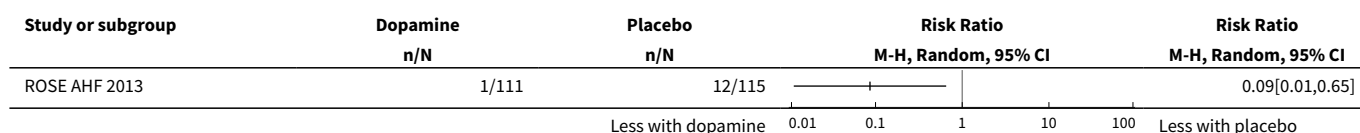
Analysis 4.1. Comparison 4 ACUTE: Dopamine versus placebo, Outcome 1 Death (any cause).



Analysis 4.2. Comparison 4 ACUTE: Dopamine versus placebo, Outcome 2 Worsening heart failure.



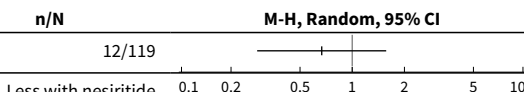
Analysis 4.3. Comparison 4 ACUTE: Dopamine versus placebo, Outcome 3 Hypotension.



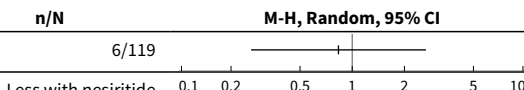
Comparison 5. ACUTE: Nesiritide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Worsening heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Hypotension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

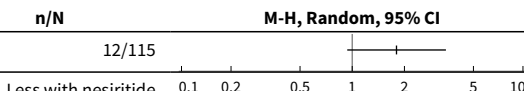
Analysis 5.1. Comparison 5 ACUTE: Nesiritide versus placebo, Outcome 1 Death (any cause).

Study or subgroup	Nesiritide n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ROSE AHF 2013	8/119	12/119		0.67[0.28,1.57]

Analysis 5.2. Comparison 5 ACUTE: Nesiritide versus placebo, Outcome 2 Worsening heart failure.

Study or subgroup	Nesiritide n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ROSE AHF 2013	5/119	6/119		0.83[0.26,2.66]

Analysis 5.3. Comparison 5 ACUTE: Nesiritide versus placebo, Outcome 3 Hypotension.

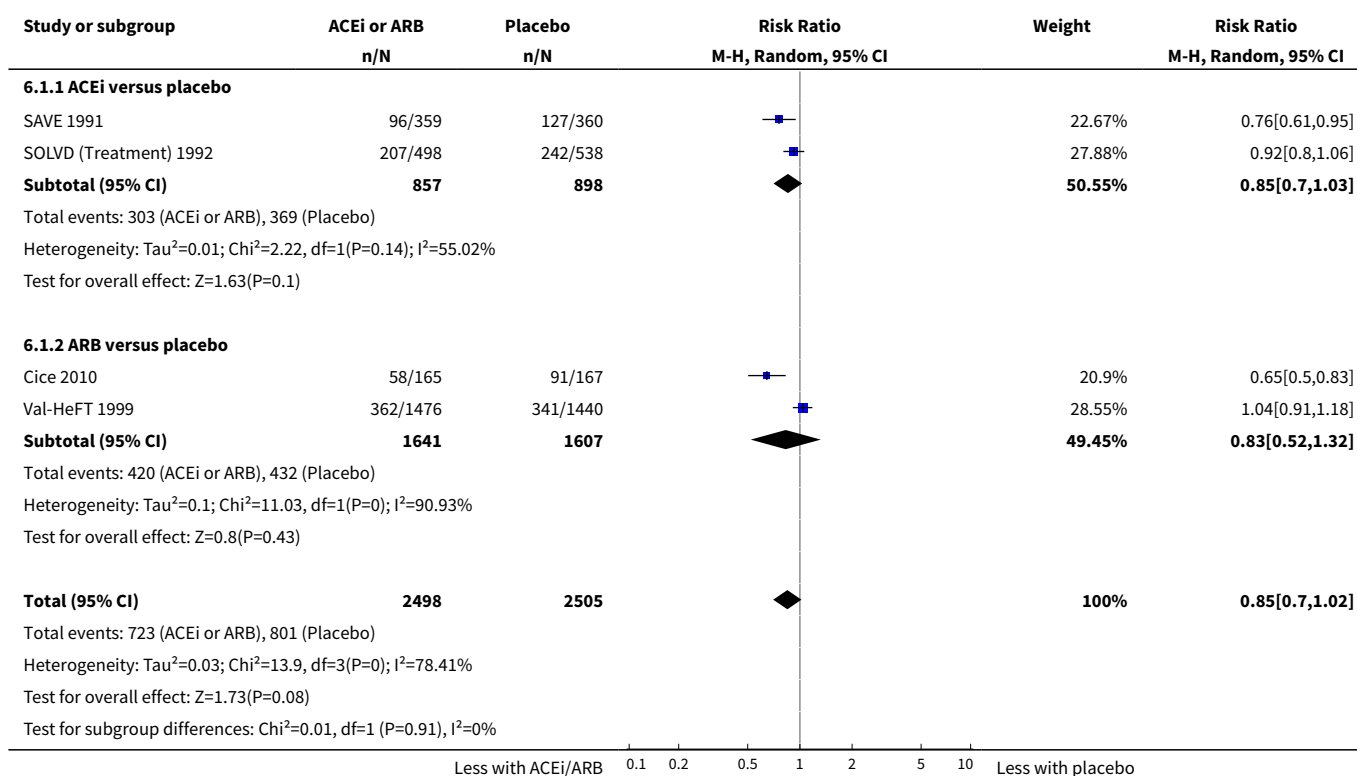
Study or subgroup	Nesiritide n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ROSE AHF 2013	22/117	12/115		1.8[0.94,3.47]

Comparison 6. CHRONIC: ACEi OR ARB versus placebo

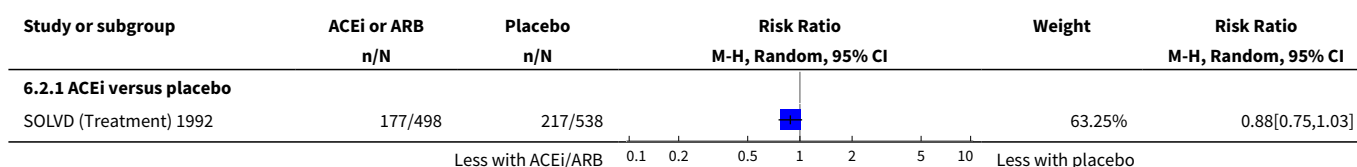
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	4	5003	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.02]
1.1 ACEi versus placebo	2	1755	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.03]
1.2 ARB versus placebo	2	3248	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.32]
2 Cardiovascular death	2	1368	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.01]
2.1 ACEi versus placebo	1	1036	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.75, 1.03]

