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Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease (Review)

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[Intervention Review]

Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease

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ABSTRACT

Background

Treatment with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) is used to reduce proteinuria and retard the progression of chronic kidney disease (CKD). However, resolution of proteinuria may be incomplete with these therapies and the addition of an aldosterone antagonist may be added to further prevent progression of CKD. This is an update of a Cochrane review first published in 2009 and updated in 2014.

Objectives

To evaluate the effects of aldosterone antagonists (selective (eplerenone), non-selective (spironolactone or canrenone), or non-steroidal mineralocorticoid antagonists (finerenone)) in adults who have CKD with proteinuria (nephrotic and non-nephrotic range) on: patient-centred endpoints including kidney failure (previously know as end-stage kidney disease (ESKD)), major cardiovascular events, and death (any cause); kidney function (proteinuria, estimated glomerular filtration rate (eGFR), and doubling of serum creatinine); blood pressure; and adverse events (including hyperkalaemia, acute kidney injury, and gynaecomastia).

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 13 January 2020 through contact with the Information Specialist 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 (RCTs) and quasi-RCTs that compared aldosterone antagonists in combination with ACEi or ARB (or both) to other anti-hypertensive strategies or placebo in participants with proteinuric CKD.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Data were summarised using random effects meta-analysis. We expressed summary treatment estimates as a risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes,

or standardised mean difference (SMD) when different scales were used together with their 95% confidence interval (CI). Risk of bias were assessed using the Cochrane tool. Evidence certainty was evaluated using GRADE.

Main results

Forty-four studies (5745 participants) were included. Risk of bias in the evaluated methodological domains were unclear or high risk in most studies. Adequate random sequence generation was present in 12 studies, allocation concealment in five studies, blinding of participant and investigators in 18 studies, blinding of outcome assessment in 15 studies, and complete outcome reporting in 24 studies.

All studies comparing aldosterone antagonists to placebo or standard care were used in addition to an ACEi or ARB (or both). None of the studies were powered to detect differences in patient-level outcomes including kidney failure, major cardiovascular events or death.

Aldosterone antagonists had uncertain effects on kidney failure (2 studies, 84 participants: RR 3.00, 95% CI 0.33 to 27.65, I^2 = 0%; *very low certainty evidence*), death (3 studies, 421 participants: RR 0.58, 95% CI 0.10 to 3.50, I^2 = 0%; *low certainty evidence*), and cardiovascular events (3 studies, 1067 participants: RR 0.95, 95% CI 0.26 to 3.56; I^2 = 42%; *low certainty evidence*) compared to placebo or standard care. Aldosterone antagonists may reduce protein excretion (14 studies, 1193 participants: SMD -0.51, 95% CI -0.82 to -0.20, I^2 = 82%; *very low certainty evidence*), eGFR (13 studies, 1165 participants, MD -3.00 mL/min/1.73 m^2, 95% CI -5.51 to -0.49, I^2 = 0%, *low certainty evidence*) and systolic blood pressure (14 studies, 911 participants: MD -4.98 mmHg, 95% CI -8.22 to -1.75, I^2 = 87%; *very low certainty evidence*) compared to placebo or standard care.

Aldosterone antagonists probably increase the risk of hyperkalaemia (17 studies, 3001 participants: RR 2.17, 95% CI 1.47 to 3.22, I^2 = 0%; *moderate certainty evidence*), acute kidney injury (5 studies, 1446 participants: RR 2.04, 95% CI 1.05 to 3.97, I^2 = 0%; *moderate certainty evidence*), and gynaecomastia (4 studies, 281 participants: RR 5.14, 95% CI 1.14 to 23.23, I^2 = 0%; *moderate certainty evidence*) compared to placebo or standard care.

Non-selective aldosterone antagonists plus ACEi or ARB had uncertain effects on protein excretion (2 studies, 139 participants: SMD -1.59, 95% CI -3.80 to 0.62, I^2 = 93%; *very low certainty evidence*) but may increase serum potassium (2 studies, 121 participants: MD 0.31 mEq/L, 95% CI 0.17 to 0.45, I^2 = 0%; *low certainty evidence*) compared to diuretics plus ACEi or ARB. Selective aldosterone antagonists may increase the risk of hyperkalaemia (2 studies, 500 participants: RR 1.62, 95% CI 0.66 to 3.95, I^2 = 0%; *low certainty evidence*) compared ACEi or ARB (or both). There were insufficient studies to perform meta-analyses for the comparison between non-selective aldosterone antagonists and calcium channel blockers, selective aldosterone antagonists plus ACEi or ARB (or both) and nitrate plus ACEi or ARB (or both), and non-steroidal mineralocorticoid antagonists and selective aldosterone antagonists.

Authors' conclusions

The effects of aldosterone antagonists when added to ACEi or ARB (or both) on the risks of death, major cardiovascular events, and kidney failure in people with proteinuric CKD are uncertain. Aldosterone antagonists may reduce proteinuria, eGFR, and systolic blood pressure in adults who have mild to moderate CKD but may increase the risk of hyperkalaemia, acute kidney injury and gynaecomastia when added to ACEi and/or ARB.

PLAIN LANGUAGE SUMMARY

Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease

What is the issue?

People who have chronic kidney disease (CKD) have a higher risk of heart disease and declining kidney function. Increased amounts of protein in the urine is a sign of kidney stress and is linked to declining kidney function. Medications used to lower blood pressure and reduce protein levels in the urine - in particular, angiotensin-converting enzyme Inhibitors (ACEi) and angiotensin receptor blockers (ARBs) -remain the core treatment to prevent the declining of kidney function in CKD.

Protecting kidney function with these medications may however be incomplete and adding an aldosterone antagonist (blocker) (for example, spironolactone, canrenone, eplerenone, or finerenone) may better protect kidney function in the long-term. By blocking the production of aldosterone, the kidneys excrete more water which can lead to a lowering of blood pressure. However, they can cause side effects including enlargement of male breast tissue, and when used with ACEi or ARBs may cause high levels of potassium in the blood or a decline in kidney function.

What did we do? We reviewed the available studies looking at the addition of aldosterone blockers to standard treatment in people with CKD to see if they slowed the decline of kidney function and the subsequent need for dialysis or a kidney transplant. We looked at whether they reduced heart disease, the amount of protein in urine, or improved blood pressure. We also looked at whether aldosterone blockers were safe in terms of risks of male breast enlargement, potassium levels in the blood, and short-term effects on kidney function.

What did we find? We found that adding aldosterone blockers to a patient's current medications (ACEi or ARBs), lowered both protein in the urine and systolic blood pressure. Kidney function declined, however the effects on survival were uncertain. The addition of aldosterone

blockers increased the amount of potassium in the blood. This may require medication changes, extra blood tests, and may be potentially harmful. Treatment with aldosterone blockers also increased the chance of short-term decline in kidney function and enlargement of male breast tissue.

Conclusions It is unclear as to whether aldosterone blockers protect kidney function or prevent heart disease in people who have CKD.

SUMMARY OF FINDINGS

Summary of findings 1. Aldosterone antagonists versus placebo or standard care for proteinuric chronic kidney disease

Aldosterone antagonist versus placebo or standard care for proteinuric CKD

Patient or population: proteinuric CKD
Intervention: aldosterone antagonist
Comparison: placebo or standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or standard care	Risk with aldosterone antagonist			
Kidney failure	0 per 1,000	0 per 1,000 (0 to 0)	RR 3.00 (0.33 to 27.65)	84 (2)	⊕⊝⊝⊝ VERY LOW [1, 2]
Hyperkalaemia	25 per 1,000	55 per 1,000 (37 to 81)	RR 2.17 (1.47 to 3.22)	3001 (17)	⊕⊕⊕⊝ MODERATE [3]
Death	14 per 1,000	8 per 1,000 (1 to 50)	RR 0.58 (0.10 to 3.50)	421 (3)	⊕⊕⊝⊝ LOW [2, 4]
Cardiovascular events	32 per 1,000	31 per 1,000 (8 to 115)	RR 0.95 (0.26 to 3.56)	1067 (3)	⊕⊕⊝⊝ LOW [2, 5]
Doubling serum creatinine	83 per 1,000	107 per 1,000 (57 to 202)	RR 1.30 (0.69 to 2.44)	875 (2)	⊕⊕⊝⊝ LOW [2, 5]
AKI	30 per 1,000	61 per 1,000 (31 to 119)	RR 2.04 (1.05 to 3.97)	1446 (5)	⊕⊕⊕⊝ MODERATE [6]
Proteinuria	The SMD was 0.51 lower with aldosterone antagonists (0.82 lower to 0.20 lower) than placebo or standard care		-	1193 (14)	⊕⊝⊝⊝ VERY LOW [7, 8, 9, 10]
eGFR (mL/min/1.73 m^2)	The mean eGFR was 3.00 mL/min/1.73 m^2 lower with aldosterone antagonists (5.51 lower to 0.49 lower) than placebo or standard care		-	1144 (12)	⊕⊕⊝⊝ LOW [2, 11]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CKD: chronic kidney disease; **CI:** confidence interval; **RR:** risk ratio; **AKI:** acute kidney injury; **eGFR:** estimated glomerular filtration rate

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Evidence quality was downgraded because of study risks of bias. Allocation concealment in no studies, blinding of outcome assessment in one study and complete outcome data in no studies
[2] Treatment estimate had a wide CI
[3] Evidence quality was downgraded because of study risks of bias. Allocation concealment in three studies, blinding of outcome assessment in seven studies, complete outcome data in 11 studies
[4] Evidence quality was downgraded because of study risks of bias. Allocation concealment in one study, blinding of outcome assessment in one study, and complete outcome data in one study
[5] Evidence quality was downgraded because of study risks of bias. Allocation concealment in one study, blinding of outcome assessment in one study, complete outcome data in one study
[6] Evidence quality was downgraded because of study risks of bias. Allocation concealment in one study, blinding of outcome assessment in three studies, complete outcome data in one study
[7] Evidence quality was downgraded because of suspected small study effects from asymmetry on inverted funnel plot
[8]Evidence quality was downgraded because of study risks of bias. Allocation concealment in one study, blinding of outcome assessment in seven studies, complete outcome data in nine studies
[9] There was significant heterogeneity between studies
[10] Evidence quality was downgraded because proteinuria is a surrogate outcome for CKD progression
[11] Evidence quality was downgraded because of study risks of bias. Allocation concealment in one study, blinding of outcome assessment in four studies, complete outcome data in six studies

Summary of findings 2. Aldosterone antagonists versus diuretics for proteinuric chronic kidney disease

Aldosterone antagonist versus diuretics for proteinuric CKD

Patient or population: proteinuric CKD
Intervention: aldosterone antagonist
Comparison: diuretics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with diuretics	Risk with aldosterone antagonist			
Kidney failure	not reported	not reported	--	--	--
Hyperkalaemia	not reported	not reported	--	--	--
Death	not reported	not reported	--	--	--