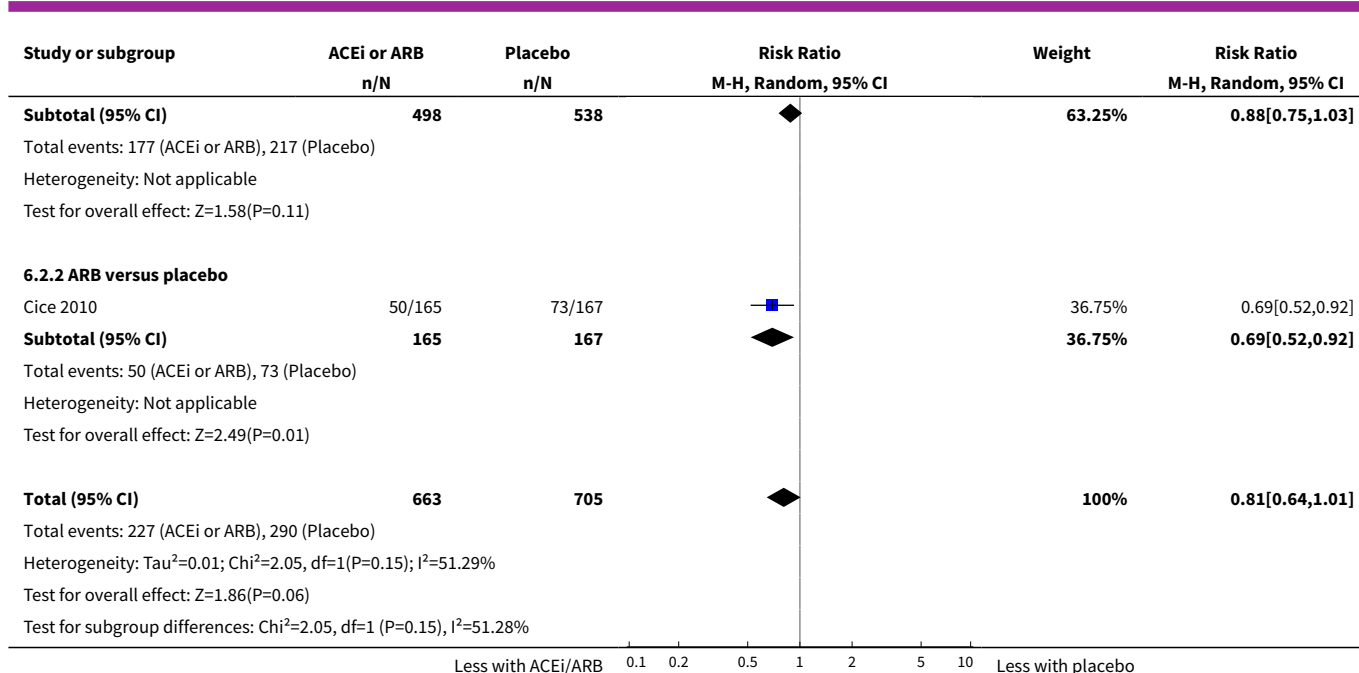
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 ARB versus placebo	1	332	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.52, 0.92]
3 Hospitalisation for heart failure	2	1368	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.43, 1.90]
3.1 ACEi versus placebo	1	1036	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.18, 1.43]
3.2 ARB versus placebo	1	332	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.48, 0.79]
4 Hypotension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 ARB versus placebo	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 CHRONIC: ACEi OR ARB versus placebo, Outcome 1 Death (any cause).

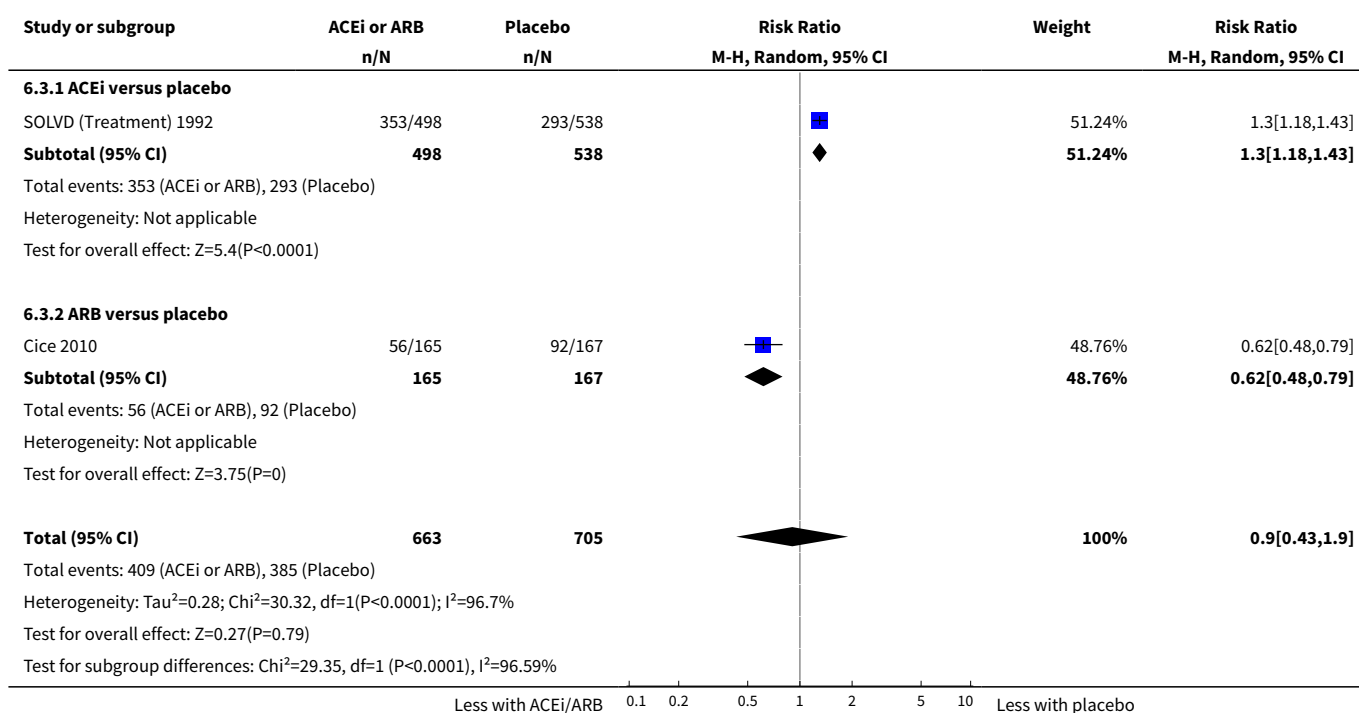


Analysis 6.2. Comparison 6 CHRONIC: ACEi OR ARB versus placebo, Outcome 2 Cardiovascular death.

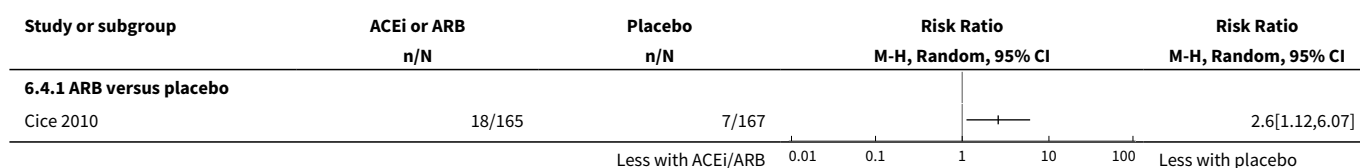




Analysis 6.3. Comparison 6 CHRONIC: ACEi OR ARB versus placebo, Outcome 3 Hospitalisation for heart failure.



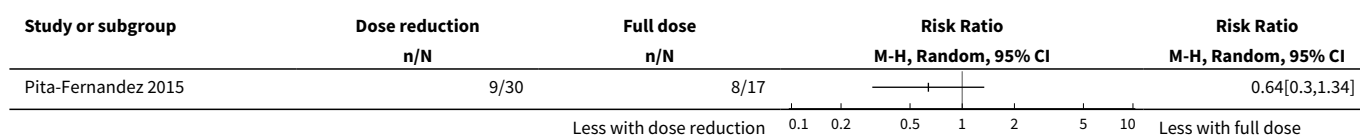
Analysis 6.4. Comparison 6 CHRONIC: ACEi OR ARB versus placebo, Outcome 4 Hypotension.



Comparison 7. CHRONIC: 50% ARB dose reduction versus full dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

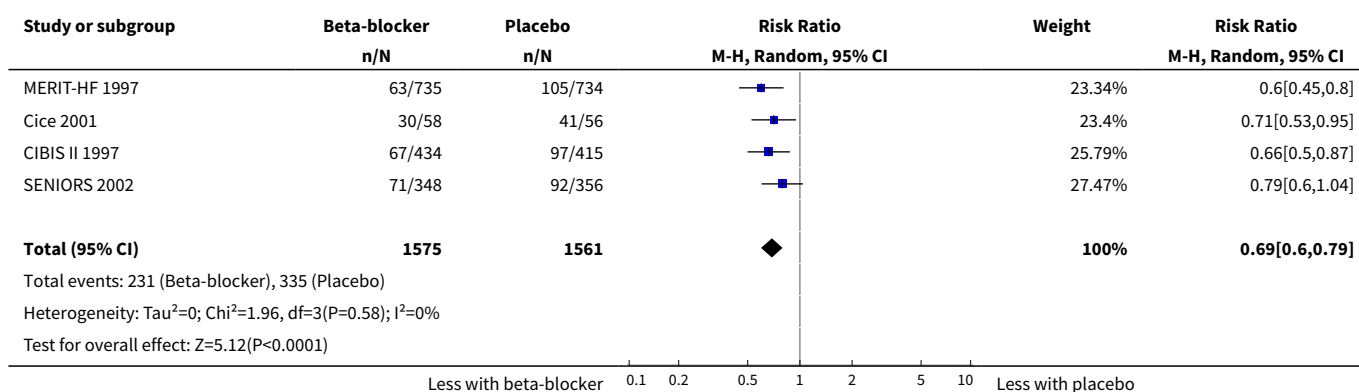
Analysis 7.1. Comparison 7 CHRONIC: 50% ARB dose reduction versus full dose, Outcome 1 Death (any cause).



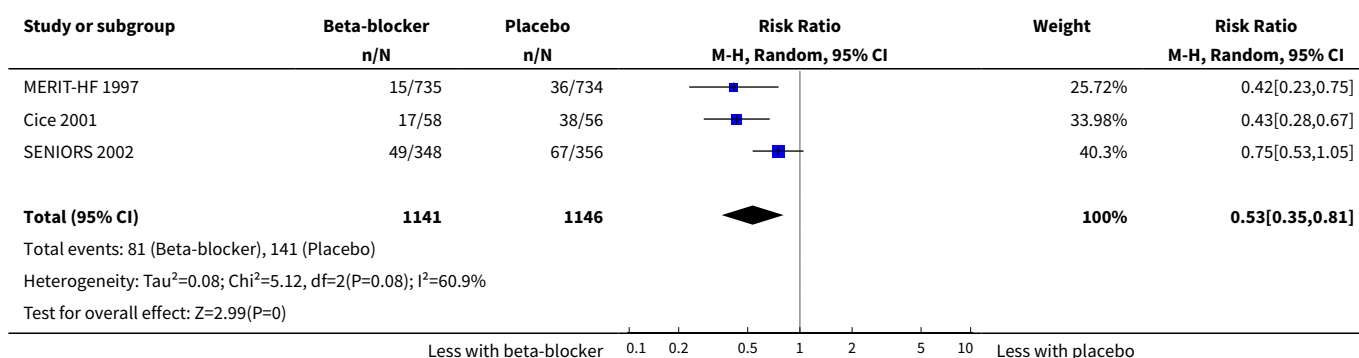
Comparison 8. CHRONIC: Beta-blockers versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	4	3136	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.79]
2 Cardiovascular death	3	2287	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.81]
3 Hospitalisation (any cause)	2	1583	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.52, 1.08]
4 Hospitalisation for heart failure	3	2287	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.05]
5 Worsening heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Worsening kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Hypotension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

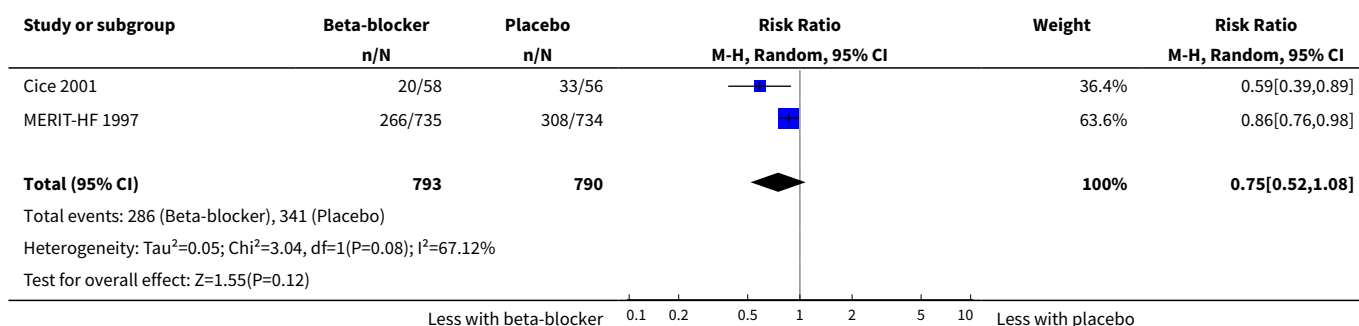
Analysis 8.1. Comparison 8 CHRONIC: Beta-blockers versus placebo, Outcome 1 Death (any cause).



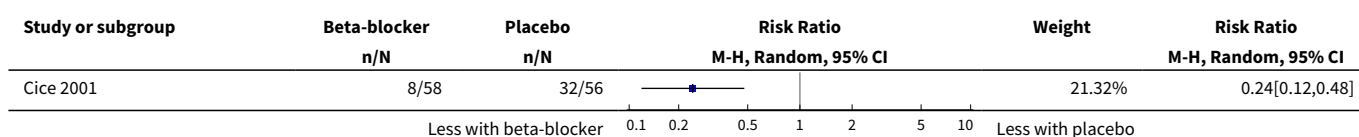
Analysis 8.2. Comparison 8 CHRONIC: Beta-blockers versus placebo, Outcome 2 Cardiovascular death.

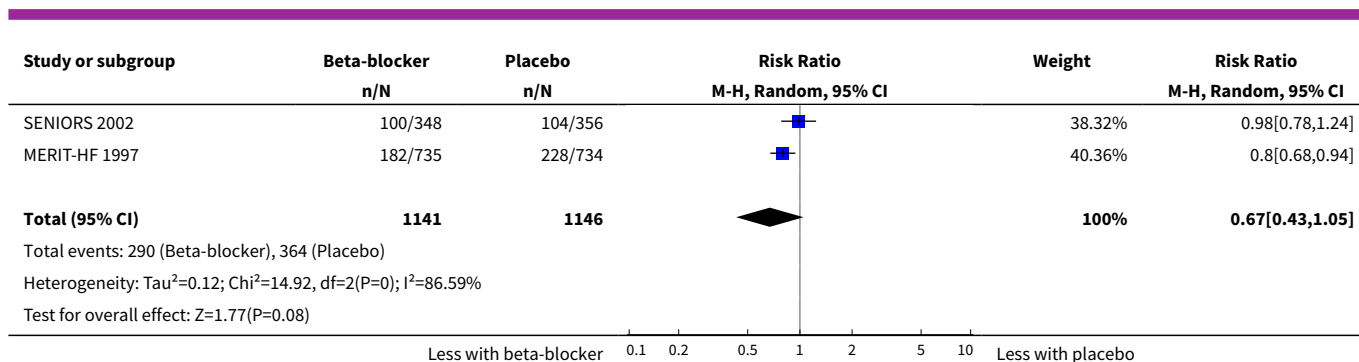


Analysis 8.3. Comparison 8 CHRONIC: Beta-blockers versus placebo, Outcome 3 Hospitalisation (any cause).

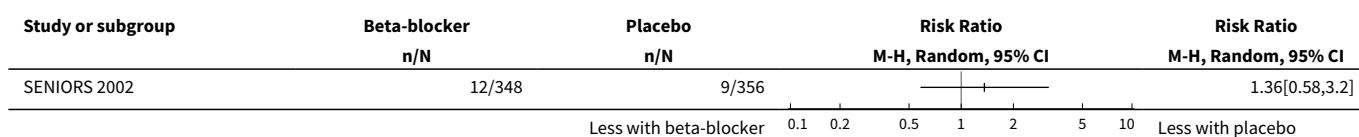


Analysis 8.4. Comparison 8 CHRONIC: Beta-blockers versus placebo, Outcome 4 Hospitalisation for heart failure.