Cardiovascular events	not reported	not reported	--	--	--
Doubling serum creatinine	not reported	not reported	--	--	--
AKI	not reported	not reported	--	--	--
Proteinuria	The SMD was 1.59 lower (3.8 lower to 0.62 higher) with aldosterone antagonists than diuretics		-	139 (2)	⊕⊖⊖⊖ VERY LOW [1, 2, 3, 4]
eGFR (mL/min/1.73 m^2)	The mean eGFR was 2 mL/min/1.73 m^2 higher with aldosterone antagonists (26.31 lower to 30.31 higher) than diuretics		-	12 (1)	⊕⊕⊖⊖ LOW [4, 5]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CKD: chronic kidney disease; **CI:** confidence interval; **RR:** risk ratio; **AKI:** acute kidney injury; **eGFR:** estimated glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Evidence quality was downgraded due to study risks of bias. Allocation concealment in no studies, blinding of outcome assessment in one study, complete data in one study
[2] There was significant heterogeneity between the studies
[3] Evidence quality was downgraded because proteinuria is a surrogate outcome for CKD progression
[4] Treatment estimate had a wide confidence interval
[5] Single study with unclear allocation concealment

Summary of findings 3. Aldosterone antagonists versus calcium channel blockers for proteinuric chronic kidney disease

Aldosterone antagonists versus calcium channel blocker for proteinuric CKD

Patient or population: proteinuric CKD
Intervention: aldosterone antagonist
Comparison: calcium channel blocker

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)

	Risk with calcium channel blocker	Risk with aldosterone antagonist			
Kidney failure	not reported	not reported	--	--	--
Hyperkalaemia	not reported	not reported	--	--	--
Death	not reported	not reported	--	--	--
Cardiovascular events	not reported	not reported	--	--	--
Doubling serum creatinine	not reported	not reported	--	--	--
AKI	not reported	not reported	--	--	--
Proteinuria	Data could not to be meta-analysed		-	37 (1)	⊕⊕⊖⊖ LOW [1, 2]
eGFR (mL/min/1.73 m^2)	not reported		--	--	--

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CKD: chronic kidney disease; **CI:** Confidence interval; **RR:** Risk ratio; **AKI:** acute kidney injury; **eGFR:** estimated glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Single study with unclear allocation concealment
[2] Evidence quality was downgraded because proteinuria is a surrogate outcome for CKD progression

Summary of findings 4. Aldosterone antagonists versus ACEi or ACEi plus ARB for proteinuric chronic kidney disease

Aldosterone antagonists versus ACEi or ACEi plus ARB for proteinuric chronic kidney disease

Patient or population: proteinuric chronic kidney disease
Intervention: aldosterone antagonist
Comparison: ACEi or ACEi plus ARB

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with ACEi or ACEi plus ARB	Risk with aldosterone antagonist			
Kidney failure	not reported	not reported	--	--	--
Hyperkalaemia	37 per 1,000	60 per 1,000 (24 to 146)	RR 1.62 (0.66 to 3.95)	500 (2)	⊕⊕⊖⊖ LOW [1, 2]
Death	not reported	not reported	--	--	--
Cardiovascular events	not reported	not reported	--	--	--
Doubling serum creatinine	not reported	not reported	--	--	--
AKI	not reported	not reported	--	--	--
Proteinuria	Data could not be meta-analysed		-	465 (4)	⊕⊖⊖⊖ VERY LOW [3, 4, 5]
GFR (mL/min/1.73 m^2)	Data could not be meta-analysed		-	18 (1)	⊕⊕⊖⊖ LOW [6, 7]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACEi: angiotensin-converting enzyme inhibitors; **ARB:** angiotensin receptor blocker; **CI:** confidence interval; **RR:** risk ratio; **AKI:** acute kidney injury; **eGFR:** estimated glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Evidence quality was downgraded due to risks of bias. Allocation concealment in no studies, blinding of outcome assessment in one study, complete outcome data in one study
[2] Treatment estimates had wide confidence intervals
[3] Evidence quality was downgraded due to risks of bias. Allocation concealment in no studies, blinding of outcome assessment in one study, complete outcome data in two studies
[4] Evidence quality was downgraded as proteinuria is a surrogate outcome for CKD progression
[5] Raw data was not available in studies to allow pooling of treatment estimates
[6] Single study with unclear allocation concealment

[7] Insufficient studies to inform precision

Summary of findings 5. Aldosterone antagonist versus nitrate for proteinuric chronic kidney disease

Aldosterone antagonist versus nitrate for proteinuric chronic kidney disease

Patient or population: proteinuric chronic kidney disease
Intervention: aldosterone antagonist
Comparison: nitrate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with nitrate	Risk with aldosterone antagonist			
Kidney failure	not reported	not reported	--	--	--
Hyperkalaemia	not reported	not reported	--	--	--
Death	not reported	not reported	--	--	--
Cardiovascular events	not reported	not reported	--	--	--
Doubling serum creatinine	not reported	not reported	--	--	--
AKI	not reported	not reported	--	--	--
Proteinuria	Data could not be meta-analysed		-	29 (1)	⊕⊕⊖⊖ LOW [1, 2]
eGFR	not reported		--	--	--

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **AKI:** acute kidney injury; **eGFR:** estimated glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Single study with unclear allocation concealment and unclear blinding of outcome assessment

[2] Evidence quality was downgraded as proteinuria is a surrogate outcome for CKD progression

Summary of findings 6. Non-steroidal mineralocorticoid receptor antagonist versus selective aldosterone antagonist for proteinuric chronic kidney disease

Non-steroidal mineralocorticoid receptor antagonist versus selective aldosterone antagonist for proteinuric chronic kidney disease

Patient or population: proteinuric chronic kidney disease
Intervention: non-steroidal mineralocorticoid receptor antagonist
Comparison: selective aldosterone antagonist

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with selective aldosterone antagonist	Risk with non-steroidal mineralocorticoid receptor antagonist			
Kidney failure	not reported	not reported	--	--	--
Hyperkalaemia	47 per 1,000	42 per 1,000 (21 to 83)	RR 0.89 (0.45 to 1.77)	1023 (1)	⊕⊕⊖⊖ LOW [1, 2]
Death	36 per 1,000	25 per 1,000 (11 to 56)	RR 0.70 (0.31 to 1.55)	1055 (1)	⊕⊕⊖⊖ LOW [1, 2]
Cardiovascular events	not reported	not reported	--	--	--
Doubling serum creatinine	1/834	0/221**	RR 0.80 (0.03 to 19.51)	1055 (1)	⊕⊕⊖⊖ LOW [1, 2]
AKI	not reported	not reported	--	--	--
Proteinuria	not reported		--	--	--
eGFR	not reported		--	--	--

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

** 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 non-steroidal mineralocorticoid receptor antagonist group

CI: confidence interval; **RR:** risk ratio; **AKI:** acute kidney injury; **eGFR:** estimated glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

---

[1] Single study
[2] Treatment estimate had a wide confidence interval

BACKGROUND

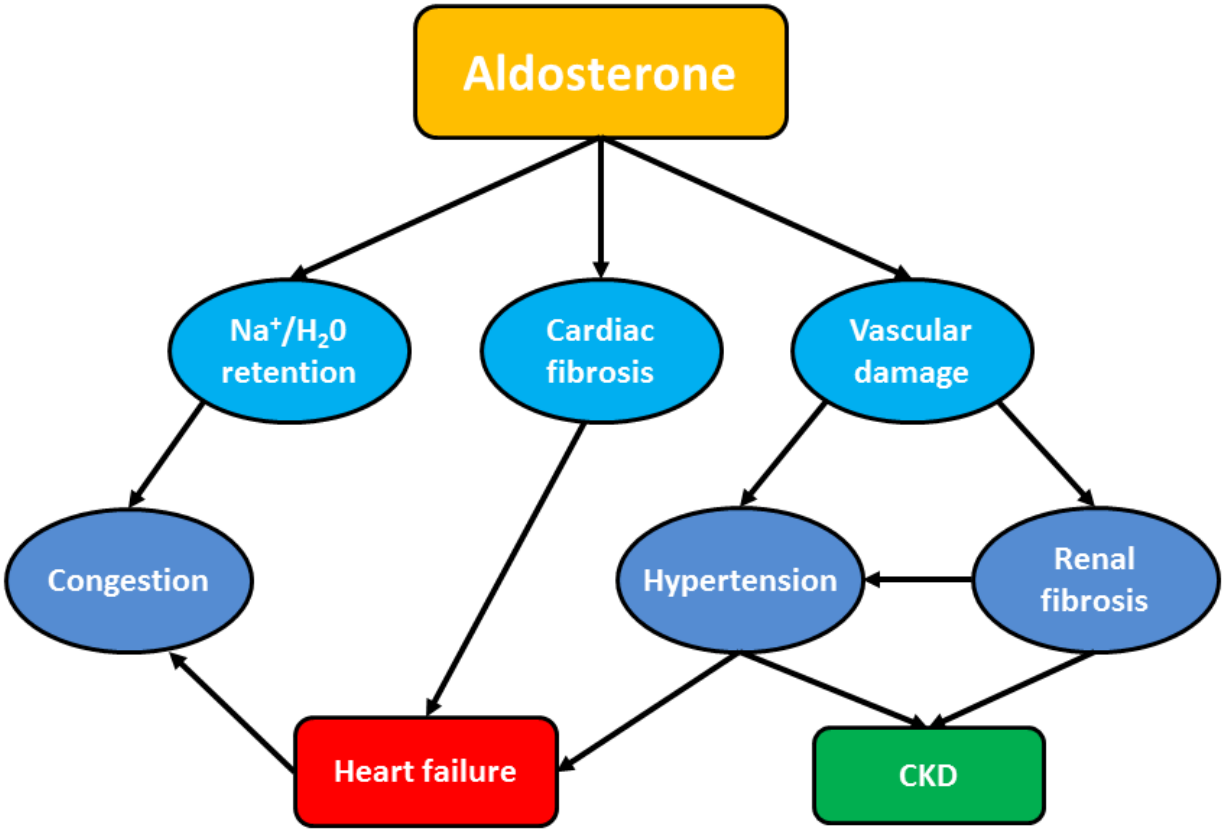
Description of the condition

Chronic kidney disease (CKD) has a global prevalence of 10% to 12% and progression to kidney failure (previously known as end-stage kidney disease (ESKD)) is rising due to the global diabetes and hypertension pandemics (Mills 2015; Nugent 2011). There is a significant associated economic burden to patients, caregivers, and society, which increases throughout disease progression (Wang 2016). Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) are the standard of care to slow progression of CKD and reduce incidence of kidney failure in patients with proteinuria irrespective of primary kidney disease (Jafar 2001; Strippoli 2006) because they lower proteinuria and blood pressure, which are both independent predictors of death in adults with CKD (Brenner 2001; GISEN 1997; Mathiesen 1999). However, ACEi or ARB slow, but may not completely retard, the progression of CKD (Schieppati 2003).