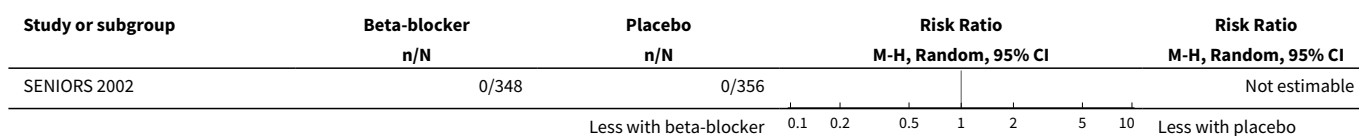




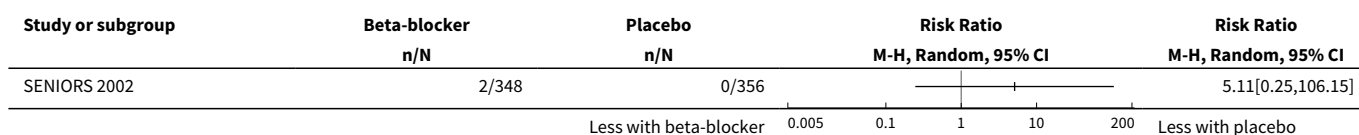
Analysis 8.5. Comparison 8 CHRONIC: Beta-blockers versus placebo, Outcome 5 Worsening heart failure.



Analysis 8.6. Comparison 8 CHRONIC: Beta-blockers versus placebo, Outcome 6 Worsening kidney function.

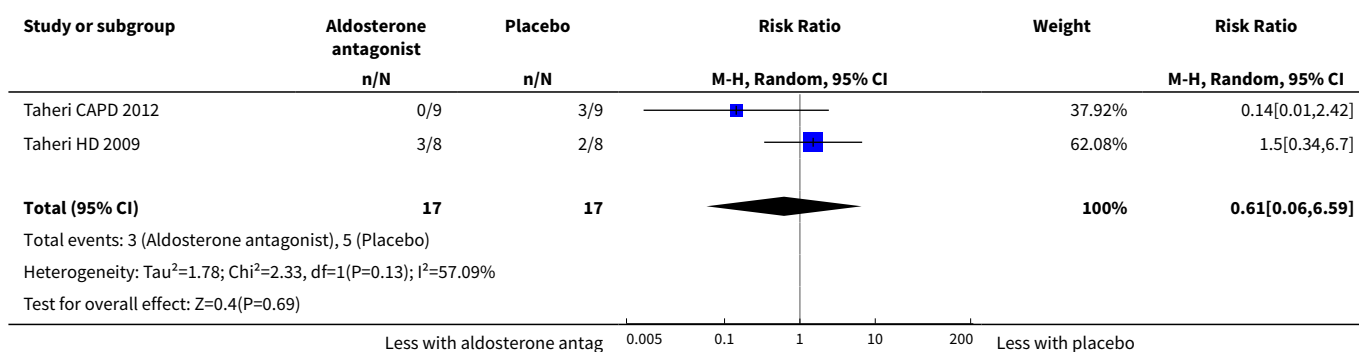
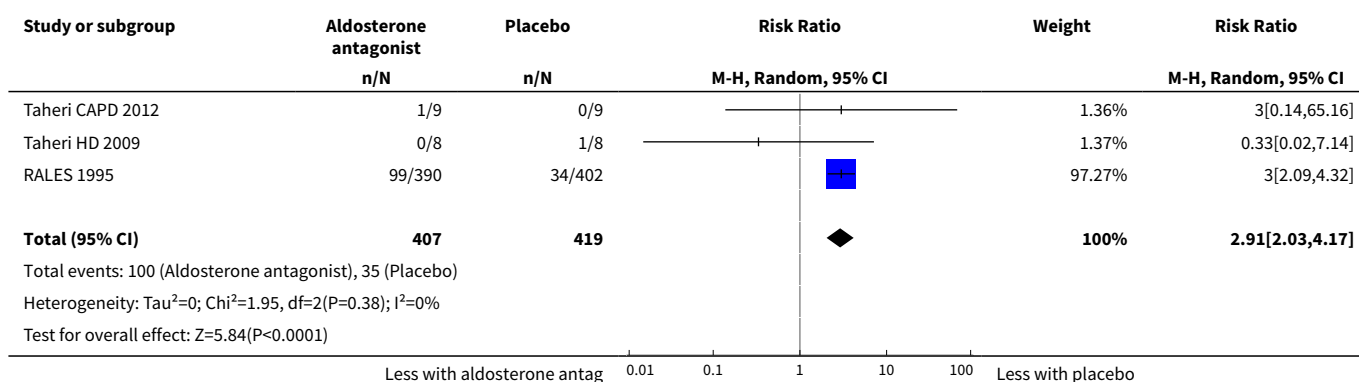


Analysis 8.7. Comparison 8 CHRONIC: Beta-blockers versus placebo, Outcome 7 Hypotension.

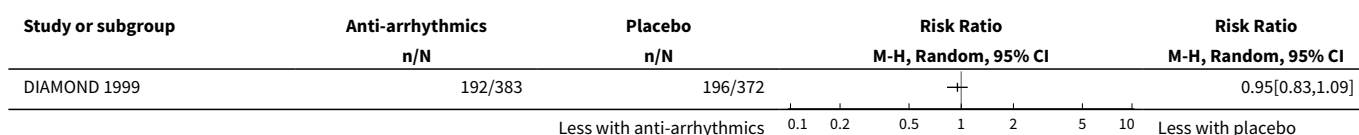


Comparison 9. CHRONIC: Aldosterone antagonists versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	2	34	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.06, 6.59]
2 Hyperkalaemia	3	826	Risk Ratio (M-H, Random, 95% CI)	2.91 [2.03, 4.17]

Analysis 9.1. Comparison 9 CHRONIC: Aldosterone antagonists versus placebo, Outcome 1 Death (any cause).**Analysis 9.2. Comparison 9 CHRONIC: Aldosterone antagonists versus placebo, Outcome 2 Hyperkalaemia.****Comparison 10. CHRONIC: Anti-arrhythmics versus placebo**

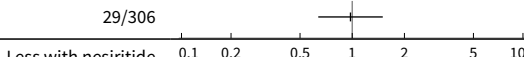
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10 CHRONIC: Anti-arrhythmics versus placebo, Outcome 1 Death (any cause).

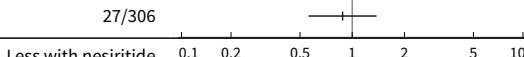
Comparison 11. CHRONIC: Nesiritide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Cardiovascular death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Hypotension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Quality of Life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

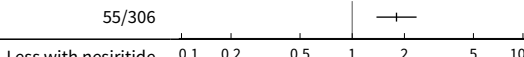
Analysis 11.1. Comparison 11 CHRONIC: Nesiritide versus placebo, Outcome 1 Death (any cause).

Study or subgroup	Nesiritide n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FUSION II 2008	56/605	29/306		0.98[0.64,1.5]

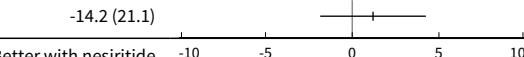
Analysis 11.2. Comparison 11 CHRONIC: Nesiritide versus placebo, Outcome 2 Cardiovascular death.

Study or subgroup	Nesiritide n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FUSION II 2008	47/605	27/306		0.88[0.56,1.38]

Analysis 11.3. Comparison 11 CHRONIC: Nesiritide versus placebo, Outcome 3 Hypotension.

Study or subgroup	Nesiritide n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
FUSION II 2008	196/605	55/306		1.8[1.38,2.35]

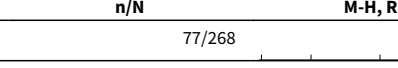
Analysis 11.4. Comparison 11 CHRONIC: Nesiritide versus placebo, Outcome 4 Quality of Life.

Study or subgroup	Nesiritide		Placebo		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
FUSION II 2008	605	-13 (24.1)	306	-14.2 (21.1)		1.2[-1.85,4.25]

Comparison 12. CHRONIC: Phosphodiesterase inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

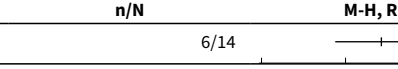
Analysis 12.1. Comparison 12 CHRONIC: Phosphodiesterase inhibitors versus placebo, Outcome 1 Death (any cause).

Study or subgroup	Phosphodiesterase inhibitors	Placebo	Risk Ratio	
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
PROMISE 1989	98/271	77/268		1.26[0.98,1.61]
Less with phosphodiesterase 0.1 0.2 0.5 1 2 5 10 Less with placebo				

Comparison 13. CHRONIC: Renin inhibitors versus placebo

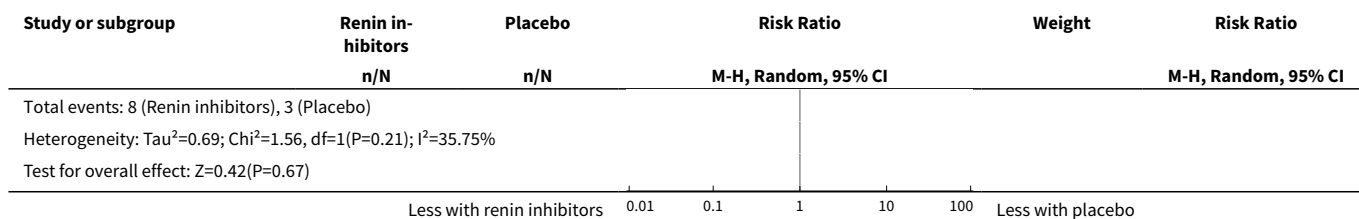
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Worsening heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Worsening kidney function	2	142	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.22, 10.33]
3 Hyperkalaemia	2	142	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.49, 1.49]
4 Hypotension	2	142	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.62, 3.31]

Analysis 13.1. Comparison 13 CHRONIC: Renin inhibitors versus placebo, Outcome 1 Worsening heart failure.

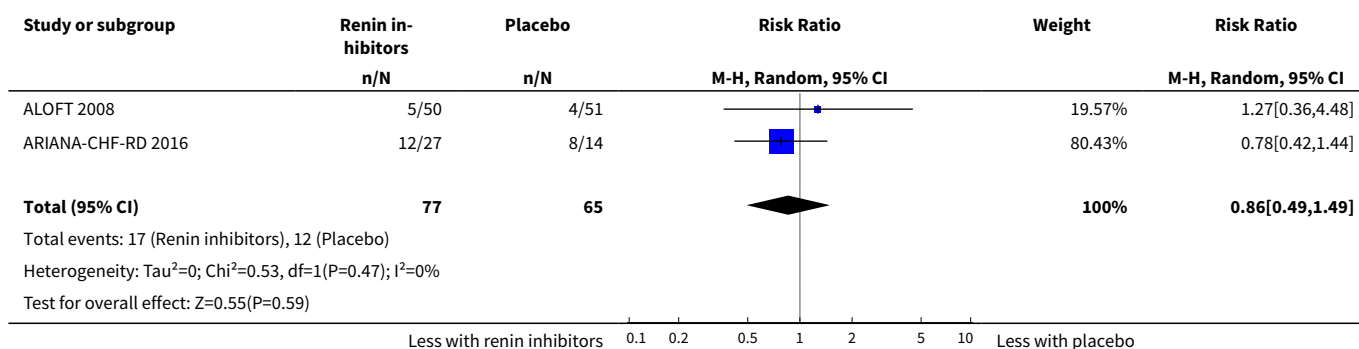
Study or subgroup	Renin inhibitors	Placebo	Risk Ratio	
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
ARIANA-CHF-RD 2016	3/27	6/14		0.26[0.08,0.88]
Less with renin inhibitors 0.01 0.1 1 10 100 Less with placebo				

Analysis 13.2. Comparison 13 CHRONIC: Renin inhibitors versus placebo, Outcome 2 Worsening kidney function.

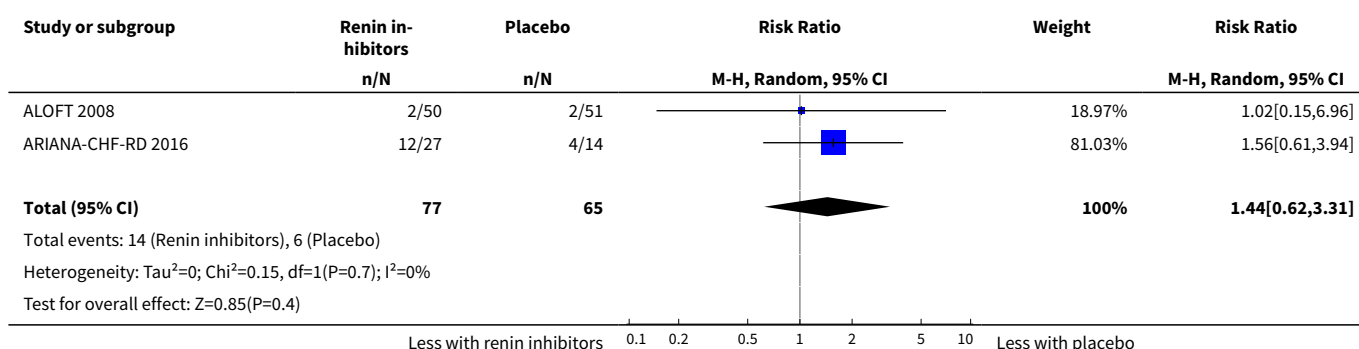
Study or subgroup	Renin in- hibitors	Placebo	Risk Ratio		Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI			
ALOFT 2008	1/50	2/51			44.51%	0.51[0.05,5.45]
ARIANA-CHF-RD 2016	7/27	1/14			55.49%	3.63[0.49,26.64]
Total (95% CI)	77	65			100%	1.52[0.22,10.33]
Less with renin inhibitors 0.01 0.1 1 10 100 Less with placebo						



Analysis 13.3. Comparison 13 CHRONIC: Renin inhibitors versus placebo, Outcome 3 Hyperkalaemia.



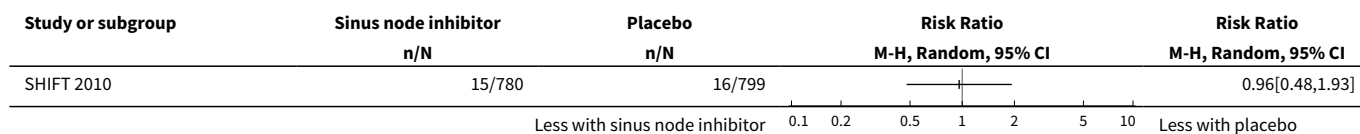
Analysis 13.4. Comparison 13 CHRONIC: Renin inhibitors versus placebo, Outcome 4 Hypotension.



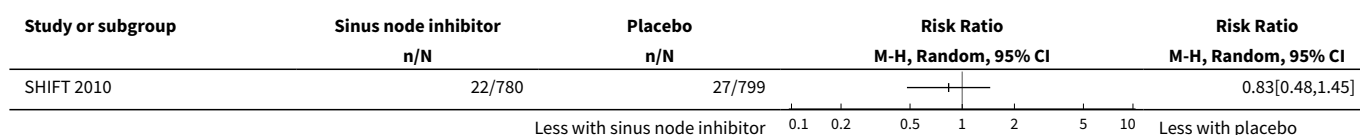
Comparison 14. CHRONIC: Sinus node inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Hospitalisation for heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Worsening kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Hyperkalaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

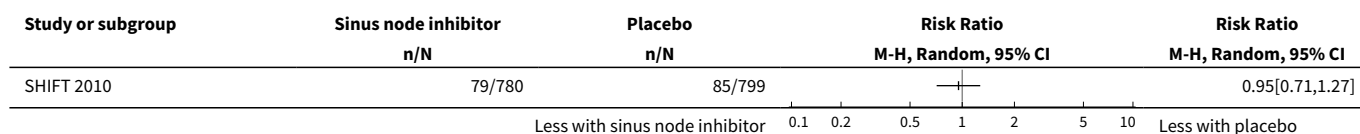
Analysis 14.1. Comparison 14 CHRONIC: Sinus node inhibitors versus placebo, Outcome 1 Cardiovascular death.