Description of the intervention

Animal studies have shown that aldosterone has an independent role in the development of hypertensive kidney disease and vascular injury resulting in myocardial and renal fibrosis (Figure 1), and exacerbates glomerulosclerosis resulting in severe proteinuria (Bomback 2007), which is reduced with aldosterone blockade (Aldigier 2005; Green 1996; Rocha 1998; Silvestre 1998). Renin-angiotensin-aldosterone system blockade with ACEi or ARB result in incomplete suppression of serum aldosterone levels and is known as the 'aldosterone escape phenomenon' (Staessen 1981). Further experimental studies have established this theory and in humans, the treatment of adults with CKD exhibiting aldosterone escape phenomenon with aldosterone antagonists reduces proteinuria (Fritsch Neves 2003). However, aldosterone antagonism may increase risks of hyperkalaemia and gynaecomastia (Nappi 2011). Novel non-steroidal mineralocorticoid receptor antagonists such as finerenone are more selective for the mineralocorticoid receptor than other steroid receptors including the glucocorticoid receptor, androgen receptor and progesterone receptor (Bramlage 2016) and may provide similar efficacy as non-selective aldosterone antagonist but improved safety profile.

Figure 1. Mechanisms of cardiac and kidney damage induced by aldosterone excess



How the intervention might work

Multiple aldosterone-mediated mechanisms have been shown to contribute to renal vascular injury and fibrosis in animal studies. These include aldosterone-mediated increases in plasminogen activator inhibitor-1 (PAI-1) which inhibits the fibrinolytic system and activates latent growth factors; up-regulation of transforming growth factor-b and associated fibroblast differentiation, up-regulation of collagen synthesis and down regulation of matrix metalloproteinase collagenase; generation of oxygen-free radicals and hydrogen peroxide; and up regulation of endothelin-1 with resultant vasoconstriction (Hollenberg 2004). However, a common

pathway is yet to be clearly defined. In a rat model, renal radiation injury resulted in an eight-fold increase in the expression of PAI-1 messenger RNA (mRNA) and non-selective aldosterone blockade (spironolactone) significantly decreased PAI-1 mRNA expression, development of glomerulosclerosis and proteinuria (Brown 2000). In human studies, beneficial effects of aldosterone blockade (non-selective and selective) have been established in congestive cardiac failure (Hostetter 2003; Pitt 1999; Pitt 2003) and proteinuric CKD (Bianchi 2006; Chrysostomou 2006; Epstein 2006; Rossing 2005; Schjoedt 2005). In animal studies, finerenone had a more potent natriuretic response than eplerenone but no impact on urinary potassium levels (Kolkhof 2014). Therefore, it is hypothesised that non-steroidal mineralocorticoid receptor antagonists will exhibit the benefits of aldosterone blockade without the risk of hyperkalaemia.

Why it is important to do this review

Aldosterone blockade in combination with ACEi or ARB may reduce proteinuria but their effects on patient-level outcomes such as kidney failure requiring dialysis or kidney transplantation or major cardiovascular events and their safety in regards to risk of hyperkalaemia and acute kidney injury, particularly in adults who have coexisting CKD, remain uncertain. Thus, we analysed the benefits and harms of aldosterone antagonists in adults who had CKD and who were or who were not already treated with ACEi or ARB (or in combination). We specifically focused on treatment effects for patient-level outcomes including kidney failure and major cardiovascular events, proteinuria, and kidney function. New relevant studies on CKD patients receiving aldosterone antagonists, including non-steroidal mineralocorticoid antagonists, have recently been completed and their inclusion to update the previous published versions of this review (Bolignano 2014; Navaneethan 2009) would be valuable.

OBJECTIVES

To evaluate the effect of aldosterone antagonists (selective (eplerenone), non-selective (spironolactone), and non-steroidal (finerenone)) in combination with ACEi or ARB in adults who have CKD with proteinuria (nephrotic and non-nephrotic range) on:

- Patient-centred endpoints including kidney failure, major cardiovascular events, and death (any cause)
- Kidney function (proteinuria, estimated glomerular filtration rate (eGFR), and doubling of serum creatinine (SCr)
- Adverse events (including hyperkalaemia, acute kidney injury, and gynaecomastia).

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs of aldosterone antagonists used in combination with ACEi or ARB (or both) were included. Data from the first period of randomised cross-over studies was also included.

Types of participants

Inclusion criteria

Studies enrolling participants with CKD stages 1 to 4, as defined by the by Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines (Levey 2003) and who had albuminuria or proteinuria were considered for inclusion. We included studies in adults who had CKD regardless of aetiology. The K/DOQI categories for kidney disease are as follows.

- CKD stage 1: eGFR > 90 mL/min/1.73 m^2 and evidence of clinically relevant structural or urinary abnormalities including haematuria or proteinuria (or both)
- CKD stage 2: eGFR 60 to 89 mL/min/1.73 m^2
- CKD stage 3: eGFR 30 to 59 mL/1.73 m^2
- CKD stage 4: eGFR 15 to 29 mL/min/1.73 m^2.

Exclusion criteria

We excluded studies in adults on dialysis, recipients of a kidney transplant, participants without evidence of CKD or proteinuria, studies less than 4 weeks of duration, and studies not evaluating any outcome of interest.

Types of interventions

We included studies evaluating aldosterone antagonist treatment given in combination with an ACEi or ARB (or both). We considered studies in which treatment duration was 4 weeks or longer. If any studies compared aldosterone antagonists alone (i.e. no additional RAS antagonists), these studies were also included,

We considered the following treatment comparisons.

- Aldosterone antagonists with RAS antagonists versus placebo or standard care
- Aldosterone antagonist with RAS antagonists versus diuretic plus ACEi or ARB
- Non-selective aldosterone antagonist with RAS antagonists versus calcium channel blocker
- Selective aldosterone antagonist with RAS antagonists versus ACEi or ARB (or both)
- Selective aldosterone antagonist with RAS antagonists versus ACEi or ARB (or both) versus ACEi or ARB (or both) plus nitrate
- Selective aldosterone antagonist with RAS antagonists versus non-steroidal mineralocorticoid antagonist.

If disaggregated outcome data were not available for the three groups (ACEi alone, ARB alone or the combination separately), we used combined data when available.

Types of outcome measures

Primary outcomes

- Kidney failure (defined as permanent worsening in eGFR requiring kidney replacement therapy)
- Hyperkalaemia (defined as serum potassium > 5.0 mEq/L or mmol/L)

Secondary outcomes

- Death (any cause)
- Major cardiovascular events as defined by the investigators (including but not limited to myocardial infarction, stroke, congestive heart failure)
- Urinary protein excretion rate (24-hour proteinuria, 24-hour albuminuria in mg/dL, urine protein:creatinine ratio, or urine albumin:creatinine ratio)

- Kidney function: estimated GFR (mL/min or mL/min/1.73 m^2); doubling of SCr; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria
- Blood pressure: systolic and diastolic blood pressure (mmHg)
- Serum potassium
- Acute kidney injury
- Gynaecomastia
- Fatigue
- Falls

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 13 January 2020 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. Searches of kidney and transplant journals, and the proceedings and abstracts from 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 update.

Searching other resources

1. Reference lists of clinical practice guidelines, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Disagreements were resolved in consultation with two authors who also provided methodological assistance throughout the review process.

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. For this update, titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however, studies and reviews that may have included relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts, and if necessary, the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data were used in the analyses. Where relevant outcomes were only published in earlier versions these data were used. Any discrepancies between published versions were highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors 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?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Were 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?

Discrepancies were resolved by discussion with a third author.

Measures of treatment effect

For dichotomous outcomes (kidney failure, death (any cause), cardiovascular events, doubling of SCr, hyperkalaemia, acute kidney injury, and gynaecomastia) results were expressed as a risk ratio (RR) with 95% confidence intervals (CI). When continuous scales of measurement were used to assess the effects of treatment (end of treatment protein excretion rate or albumin excretion rate, eGFR or creatinine clearance, blood pressure, and serum potassium), we used the mean difference (MD) or the standardised mean difference (SMD) when different measurement scales were used.

Dealing with missing data

We contacted study authors to seek additional information. We were successful in obtaining additional data from Drs KJ Schjoedt, K Rossing, A Chrysostomou, S Bianchi, S Nielsen, and K Takebayashi. These data were included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT), as-treated and per-protocol (PP) population were performed. Attrition rates, such as drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods were critically appraised (Higgins 2011).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows.

- 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 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

We planned to assess for the potential existence of small study bias (Higgins 2011) for outcomes in which sufficient data observations were available (10 or more studies) and in which there was low or no statistical heterogeneity between studies.

Data synthesis

Data were pooled using random effects meta-analysis, but the fixed effects model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity. Heterogeneity among participants could be related to age, stage of kidney disease, aetiology of kidney disease and amount of proteinuria. Heterogeneity in treatments could be related to prior agent(s) used and the agent (selective or non-selective aldosterone antagonist), dose, duration of aldosterone antagonists and the concomitant use of ACEi or ARB (or both).

'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 or association 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). We presented the following outcomes in the 'Summary of findings' tables. The absolute treatment effects for dichotomous outcomes was estimated using the risk estimate and 95% CI obtained from the corresponding meta-analysis.

Primary efficacy outcome

- Kidney failure

Primary safety outcome

- Hyperkalaemia

Secondary outcomes

- Death (any cause)
- Cardiovascular events
- Doubling SCr
- Acute kidney injury
- Proteinuria
- eGFR

RESULTS

Description of studies

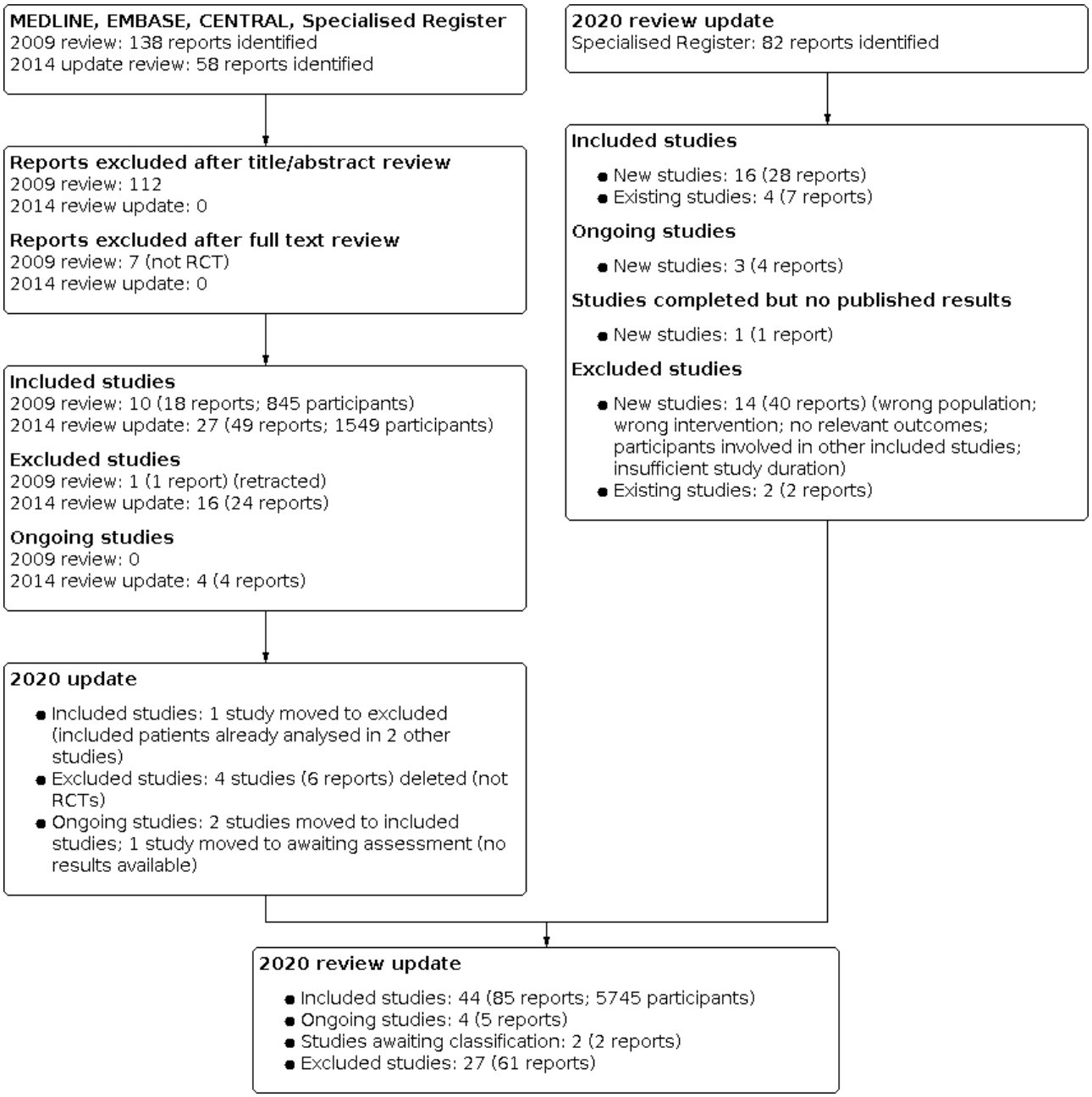
Results of the search

For this 2020 update a search of The Cochrane Kidney and Transplant Register of Studies identified 83 reports. We identified 18 new included studies (32 reports), and four reports of two existing included studies; three new ongoing studies (four reports); 13 new excluded studies (40 reports), and two reports of two existing excluded studies. One study (one report) has been recently completed but no results have been published and is awaiting assessment.

In addition to the new reports, one previously included study has been move to excluded (Schjoedt 2006) as a proportion of the patients have been reported in two other included studies (Schjoedt 2005; Rossing 2005). Two previous ongoing studies have now been included (Abolghasmi 2011; EVALUATE 2010) and one study, while complete, is yet to publish any results and is awaiting assessment (NCT00315016). Four non-RCTs have been removed from this update.

See Figure 2.

Figure 2. Study flow diagram.



Included studies

For this 2020 update we included 18 new studies (4248 participants) (ARTS 2012; ARTS-DN 2015; ARTS-HF 2015; Bianchi 2010; Boesby 2013; Chen 2018b; Esteghamati 2013; EVALUATE 2010; Fogari 2014; Hamid 2017a; Hase 2013; Horestani 2012; Ito 2019a; Kato 2015; Morales 2015; Tylicki 2012; Wang 2013g; Ziaee 2013). This brings the total number of included studies to 44 (85 reports, 5745 participants).

Ten studies were cross-over studies (Boesby 2011; Morales 2009; Morales 2015; Nielsen 2012; Saklayen 2008; Smolen 2006; Rossing 2005; Schjoedt 2005; Tylicki 2008; Tylicki 2012).

Twenty-three studies included participants who had kidney disease secondary to diabetes mellitus (ARTS-DN 2015; Chen 2018b; Chrysostomou 2006; Epstein 2002; Epstein 2006; Esteghamati 2013; Fogari 2014; Hamid 2017a; Hase 2013; Horestani 2012; Ito 2019a; Kato 2015; Koroshi 2010; Mehdi 2009; Nielsen 2012; Ogawa 2006a; Rossing 2005; Saklayen 2008; Schjoedt 2005; Takebayashi 2006; van den Meiracker 2006; Zheng 2011; Ziaee 2013). Two studies included participants with heart failure with associated proteinuric CKD (ARTS 2012; ARTS-HF 2015). The remaining studies included participants with non-diabetic kidney disease encompassing IgA nephropathy, benign nephrosclerosis, membranous nephropathy, or idiopathic chronic glomerulonephritis (Abolghasmi 2011; Bianchi 2006; Bianchi 2010; Boesby 2011; Boesby 2013; Cohen 2010; CRIBS II 2009; Furumatsu 2008; Guney 2009; Haykal 2007; Lv 2009a;

Morales 2009; Morales 2015; Smolen 2006; Tokunaga 2008a; Tylicki 2008; Tylicki 2012; Wang 2013g). All studies excluded participants with an eGFR below 15 mL/min/1.73 m^2. For studies measuring 24-hour urine protein or albumin, the baseline albuminuria/proteinuria excretion rates ranged from 0.15 to 3.6 g/day. Study duration varied from one to 36 months with a median duration of 3 months. Sample size of all studies was variable (range 16 to 1055) and none were powered to detect hard primary outcomes including kidney failure, death, or major cardiovascular events.

Among studies using non-selective aldosterone antagonists, 22 studies (1441 participants) compared spironolactone plus ACEi or ARB (or both) to ACEi or ARB (or both) (Abolghasmi 2011; Bianchi 2006; Chen 2018b; Chrysostomou 2006; CRIBS II 2009; Furumatsu 2008; Guney 2009; Kato 2015; Koroshi 2010; Lv 2009a; Mehdi 2009; Nielsen 2012; Ogawa 2006a; Rossing 2005; Saklayen 2008; Schjoedt 2005; Tokunaga 2008a; Tylicki 2008; van den Meiracker 2006; Wang 2013g; Zheng 2011; Ziaee 2013). Five studies (220 participants) compared spironolactone plus ACEi or ARB to diuretics plus ACEi or ARB (Hamid 2017a; Hase 2013, Horestani 2012; Morales 2015; Smolen 2006); one study (37 participants) compared spironolactone to calcium channel blockers (Takebayashi 2006); one study (136 participants) compared spironolactone plus ARB to ACEi plus ARB (Esteghamati 2013); one study (120 participants) compared canrenone plus ARB and calcium channel blockers to hydrochlorothiazide plus ARB and calcium channel blockers (Fogari 2014); and one study (128 participants) compared spironolactone plus ACEi and ARB to ACEi (Bianchi 2010). In the studies that analysed the efficacy of non-selective aldosterone antagonists, 25 mg/day of spironolactone was used throughout the study period except for Abolghasmi 2011, Saklayen 2008 and van den Meiracker 2006 who used 25 to 50 mg/day. Chen 2018b, Lv 2009a, Wang 2013g and Zheng 2011 used 20 mg/day; Horestani 2012, Koroshi 2010and Takebayashi 2006 used 50 mg/day; Mehdi 2009 used 12.5 to 25 mg/day of spironolactone; and Bianchi 2010 used 25 mg three times/week to 50 mg/day of spironolactone. Fogari 2014 used 25 mg/day of canrenone. In Hamid 2017a, the dose of spironolactone was not defined.

Six studies (925 participants) compared the selective aldosterone antagonist eplerenone plus ACEi or ARB (or both) to ACEi or ARB (or both) (Boesby 2011; Haykal 2007; Epstein 2002; Epstein 2006; EVALUATE 2010; Tylicki 2012). One study (34 participants) compared eplerenone plus ACEi or ARB (or both) to ACEi or ARB (or both) and to ACEi or ARB (or both) plus nitrate (Cohen 2010), and one study (54 participants) compared the selective aldosterone antagonist eplerenone to placebo (Boesby 2013). Studies that analysed the efficacy of selective aldosterone antagonists used eplerenone at the dose of 200 mg/day (Epstein 2002), 50 to 100 mg/day (Epstein 2006), 25 to 50 mg/day (Boesby 2011; Boesby 2013; Haykal 2007), and 50 mg/day (EVALUATE 2010; Tylicki 2012). In Cohen 2010 the dose of eplerenone administered was not defined.

One cross-over study (12 participants) compared eplerenone alone (25 mg/day) to ACEi alone (20 mg/day) or ACEi (10 mg/day) plus ARB (16 mg/day) (Morales 2009).

Among studies using non-steroidal mineralocorticoid antagonists, one study (821 participants) compared finerenone to placebo (ARTS-DN 2015), one study (392 participants) compared finerenone to placebo or spironolactone (ARTS 2012), one study (1055 participants) compared finerenone to eplerenone (ARTS-HF 2015), and one study (358 participants) compared esaxerenone to placebo (Ito 2019a). Studies that analysed the efficacy of non-steroidal mineralocorticoid antagonists used finerenone at the dose of 2.5 to 10 mg/day (ARTS 2012), 1.25 to 25 mg/day (ARTS-DN 2015), 5 to 20 mg/day (ARTS-HF 2015), and esaxerenone 0.625 to 5 mg/day (Ito 2019a). Other characteristics of the participants and the interventions of the included studies are detailed in the Characteristics of included studies.

Excluded studies

Twenty-seven studies (61 reports) were excluded because; they did not include adults with CKD (17 studies); were not studies comparing aldosterone antagonists with or without ACEi or ARB (3); were of short duration (1); included participants already reported in other included studies (1); were terminated early with no reported outcomes (1); or they did not examine outcomes of interest (e.g. pharmacokinetic studies) (1). One study was retracted (1).

For this 2020 update, non-RCTs have been deleted.

See Characteristics of excluded studies

Risk of bias in included studies

Risks of bias in the available studies are shown in Figure 3 and Figure 4.