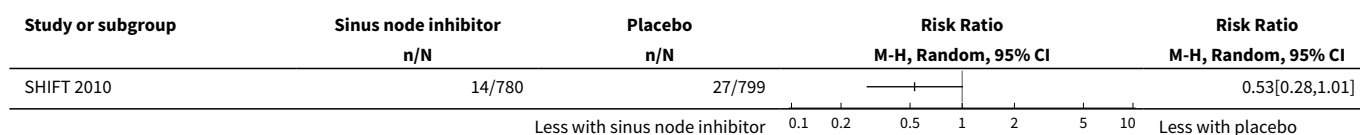
Analysis 14.2. Comparison 14 CHRONIC: Sinus node inhibitors versus placebo, Outcome 2 Hospitalisation for heart failure.



Analysis 14.3. Comparison 14 CHRONIC: Sinus node inhibitors versus placebo, Outcome 3 Worsening kidney function.



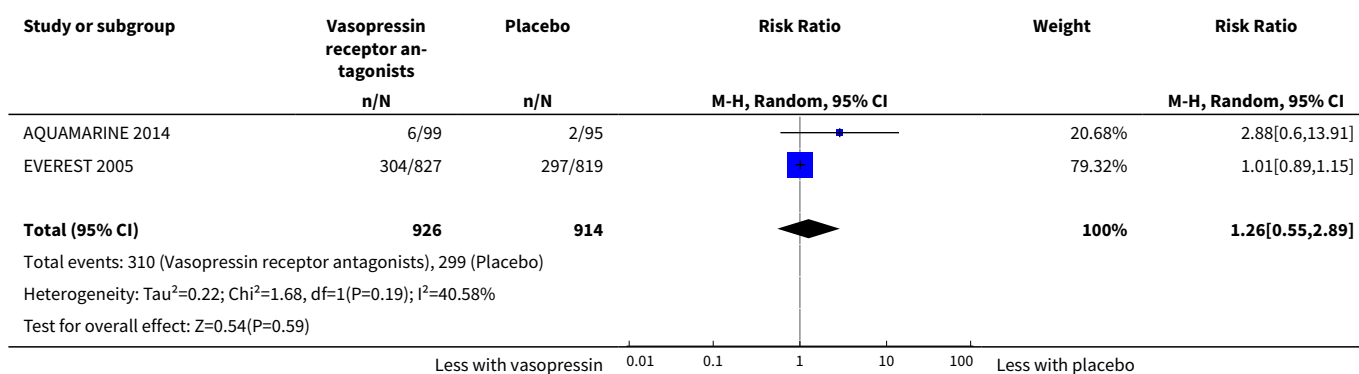
Analysis 14.4. Comparison 14 CHRONIC: Sinus node inhibitors versus placebo, Outcome 4 Hyperkalaemia.



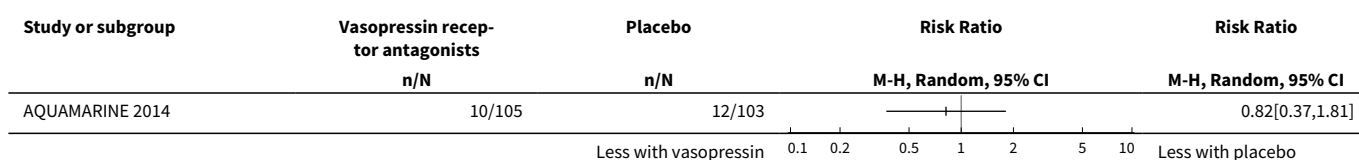
Comparison 15. CHRONIC: Vasopressin receptor antagonists versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any cause)	2	1840	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.55, 2.89]
2 Hospitalisation for heart failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Worsening kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

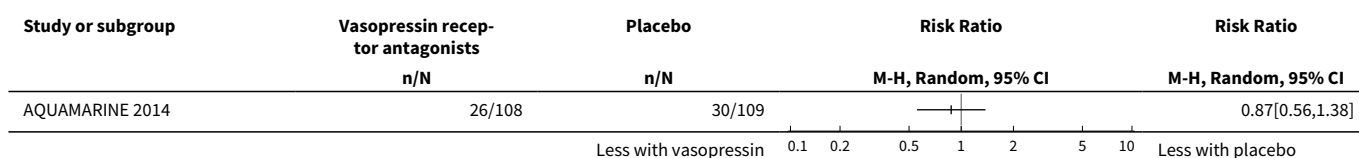
Analysis 15.1. Comparison 15 CHRONIC: Vasopressin receptor antagonists versus placebo, Outcome 1 Death (any cause).



Analysis 15.2. Comparison 15 CHRONIC: Vasopressin receptor antagonists versus placebo, Outcome 2 Hospitalisation for heart failure.



Analysis 15.3. Comparison 15 CHRONIC: Vasopressin receptor antagonists versus placebo, Outcome 3 Worsening kidney function.



ADDITIONAL TABLES

Table 1. Additional Summary of Findings

Comparison	Outcome	Relative effect (95% CI)	No. participants (studies)	Quality of the evidence (GRADE)
Acute heart failure				
Adenosine A1-receptor antagonist versus placebo	Death (any cause)	RR 0.71 (0.39 to 1.26)	2078 (2)	⊕⊕⊕⊖ low ^{2,3,4}
	Cardiovascular death	Not reported		--

Table 1. Additional Summary of Findings (Continued)

	Hospitalisation (any cause)	RR 0.85 (0.43 to 1.68)	45 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Heart failure hospitalisation	Not reported		--
	Worsening heart failure	RR 0.93 (0.70 to 1.24)	2033 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Worsening kidney function	1.14 (0.89 to 1.48)	2033 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Hyperkalaemia	Not reported		--
	Hypotension	Not reported		--
	Quality of life	Not reported		--
Diuretic bolus versus continuous infusion	Death (any cause)	Not reported		--
	Cardiovascular death	RR 0.56 (0.15 to 2.01)	57 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Hospitalisation (any cause)	Not reported		--
	Heart failure hospitalisation	RR 0.83 (0.33 to 2.10)	57 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Worsening heart failure	Not reported		--
	Worsening kidney function	Not reported		--
	Hyperkalaemia	Not reported		--
	Hypotension	Not reported		--
	Quality of life	Not reported		--
Dopamine versus placebo	Death (any cause)	RR 0.89 (0.41 to 1.95)	241 (1)	⊕⊕⊕⊕ very low ^{1,2,3,4}
	Cardiovascular death	Not reported		--
	Hospitalisation (any cause)	Not reported		--
	Heart failure hospitalisation	Not reported		--
	Worsening heart failure	RR 2.15 (0.77 to 5.99)	241 (1)	⊕⊕⊕⊕ very low ^{1,2,3,4}
	Worsening kidney function	Not reported		--
	Hyperkalaemia	Not reported		--

Table 1. Additional Summary of Findings (Continued)

	Hypotension	RR 0.09 (0.01 to 0.65)	226 (1)	⊕⊕⊕⊕ very low ^{1,2,3,4}
	Quality of life	Not reported		--
Nesiritide ver-				
sus placebo				
	Death (any cause)	RR 0.67 (0.28 to 1.57)	238 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Cardiovascular death	Not reported		--
	Hospitalisation (any cause)	Not reported		--
	Heart failure hospitalisation	Not reported		--
	Worsening heart failure	RR 0.83 (0.26 to 2.66)	238 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Worsening kidney function	Not reported		--
	Hyperkalaemia	Not reported		--
	Hypotension	RR 1.80 (0.94 to 3.47)	232 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Quality of life	Not reported		--
Chronic heart failure				
Anti-arrhyth-				
mics versus				
placebo				
	Death (any cause)	RR 0.95 (0.83 to 1.09)	755 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Cardiovascular death	Not reported		--
	Hospitalisation (any cause)	Not reported		--
	Heart failure hospitalisation	Not reported		--
	Worsening heart failure	Not reported		--
	Worsening kidney function	Not reported		--
	Hyperkalaemia	Not reported		--
	Hypotension	Not reported		--
	Quality of life	Not reported		--
Nesiritide ver-				
sus placebo				
	Death (any cause)	RR 0.98 (0.64 to 1.50)	911 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Cardiovascular death	RR 0.88 (0.56 to 1.38)	911 (1)	⊕⊕⊕⊕ very low ^{2,3,4}