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

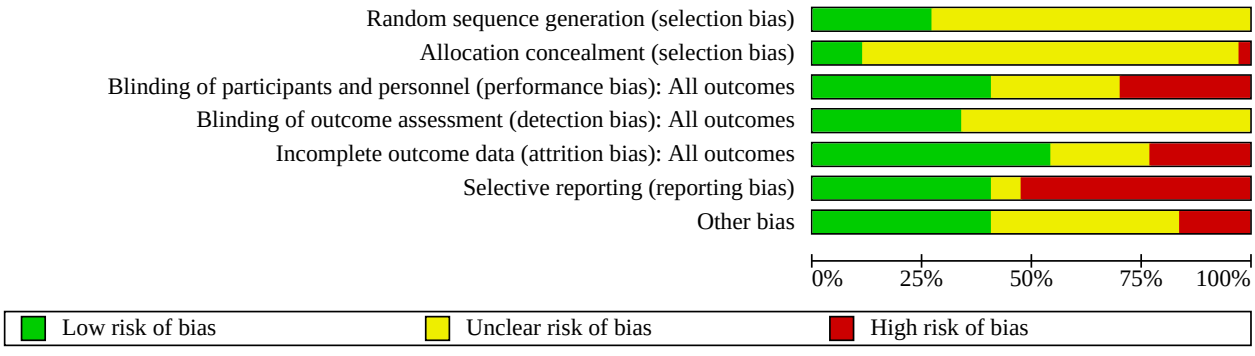


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

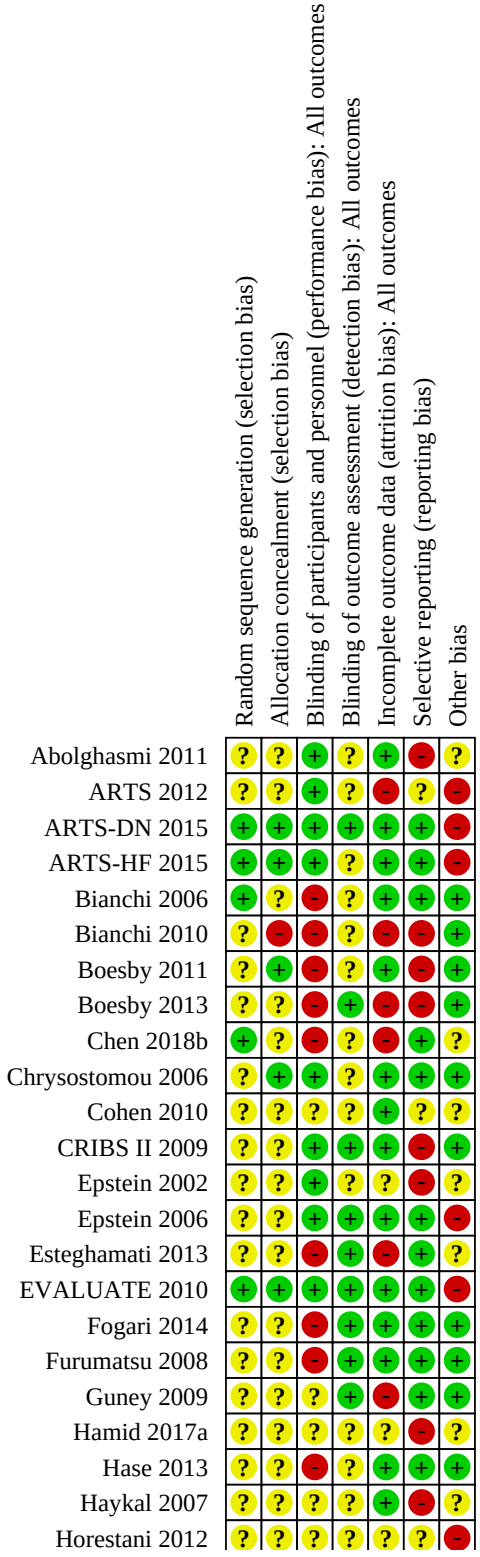
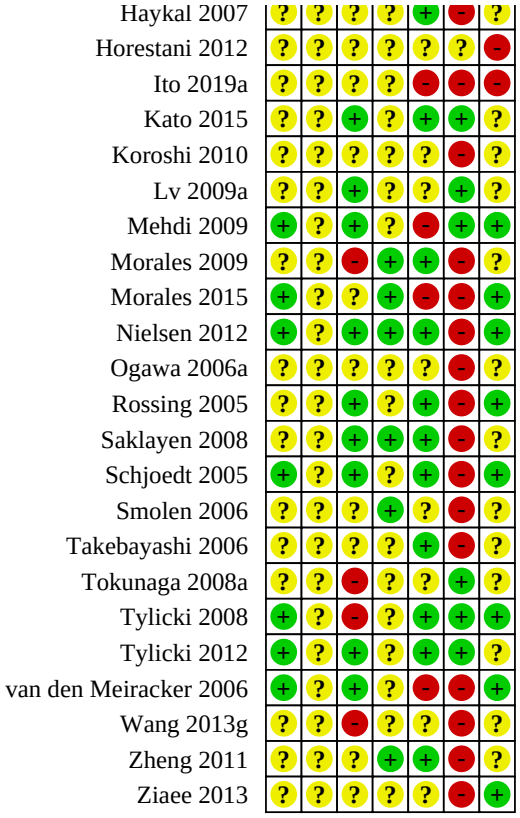


Figure 4. (Continued)



Allocation

Random sequence generation was judged to be at low risk of bias in 12 studies (ARTS-DN 2015; ARTS-HF 2015; Bianchi 2006; Chen 2018b; EVALUATE 2010; Mehdi 2009; Morales 2015; Nielsen 2012; Schjoedt 2005; Tylicki 2008; Tylicki 2012; van den Meiracker 2006) and unclear in the remaining 32 studies.

Allocation concealment was judged to be at low risk in five studies (ARTS-DN 2015; ARTS-HF 2015; Boesby 2011; Chrysostomou 2006; EVALUATE 2010), one study was judged to be a high risk of bias (Bianchi 2010), and unclear in the remaining 38 studies.

Blinding

Participants and investigators were blinded in 18 studies (Abolghasmi 2011; ARTS 2012; ARTS-DN 2015; ARTS-HF 2015; Chrysostomou 2006; CRIBS II 2009; Epstein 2002; Epstein 2006; EVALUATE 2010; Kato 2015; Lv 2009a; Mehdi 2009; Nielsen 2012; Rossing 2005; Saklayen 2008; Schjoedt 2005; Tylicki 2012; van den Meiracker 2006) and not blinded in 13 studies (Bianchi 2006; Bianchi 2010; Boesby 2011; Boesby 2013; Chen 2018b; Esteghamati 2013; Fogari 2014; Furumatsu 2008; Hase 2013; Morales 2009; Tokunaga 2008a; Tylicki 2008; Wang 2013g); blinding was unclear in the remaining 13 studies.

Outcome assessors were not aware of treatment allocation or outcomes were unlikely influenced by treatment allocation in 15 studies (ARTS-DN 2015; Boesby 2013; CRIBS II 2009; Epstein 2006; Esteghamati 2013; EVALUATE 2010; Fogari 2014; Furumatsu 2008; Guney 2009; Morales 2009; Morales 2015; Nielsen 2012; Saklayen 2008; Smolen 2006; Zheng 2011). Blinding of outcome assessors was unclear in the remaining 29 studies.

Incomplete outcome data

Twenty-four studies were judged to be at low risk of bias (Abolghasmi 2011; ARTS-DN 2015; ARTS-HF 2015; Bianchi 2006; Boesby 2011; Chrysostomou 2006; Cohen 2010; CRIBS II 2009; Epstein 2006; EVALUATE 2010; Fogari 2014; Furumatsu 2008; Hase 2013; Haykal 2007; Kato 2015; Morales 2009; Nielsen 2012; Rossing 2005; Saklayen 2008; Schjoedt 2005; Takebayashi 2006; Tylicki 2008; Tylicki 2012; Zheng 2011). Seven studies where there was some loss to follow-up (ARTS-DN 2015; Bianchi 2006; Boesby 2011; Chen 2018b; Epstein 2006; Cohen 2010; CRIBS II 2009) were analysed on an intention-to-treat basis. Ten studies were judged to be at high risk of bias (ARTS 2012; Bianchi 2010; Boesby 2013; Chen 2018b; Esteghamati 2013; Guney 2009; Ito 2019a; Mehdi 2009; Morales 2015; van den Meiracker 2006). The dropout rate from study follow-up ranged from 0% to 37% and did not differ between the treatment and control groups.

Selective reporting

All the pre-specified outcomes and all relevant outcomes were reported in 18 studies (ARTS-DN 2015; ARTS-HF 2015; Bianchi 2006; Chen 2018b; Chrysostomou 2006; Epstein 2006; Esteghamati 2013; EVALUATE 2010; Fogari 2014; Furumatsu 2008; Guney 2009; Hase 2013; Kato 2015; Lv 2009a; Mehdi 2009; Tokunaga 2008a; Tylicki 2008; Tylicki 2012). Selective reporting was judged to be at high risk

of bias in 23 studies (Abolghasmi 2011; Bianchi 2006; Bianchi 2010; Boesby 2011; CRIBS II 2009; Epstein 2002; Hamid 2017a; Haykal 2007; Ito 2019a; Koroshi 2010; Morales 2009; Morales 2015; Nielsen 2012; Ogawa 2006a; Rossing 2005; Saklayen 2008; Schjoedt 2005; Smolen 2006; Takebayashi 2006; van den Meiracker 2006; Wang 2013g; Zheng 2011; Ziaee 2013), and unclear in the remaining three studies.

Other potential sources of bias

Eighteen studies were judged to be at low risk of bias due to funding (Bianchi 2006; Bianchi 2010; Boesby 2011; Boesby 2013; Chrysostomou 2006; CRIBS II 2009; Fogari 2014; Furumatsu 2008; Guney 2009; Hase 2013; Mehdi 2009; Morales 2015; Nielsen 2012; Rossing 2005; Schjoedt 2005; Tylicki 2008; van den Meiracker 2006; Ziaee 2013); six studies were funded by a pharmaceutical company (ARTS 2012; ARTS-DN 2015; ARTS-HF 2015; Epstein 2006; EVALUATE 2010; Ito 2019a;); one study excluded participants after randomisation due change in treatment (Horestani 2012) and the risk of bias was unclear in the remaining 19 studies.