Table 1. Additional Summary of Findings (Continued)

	Hospitalisation (any cause)	Not reported	--	
	Heart failure hospitalisation	Not reported	--	
	Worsening heart failure	Not reported	--	
	Worsening kidney function	Not reported	--	
	Hyperkalaemia	Not reported	--	
	Hypotension	RR 1.80 (1.38 to 2.35)	911 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Quality of Life	MD 1.20 (-1.85 to 4.25)	911 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
Phosphodiesterase inhibitors versus placebo	Death (any cause)	RR 1.26 (0.98 to 1.61)	539 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Cardiovascular death	Not reported	--	
	Hospitalisation (any cause)	Not reported	--	
	Heart failure hospitalisation	Not reported	--	
	Worsening heart failure	Not reported	--	
	Worsening kidney function	Not reported	--	
	Hyperkalaemia	Not reported	--	
	Hypotension	Not reported	--	
	Quality of life	Not reported	--	
Renin inhibitors versus placebo	Death (any cause)	Not reported	--	
	Cardiovascular death	Not reported	--	
	Hospitalisation (any cause)	Not reported	--	
	Heart failure hospitalisation	Not reported	--	
	Worsening heart failure	RR 0.26 (0.08 to 0.88)	41 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Worsening kidney function	RR 1.52 (0.22 to 10.33)	142 (2)	⊕⊕⊕⊕ very low ^{2,3,4}
	Hyperkalaemia	RR 0.86 (0.49 to 1.49)	142 (2)	⊕⊕⊕⊕ very low ^{2,3,4}

Table 1. Additional Summary of Findings (Continued)

	Hypotension	RR 1.44 (0.62 to 3.31)	142 (2)	⊕⊕⊕⊕ very low ^{2,3,4}
	Quality of life	Not reported		--
Sinus node inhibitors versus placebo	Death (any cause)	Not reported		
	Cardiovascular death	RR 0.96 (0.48 to 1.93)	1576 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Hospitalisation (any cause)	Not reported		--
	Heart failure hospitalisation	RR 0.83 (0.48 to 1.45)	1576 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Worsening heart failure	Not reported		--
	Worsening kidney function	RR 0.95 (0.71 to 1.27)	1576 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Hyperkalaemia	RR 0.53 (0.28 to 1.01)	1576 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Hypotension	Not reported		--
	Quality of life	Not reported		--
Vasopressin receptor antagonists versus placebo	Death (any cause)	RR 1.26 (0.55 to 2.89)	1840 (2)	⊕⊕⊕⊕ low ^{2,3,4}
	Cardiovascular death	Not reported		--
	Hospitalisation (any cause)	Not reported		--
	Heart failure hospitalisation	RR 0.82 (0.37 to 1.81)	208 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Worsening heart failure	Not reported		--
	Worsening kidney function	RR 0.87 (0.56 to 1.38)	217 (1)	⊕⊕⊕⊕ very low ^{2,3,4}
	Hyperkalaemia	Not reported		--
	Hypotension	Not reported		--
	Quality of life	Not reported		--

CI: Confidence interval; **RR:** Risk Ratio; **MD:** Mean difference

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Table 1. Additional Summary of Findings (Continued)

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Important study limitations due to risks of bias

² The confidence intervals include potential for important benefits and harms

³ Important and unexplained heterogeneity present (or insufficient data observations to evaluate)

⁴ Insufficient data observations to evaluate

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Heart Failure] explode all trees 2. MeSH descriptor: [Ventricular Dysfunction, Left] this term only 3. MeSH descriptor: [Ventricular Dysfunction] explode all trees 4. ventricular dysfunction*:ti,ab,kw (Word variations have been searched) 5. ventricular hypertrophy:ti,ab,kw (Word variations have been searched) 6. heart failure or heart disease*:ti,ab,kw (Word variations have been searched) 7. or #1-#6} 8. MeSH descriptor: [Kidney Diseases] explode all trees 9. MeSH descriptor: [Renal Replacement Therapy] explode all trees 10. MeSH descriptor: [Renal Insufficiency] explode all trees 11. MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 12. dialysis:ti,ab,kw (Word variations have been searched) 13. hemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched) 14. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched) 15. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched) 16. kidney disease* or renal disease* or kidney failure or renal failure:ti,ab,kw (Word variations have been searched) 17. ESRF or ESKF or ESRD or ESKD:ti,ab,kw (Word variations have been searched) 18. CKF or CKD or CRF or CRD:ti,ab,kw (Word variations have been searched) 19. CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched) 20. predialysis or pre-dialysis:ti,ab,kw (Word variations have been searched) 21. {or #8-#20} 22. {and #7, #21} 23. MeSH descriptor: [Antihypertensive Agents] explode all trees 24. MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] 1 tree(s) exploded 25. MeSH descriptor: [Angiotensin II Type 1 Receptor Blockers] 1 tree(s) exploded 26. aliskiren:ti,ab,kw (Word variations have been searched) 27. MeSH descriptor: [Adrenergic alpha-Antagonists] 2 tree(s) exploded 28. MeSH descriptor: [Calcium Channel Blockers] 2 tree(s) exploded 29. MeSH descriptor: [Vasodilator Agents] explode all trees 30. MeSH descriptor: [Endothelin Receptor Antagonists] 1 tree(s) exploded 31. MeSH descriptor: [Diuretics] 1 tree(s) exploded 32. MeSH descriptor: [Hypolipidemic Agents] explode all trees

(Continued)

- 33.ezetimibe:ti,ab,kw (Word variations have been searched)
- 34.MeSH descriptor: [Fibric Acids] 3 tree(s) exploded
- 35.MeSH descriptor: [Cardiotonic Agents] 2 tree(s) exploded
- 36.MeSH descriptor: [Phosphodiesterase Inhibitors] explode all trees
- 37.MeSH descriptor: [Cardiovascular Agents] 1 tree(s) exploded
- 38.MeSH descriptor: [Cyclooxygenase Inhibitors] explode all trees
- 39.MeSH descriptor: [Purinergic P2Y Receptor Antagonists] explode all trees
- 40.MeSH descriptor: [Receptors, Thrombin] 5 tree(s) exploded
- 41.MeSH descriptor: [Thromboxanes] 3 tree(s) exploded
- 42.MeSH descriptor: [Dipyridamole] this term only
- 43.MeSH descriptor: [Dietary Supplements] 1 tree(s) exploded
- 44.MeSH descriptor: [Fatty Acids, Omega-3] 3 tree(s) exploded
- 45.MeSH descriptor: [Ubiquinone] this term only
- 46.Ubiquinone:ti,ab,kw (Word variations have been searched)
- 47.carnitine:ti,ab,kw (Word variations have been searched)
- 48."coenzyme q10":ti,ab,kw (Word variations have been searched)
- 49.MeSH descriptor: [Thiamine] 4 tree(s) exploded
- 50.MeSH descriptor: [Vitamin D] 4 tree(s) exploded
- 51.MeSH descriptor: [Guanidines] 1 tree(s) exploded
- 52.creatine or "creatine analog":ti,ab,kw (Word variations have been searched)
- 53.antihypertensive agent*:ti,ab,kw (Word variations have been searched)
- 54.statin*:ti,ab,kw (Word variations have been searched)
- 55.neprilysin inhibitor*:ti,ab,kw (Word variations have been searched)
- 56.{or #23-#55}
- 57.{and #22, #56}

MEDLINE

1. exp Heart Failure/
2. exp Ventricular Dysfunction, Left/
3. Ventricular Dysfunction, Right/
4. exp ventricular outflow obstruction/
5. ventricular dysfunction.tw.
6. ventricular hypertrophy.tw.
7. heart failure.tw.
8. or/1-7
9. Kidney Diseases/
- 10.exp Renal Replacement Therapy/
- 11.Renal Insufficiency/
- 12.exp Renal Insufficiency, Chronic/
- 13.dialysis.tw.
- 14.(hemodialysis or haemodialysis).tw.
- 15.(hemofiltration or haemofiltration).tw.
- 16.(hemodiafiltration or haemodiafiltration).tw.
- 17.(kidney disease* or renal disease* or kidney failure or renal failure).tw.
- 18.(ESRF or ESKF or ESRD or ESKD).tw.
- 19.(CKF or CKD or CRF or CRD).tw.
- 20.(CAPD or CCPD or APD).tw.
- 21.(predialysis or pre-dialysis).tw.
- 22.or/9-21
- 23.exp Angiotensin-Converting Enzyme Inhibitors/
- 24.exp Angiotensin II Type 1 Receptor Blockers/
- 25.exp Antihypertensive Agents/
- 26.aliskiren.tw.

(Continued)

27.exp Adrenergic alpha-Antagonists/
 28.exp Calcium Channel Blockers/
 29.exp Vasodilator Agents/
 30.exp Endothelin Receptor Antagonists/
 31.exp Diuretics/
 32.or/23-31
 33.exp Hypolipidemic Agents/
 34.exp Ezetimibe/
 35.exp Fibrin Acids/
 36.or/33-35
 37.exp Cardiotonic Agents/
 38.exp Phosphodiesterase Inhibitors/
 39.exp Cardiovascular Agents/
 40.or/37-39
 41.exp Platelet Aggregation Inhibitors/
 42.exp Cyclooxygenase Inhibitors/
 43.exp Purinergic P2Y Receptor Antagonists/
 44.exp Receptors, Thrombin/
 45.exp Thromboxanes/
 46.exp Dipyridamole/
 47.or/41-46
 48.exp Dietary Supplements/
 49.exp Fatty Acids, Omega-3/
 50.Ubiquinone/
 51."coenzyme q10".tw.
 52.exp Carnitine/
 53.l-carnitine.tw.
 54.exp Thiamine/
 55.exp Vitamin D/
 56.exp Guanidines/
 57.(creatine or creatine analog\$.tw.
 58.or/48-57
 59.neprilysin inhibitor\$.tw
 60.sacubitril valsartan.tw
 61.LCZ696.tw
 62.or/59-61
 63.or/32,36,40,47,58,62
 64.and/8,22,63

EMBASE

1. exp heart failure/
 2. heart ventricle function/
 3. exp heart left ventricle failure/
 4. heart right ventricle failure/
 5. ventricular dysfunction.tw.
 6. ventricular hypertrophy.tw.
 7. heart failure.tw.
 8. or/1-7
 9. exp renal replacement therapy/
 10.kidney disease/
 11.chronic kidney disease/
 12.kidney failure/
 13.chronic kidney failure/

(Continued)

- 14.mild renal impairment/
- 15.stage 1 kidney disease/
- 16.moderate renal impairment/
- 17.severe renal impairment/
- 18.end stage renal disease/
- 19.renal replacement therapy-dependent renal disease/
- 20.kidney transplantation/
- 21.(hemodialysis or haemodialysis).tw.
- 22.(hemofiltration or haemofiltration).tw.
- 23.(hemodiafiltration or haemodiafiltration).tw.
- 24.dialysis.tw.
- 25.(CAPD or CCPD or APD).tw.
- 26.(kidney disease* or renal disease* or kidney failure or renal failure).tw.
- 27.(CKF or CKD or CRF or CRD).tw.
- 28.(ESRF or ESKF or ESRD or ESKD).tw.
- 29.(predialysis or pre-dialysis).tw.
- 30.((kidney or renal) adj (transplant* or graft* or allograft*)).tw.
- 31.or/9-30
- 32.exp antihypertensive agent/
- 33.exp adrenergic receptor blocking agent/
- 34.exp angiotensin receptor antagonist/
- 35.exp dipeptidyl carboxypeptidase inhibitor/
- 36.exp calcium channel blocking agent/
- 37.exp diuretic agent/
- 38.exp vasodilator agent/
- 39.exp endothelin receptor antagonist/
- 40.or/32-39
- 41.inotropic agent/
- 42.digoxin/
- 43.exp phosphodiesterase inhibitor/
- 44.or/41-43
- 45.exp antilipemic agent/
- 46.exp hypocholesterolemic agent/
- 47.exp fibric acid derivative/
- 48.or/45-47
- 49.exp antithrombocytic agent/
- 50.exp prostaglandin synthase inhibitor/
- 51.exp anticoagulant agent/
- 52.exp thromboxane receptor affecting agent/
- 53.or/49-52
- 54.diet supplementation/
- 55.omega 3 fatty acid/
- 56.ubidecarenone/
- 57.creatine kinase/
- 58.creatine analog\$.tw.
- 59.carnitine/
- 60.exp vitamin b group/
- 61.exp vitamin D/
- 62.or/54-61
- 63.exp enkephalinase inhibitor/
- 64.neprilysin inhibitor\$.tw.

(Continued)

65.or/63-64
66.or/40,44,48,53,62,65
67.and/8,31,66

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random). <i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention. <i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes). <i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure. <i>Unclear:</i> Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. <i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. <i>Unclear:</i> Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	<i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. <i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. <i>Unclear:</i> Insufficient information to permit judgement
Incomplete outcome data	<i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across

(Continued)

Attrition bias due to amount, nature or handling of incomplete outcome data.

groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Unclear: Insufficient information to permit judgement

Selective reporting

Reporting bias due to selective outcome reporting

Low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: PR, RQ, GS
2. Study selection: PR, ML
3. Extract data from studies: PR, ML, MR, PN
4. Enter data into RevMan: PR, ML, MR, PN
5. Carry out the analysis: PR, ML
6. Interpret the analysis: PR, RQ, GS, ML, MT, PER, IK, SP
7. Draft the final review: PR, RQ, GS, ML, MT, PER, IK, MR, PN, SP
8. Disagreement resolution: GS, SP
9. Update the review: PR, RQ, ML, GS, SP

DECLARATIONS OF INTEREST

Daichi Sankyo awarded a grant to Dr Marcello Tonelli's institution in lieu of a personal honorarium for a lecture at a scientific meeting in 2017.

All other authors have no known declarations of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no major discrepancies between the protocol and the review. The background was slightly restructured to be more succinct and clear; however, these changes did not affect the rationale of why it was important to do this study. Eligibility criteria were not changed but better specified in the review, as definitions of CKD and HF are not always consistent across publications.

We modified secondary outcome measures slightly. In the protocol, these outcomes were: ESKD (need for dialysis or kidney transplantation, fatal and non-fatal MI, fatal and non-fatal stroke, and sudden death. Additional secondary outcomes were related to heart performance, kidney dysfunction, or any adverse events of treatment or worsening of the disease course, and quality of life. The review includes secondary outcomes as cardiovascular death, all-cause hospitalisation, dichotomous measures of worsening HF or worsening kidney failure (as defined by authors), quality of life, and two adverse effects: hyperkalaemia and hypotension. These changes were made to match the data available in most studies (e.g. cardiovascular death was often reported, not death due to MI or stroke). Minor changes were made to the data collection and analysis methods. As no count or continuous data were available, we did not estimate incidence risk ratios.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [therapeutic use]; Antidiuretic Hormone Receptor Antagonists [therapeutic use]; Antihypertensive Agents [*therapeutic use]; Heart Failure [*drug therapy] [mortality]; Hospitalization; Mineralocorticoid Receptor Antagonists [therapeutic use]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*complications] [drug therapy]

MeSH check words

Humans