Effects of interventions

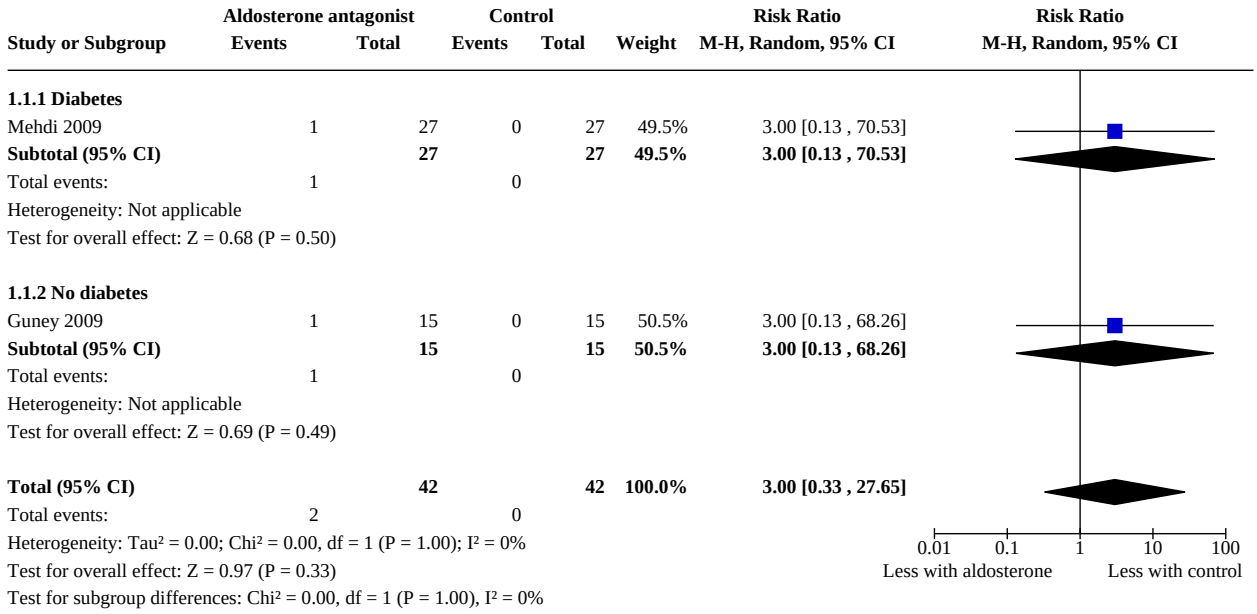
See: **Summary of findings 1** Aldosterone antagonists versus placebo or standard care for proteinuric chronic kidney disease; **Summary of findings 2** Aldosterone antagonists versus diuretics for proteinuric chronic kidney disease; **Summary of findings 3** Aldosterone antagonists versus calcium channel blockers for proteinuric chronic kidney disease; **Summary of findings 4** Aldosterone antagonists versus ACEi or ACEi plus ARB for proteinuric chronic kidney disease; **Summary of findings 5** Aldosterone antagonist versus nitrate for proteinuric chronic kidney disease; **Summary of findings 6** Non-steroidal mineralocorticoid receptor antagonist versus selective aldosterone antagonist for proteinuric chronic kidney disease

Aldosterone antagonists (selective or non-selective) versus placebo or standard care

Kidney failure

In very low certainty evidence, aldosterone antagonists have uncertain effects on kidney failure (Analysis 1.1 (2 studies, 84 participants): RR 3.00, 95% CI 0.33 to 27.65; I^2 = 0%) (Figure 5) compared to placebo or standard care.

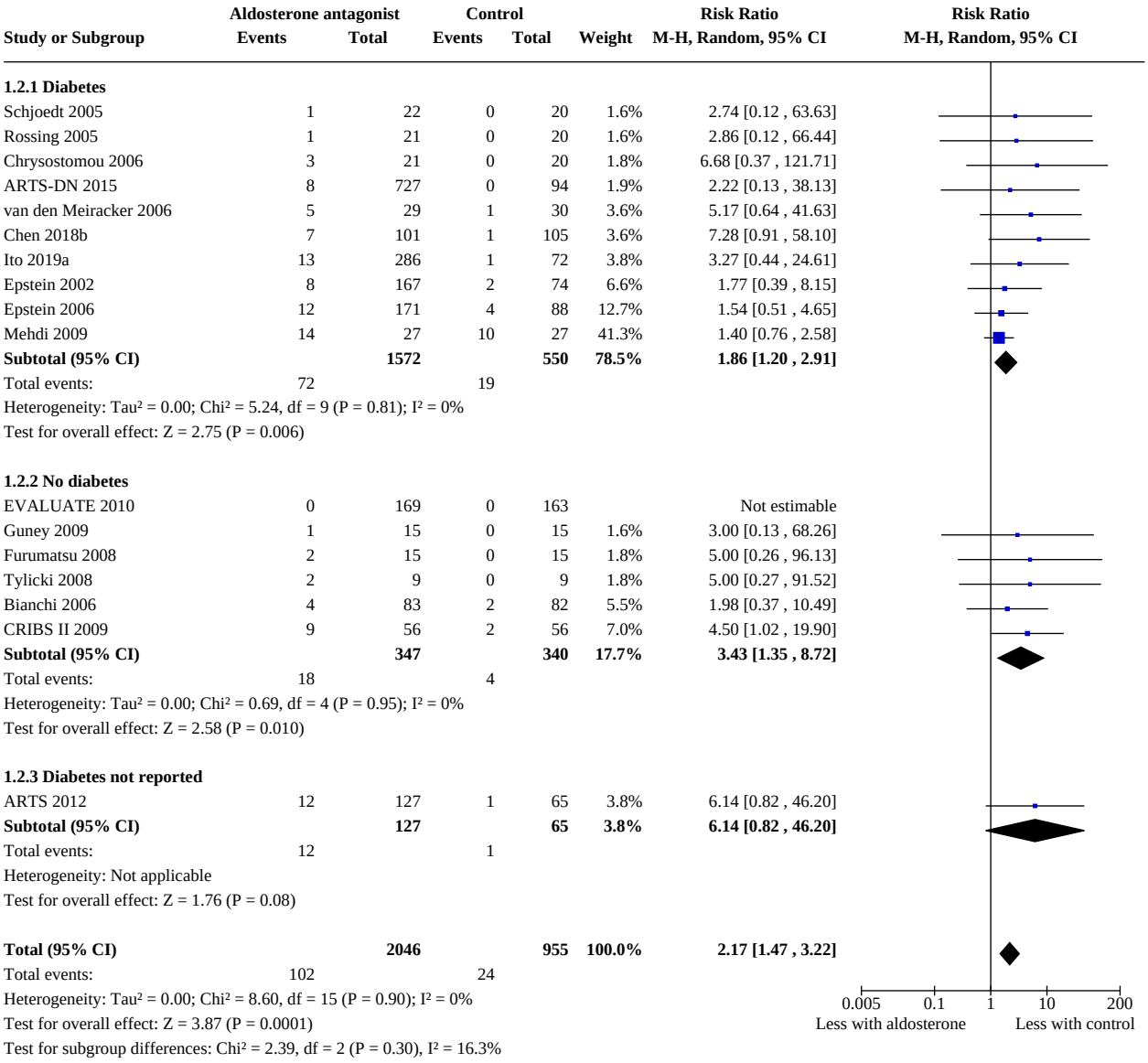
Figure 5. Effect of aldosterone antagonists versus placebo or standard care on kidney failure



Hyperkalaemia

In moderate certainty evidence, aldosterone antagonists probably increases risk of hyperkalaemia (Analysis 1.2 (17 studies, 3001 participants): RR 2.17, 95% CI 1.47 to 3.22; I^2 = 0%) (numbers needed to treat for an additional harmful outcome (NNTH) 41) (Figure 6) compared to placebo or standard care, regardless of whether aldosterone antagonists were combined with one ACEi or ARB (Analysis 1.3.1 (11 studies, 1828 participants): RR 2.05, 95% CI 1.28 to 3.28; I^2 = 0%), or combined with ACEi plus ARB (Analysis 1.3.2 (4 studies, 149 participants): RR 4.30, 95% CI 1.12 to 16.51; I^2 = 0%).

Figure 6. Effect of aldosterone antagonists versus placebo or standard care on hyperkalaemia



Death

In low certainty evidence, aldosterone antagonists have uncertain effects on death (any cause) (Analysis 1.5 (3 studies, 421 participants): RR 0.58, 95% CI 0.10 to 3.50; I^2 = 0%) compared to placebo or standard care.

Cardiovascular events

In low certainty evidence, aldosterone antagonists have uncertain effects on cardiovascular events (Analysis 1.6 (3 studies, 1067 participants): RR 0.95, 95% CI 0.26 to 3.56; I^2 = 42%) compared to placebo or standard care.

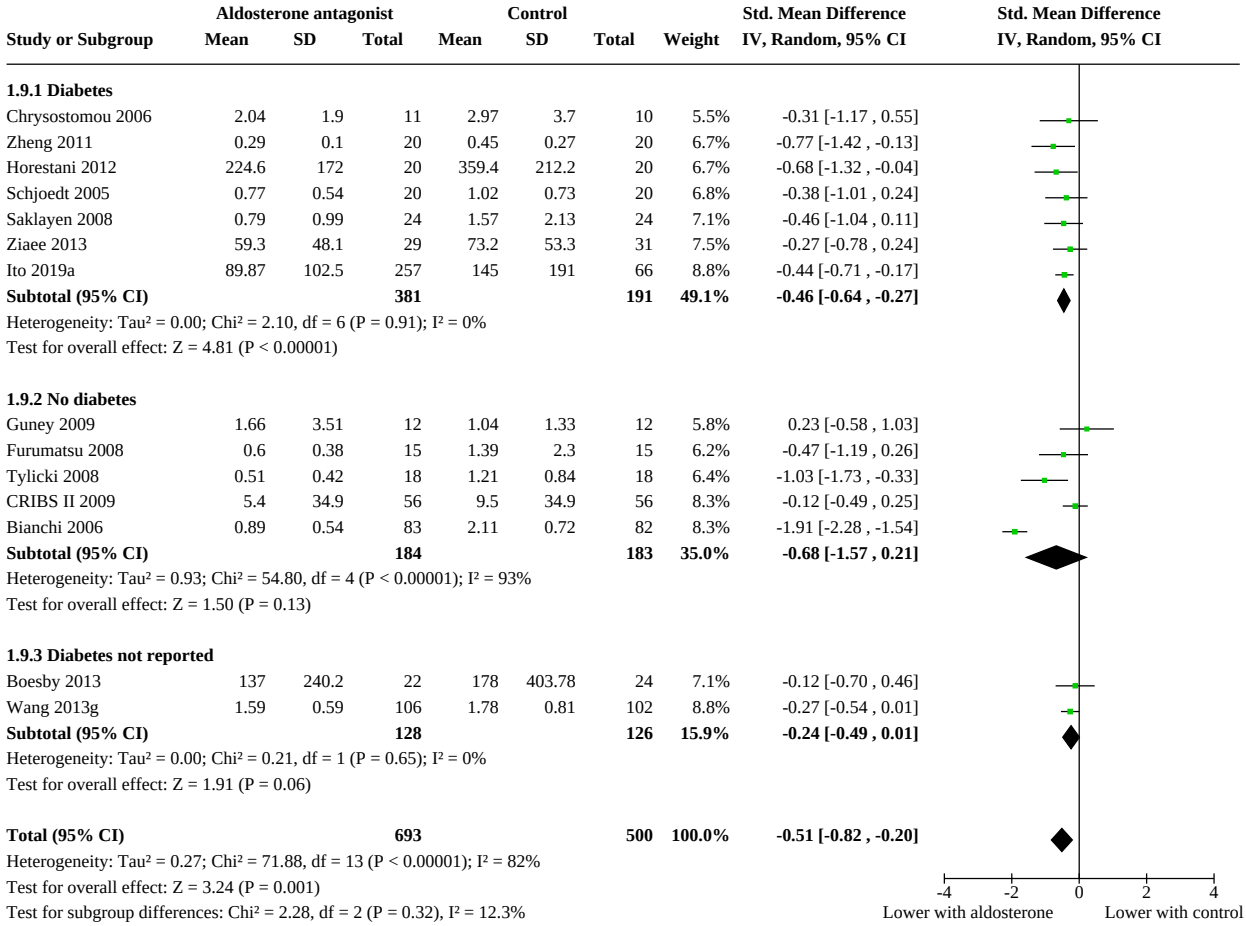
Mehdi 2009 reported one myocardial infarction in the aldosterone antagonist group. Meta-analysis was not performed.

Aldosterone antagonists had uncertain effects on stroke compared to placebo or standard care (Analysis 1.8 (3 studies, 1233 participants): RR 0.65, 95% CI 0.12 to 3.44; I^2 = 11%).

Proteinuria

In very low certainty evidence, aldosterone antagonists may reduce proteinuria (Analysis 1.9 (14 studies, 1193 participants): SMD -0.51, 95% CI -0.82 to -0.20; I^2 = 82%) (Figure 7) compared to placebo or standard care. There was significant heterogeneity.

Figure 7. Effect of aldosterone antagonists versus placebo or standard care on proteinuria.

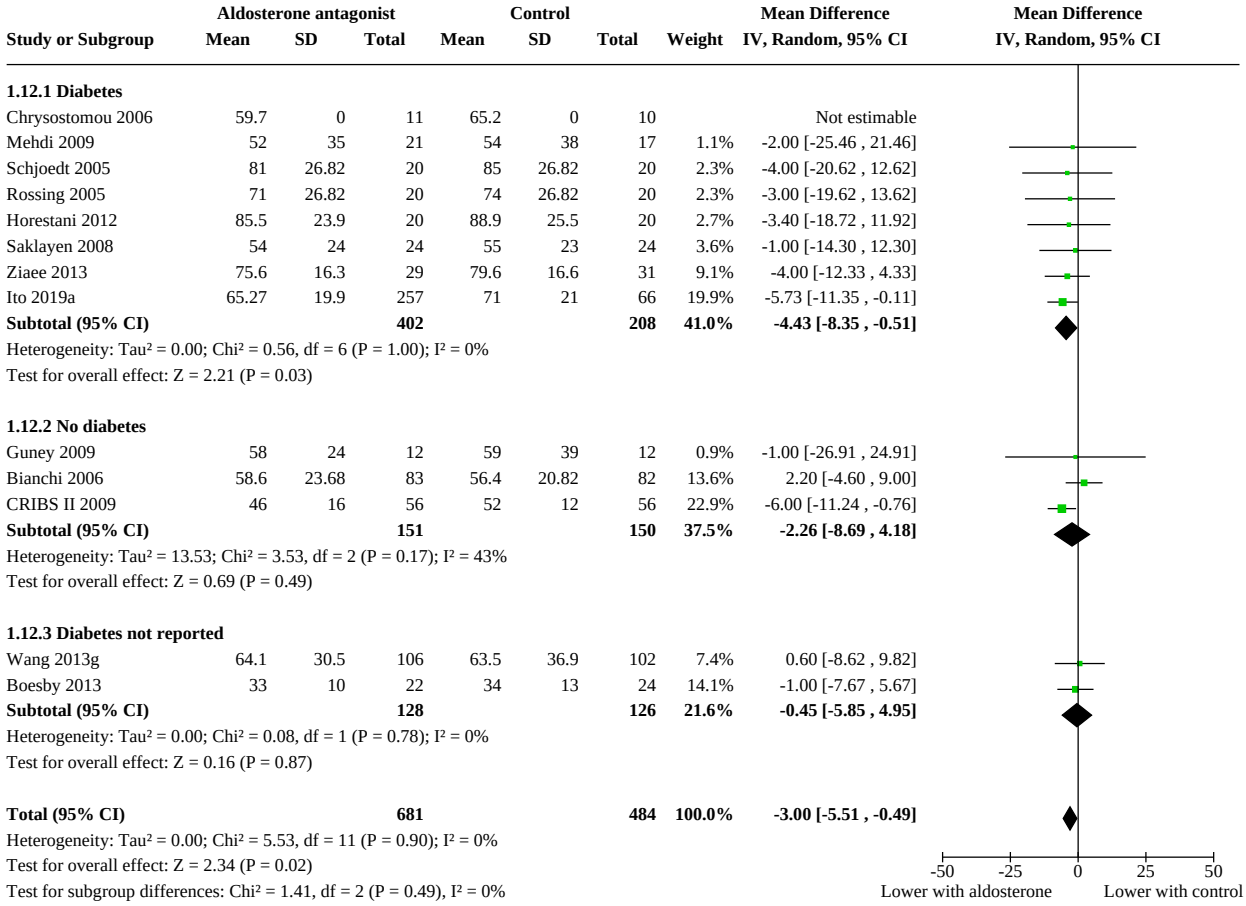


Kidney function

Glomerular filtration rate

In low certainty evidence, aldosterone antagonists may reduce eGFR (Analysis 1.12 (13 studies, 1165 participants): MD -3.00 mL/min/1.73 m^2, 95% CI -5.51 to -0.49; I^2 = 0%) (Figure 8) compared to placebo or standard care.

Figure 8. Effect of aldosterone antagonists versus placebo or standard care on GFR [mL/min/1.73 m²].



Doubling of serum creatinine

Two studies (ARTS-DN 2015; Mehdi 2009) reported doubling of SCr (or equivalent eGFR decline ≥ 57%) with events only occurring in Mehdi 2009. Meta-analysis was not performed.

Blood pressure

In very low certainty evidence, aldosterone antagonists may reduce systolic blood pressure (Analysis 1.16 (14 studies, 911 participants): MD -4.98 mmHg, 95% CI -8.22 to -1.75; I^2 = 87%) but had uncertain effects on diastolic blood pressure (Analysis 1.17 (13 studies, 875 participants): MD -1.04 mmHg, 95% CI -2.82 to 0.73; I^2 = 79%) compared to placebo or standard care. There was significant heterogeneity in both analyses.

Serum potassium

In very low certainty evidence, aldosterone antagonists may increase serum potassium (Analysis 1.20 (17 studies, 1326 participants): MD 0.19 mEq/L, 95% CI 0.10 to 0.29; I^2 = 81%) compared to placebo or standard care. There was significant heterogeneity.

Acute kidney injury

In moderate certainty evidence, aldosterone antagonists probably increases the risk of acute kidney injury (Analysis 1.22 (5 studies, 1446 participants): RR 1.94, 95% CI 0.99 to 3.79; I^2 = 0%) compared to placebo or standard care.

Gynaecomastia

In moderate certainty evidence, aldosterone antagonists probably increases the risk of gynaecomastia (Analysis 1.23 (4 studies, 281 participants): RR 5.14, 95% CI 1.14 to 23.23; I^2 = 0%) compared to placebo or standard care.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria; regression from micro- to normoalbuminuria; falls; and fatigue.

Analysis of heterogeneity

Heterogeneity in the effects of spironolactone on proteinuria was explored through sub-group analyses.

Baseline kidney disease

Aldosterone antagonists reduced proteinuria in diabetic kidney disease (Analysis 1.9.1 (7 studies, 572 participants): SMD -0.46, 95% CI -0.64 to -0.27; I^2 = 0%) but had unclear effects on non-diabetic kidney disease (Analysis 1.9.2 (5 studies, 367 participants): SMD

-0.68, 95% CI -1.57 to 0.21; I^2 = 93%) compared to placebo or standard care.

Aldosterone antagonists reduced systolic blood pressure to a greater extent in non-diabetic kidney disease (Analysis 1.16.2 (5 studies, 367 participants): MD -3.35, 95% CI -5.06 to -1.65; I^2 = 0%) than diabetic kidney disease (Analysis 1.16.1 (5 studies, 228 participants): MD -1.07, 95% CI -1.82 to -0.32; I^2 = 0%) compared to placebo or standard care.

Aldosterone antagonists reduced diastolic blood pressure in non-diabetic kidney disease (Analysis 1.17.2 (4 studies, 331 participants): MD -1.62, 95% CI -2.86 to -0.38; I^2 = 0%) but had unclear effects on diabetic kidney disease (Analysis 1.17.1 (5 studies, 249 participants): MD -1.06, 95% CI -1.80 to -0.31; I^2 = 25%) compared to placebo or standard care.

Aldosterone antagonists increased serum potassium in both diabetic kidney disease (Analysis 1.20.1 (9 studies, 664 participants): MD 0.21 mEq/L, 95% CI 0.14 to 0.28; I^2 = 0%) and non-diabetic kidney disease (Analysis 1.20.2 (6 studies, 367 participants): MD 0.30 mEq/L, 95% CI 0.10 to 0.50; I^2 = 92%) compared to placebo or standard care.

Study duration

Aldosterone antagonists reduced proteinuria in studies reporting follow-up of less than six months (Analysis 1.24.1 (9 studies, 822 participants): SMD -0.39, 95% CI -0.54 to -0.24; I^2 = 0%) but had unclear effects in studies reporting follow-up of longer than six months (Analysis 1.24.2 (4 studies, 331 participants): SMD -0.59, 95% CI -1.68 to 0.50; I^2 = 95%) compared to placebo or standard care.

Aldosterone antagonists reduced systolic blood pressure in both studies reporting follow-up of less than six months (Analysis 1.25.1 (10 studies, 580 participants): MD -5.65, 95% CI -10.96 to -0.33; I^2 = 90%) and studies reporting follow-up of longer than six months (Analysis 1.25.2 (4 studies, 331 participants): MD -3.62, 95% CI -6.09 to -1.15; I^2 = 15%).

Aldosterone antagonists reduced diastolic blood pressure in studies reporting follow-up longer than six months (Analysis 1.26.2 (4 studies, 331 participants): MD -1.62, 95% CI -2.86 to -0.38; I^2 = 0%) but had unclear effect in studies reporting follow-up less than six months (Analysis 1.26.1 (9 studies, 553 participants): MD -0.98, 95% CI -3.71 to 1.75; I^2 = 83%).

Aldosterone antagonists increased serum potassium in both studies reporting follow up less than six months (Analysis 1.27.1 (12 studies, 954 participants): MD 0.16 mEq/L, 95% CI 0.10 to 0.22; I^2 = 23%) and studies reporting follow-up longer than six months (Analysis 1.27.2 (4 studies, 331 participants): MD 0.35 mEq/L, 95% CI 0.04 to 0.65; I^2 = 93%).

Aldosterone antagonist selectivity

A single study (Boesby 2013) reported the effect of the selective aldosterone antagonist eplerenone on proteinuria, systolic blood pressure, diastolic blood pressure and serum potassium. All other studies reported the effect of the non-selective aldosterone antagonist spironolactone on these outcomes. Subgroup analysis was not performed.

Baseline proteinuria or albuminuria

Single studies specified baseline albuminuria > 100mg/g (Kato 2015), > 300mg/g (Rossing 2005), > 300mg/day (Schjoedt 2005) and 45 to 300 mg/day (Ito 2019a), and which reported on proteinuria and serum potassium. Subgroup analysis was not performed.

Single studies specified baseline proteinuria > 150mg/day (Horestani 2012), > 0.3g/day (Tylicki 2008), >1g/g (Bianchi 2006), and > 1.5g/day (Chrysostomou 2006), and which reported on proteinuria, systolic blood pressure, diastolic blood pressure, and serum potassium. All other studies specified baseline proteinuria > 0.5g/day or did not specific baseline proteinuria. Subgroup analysis was not performed.

Baseline kidney function

Single studies specified baseline eGFR 15 to 60 mL/min/1.73 m^2 (Boesby 2013), eGFR 25 to 50 mL/min/1.73 m^2 (Abolghasmi 2011), eGFR > 45 mL/min/1.73 m^2 (Tylicki 2008), and which reported on proteinuria, systolic blood pressure, diastolic blood pressure, and serum potassium. All other studies specified baseline eGFR > 30 mL/min/1.73 m^2 or did not specific baseline kidney function. Subgroup analysis was not performed.

Non-selective aldosterone antagonists (spironolactone or canrenone) plus ACEi or ARB versus diuretics plus ACEi or ARB

Proteinuria

In very low certainty evidence, non-selective aldosterone antagonists plus ACEi or ARB had an uncertain effect on proteinuria (Analysis 2.1 (2 studies, 139 participants): SMD -1.59, 95% CI -3.80 to 0.62; I^2 = 93%) compared to diuretics plus ACEi or ARB. There was significant heterogeneity.

Glomerular filtration rate

One study reported eGFR (Morales 2015) and one cross-over study (Smolen 2006) did not report individual study periods. Meta-analysis was not performed due to inability to combine study data.

Blood pressure

In very low certainty evidence, non-selective aldosterone antagonists plus ACEi or ARB had an uncertain effect on systolic blood pressure (Analysis 2.8 (3 studies, 151 participants): MD -3.79, 95% CI -14.36 to 6.79; I^2 = 90%) and diastolic blood pressure (Analysis 2.7 (3 studies, 151 participants): MD -1.56, 95% CI -3.52 to 0.41; I^2 = 3%) compared to diuretics plus ACEi or ARB. There was significant heterogeneity in the analysis for systolic blood pressure.

Serum potassium

In low certainty evidence, non-selective aldosterone antagonists plus ACEi or ARB may increase serum potassium (Analysis 2.11 (2 studies, 121 participants): MD 0.31, 95% CI 0.17 to 0.45; I^2 = 0%) compared to diuretics plus ACEi or ARB.

Fatigue

Fogari 2014 reported no difference in fatigue between the two groups. Meta-analysis was not performed.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the

available studies: kidney failure; hyperkalaemia; death (any cause); cardiovascular events; doubling of SCr; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria; acute kidney injury; gynaecomastia; and falls.

Non-selective aldosterone antagonists (spironolactone) versus calcium channel blockers

Proteinuria

Takebayashi 2006 reported spironolactone reduced urinary albumin excretion but did not change in amlodipine group. Meta-analysis was not performed.

Blood pressure

Takebayashi 2006reported no change in systolic or diastolic blood pressure between the two groups. Meta-analysis was not performed.

Serum potassium

Takebayashi 2006 reported serum potassium was lower in the calcium channel blocker group compared to the spironolactone group. Meta-analysis was not performed.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: kidney failure; hyperkalaemia; death (any cause); cardiovascular events; eGFR; doubling of SCr; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria; blood pressure; acute kidney injury; gynaecomastia; fatigue; and falls.

Selective aldosterone antagonists (eplerenone) alone versus ACEi alone

Hyperkalaemia

One cross-over study reported hyperkalaemia (Morales 2009). Meta-analysis was not performed.

Proteinuria

One cross-over study reported proteinuria (Morales 2009). Meta-analysis was not performed.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: kidney failure; death (any cause); cardiovascular events; eGFR; doubling of SCr; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria; blood pressure: serum potassium; acute kidney injury; gynaecomastia; fatigue; and falls.

Selective aldosterone antagonists (eplerenone) alone versus ACEi plus ARB

Hyperkalaemia

One cross-over study reported hyperkalaemia (Morales 2009). Meta-analysis was not performed.

Proteinuria

One cross-over study reported proteinuria (Morales 2009). Meta-analysis was not performed.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: kidney failure; death (any cause); cardiovascular events; eGFR; doubling of SCr; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria; blood pressure: serum potassium; acute kidney injury; gynaecomastia; fatigue; and falls.

Selective aldosterone antagonists (eplerenone) plus ACEi or ARB (or both) versus ACEi or ARB (or both)

Hyperkalaemia

Selective aldosterone antagonists plus ACEi or ARB (or both) may increase the risk of hyperkalaemia (Analysis 6.1 (2 studies, 500 participants): RR 1.62, 95% CI 0.66 to 3.95; I^2 = 0%; low certainty evidence).

Proteinuria

Six studies reported proteinuria, however data could not be meta-analysed (Boesby 2011; Cohen 2010; Epstein 2002; Epstein 2006; Haykal 2007; Tylicki 2012).

Blood pressure

Four studies reported blood pressure, however data could not be meta-analysed (Cohen 2010; Epstein 2002; Epstein 2006; Haykal 2007).

Glomerular filtration rate

One cross-over study (Tylicki 2012) reported no difference in eGFR between the two groups. Meta-analysis was not performed.

Serum potassium

One cross-over study (Tylicki 2012) reported no difference in serum potassium between the two groups. Meta-analysis was not performed.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: kidney failure; death (any cause); cardiovascular events; doubling of SCr; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria; acute kidney injury; gynaecomastia; fatigue; and falls.

Selective aldosterone antagonists (eplerenone) plus ACEi or ARB (or both) versus ACEi or ARB (or both) plus nitrate

Proteinuria

Cohen 2010 reported urine protein excretion was significantly reduced after four weeks of eplerenone while it increased in the comparator group. We could not conduct a meta-analysis as additional data could not be obtained from the investigators.

Blood pressure

Cohen 2010 reported systolic blood pressure was reduced by 9.7 ± 6.4 mmHg in the eplerenone group and by 1.0 ± 5.4 mmHg in the ACEi/ARB plus isosorbide group at 4 weeks. No data were available about diastolic blood pressure. We could not conduct a meta-analysis as additional data could not be obtained from the investigators.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: kidney failure; hyperkalaemia; death (any cause); cardiovascular events; eGFR; doubling of SCr; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria: serum potassium; acute kidney injury; gynaecomastia; fatigue; and falls.

Non-steroidal mineralocorticoid antagonists (finerenone) versus selective aldosterone antagonist (eplerenone)

Hyperkalaemia

ARTS-HF 2015 reported no difference in the risk of hyperkalaemia between the two groups. Meta-analysis was not performed.

Death

ARTS-HF 2015 reported no difference in the risk of death between the two groups. Meta-analysis was not performed.

Glomerular filtration rate

ARTS-HF 2015 reported no significant change in GFR from baseline in either group. Meta-analysis was not performed.

Doubling of serum creatinine

ARTS-HF 2015 reported no difference in the risk of doubling of SCr between the two groups. Meta-analysis was not performed.

Blood pressure

ARTS-HF 2015 reported no significant change in systolic blood pressure from baseline in either group. Meta-analysis was not performed.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: kidney failure; cardiovascular events; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria: serum potassium; acute kidney injury; gynaecomastia; fatigue; and falls.

Non-selective aldosterone antagonists (spironolactone) plus ACEi and ARB versus ACEi

Hyperkalaemia

Bianchi 2010 reported hyperkalaemia in 9/64 patients in the spironolactone plus ACEi and ARB group and 3/64 patients in the ACEi group. Meta-analysis was not performed.

Proteinuria

Bianchi 2010 reported proteinuria was significantly lower in the spironolactone plus ACEi and ARB group compared to ACEi group. Meta-analysis was not performed.

Glomerular filtration rate

Bianchi 2010 reported eGFR was lower in ACEi group compared to the spironolactone plus ACEi and ARB group. Meta-analysis was not performed.

Blood pressure

Bianchi 2010 systolic and diastolic blood pressure was lower in the spironolactone plus ACEi and ARB group compared to the ACEi group. Meta-analysis was not performed.

Serum potassium

Bianchi 2010 reported serum potassium was lower in the ACEi group compared to the spironolactone plus ACEi and ARB group. Meta-analysis was not performed.

Gynaecomastia

Bianchi 2010 reported gynaecomastia in 9/64 patients in the spironolactone plus ACEi and ARB group and 0/64 patients in the ACEi group. Meta-analysis was not performed.

Other outcomes

Data for the following outcomes were not extractable in a format required for inclusion in analyses or not reported in the available studies: kidney failure; death; cardiovascular events; progression from micro- to macroalbuminuria; regression from macro- to microalbuminuria and regression from micro- to normoalbuminuria: acute kidney injury; fatigue; and falls.

Publication bias

Overall, there were sufficient data and lack of statistical heterogeneity for the outcomes eGFR and hyperkalaemia for the comparison of aldosterone antagonists and placebo or standard care. There was no evidence of small study effects in the analysis of eGFR (Figure 9) or hyperkalaemia (Figure 10).

Figure 9. Funnel plot of comparison studies comparing aldosterone antagonist versus control for the study endpoint of GFR [mL/min/1.73 m^2].

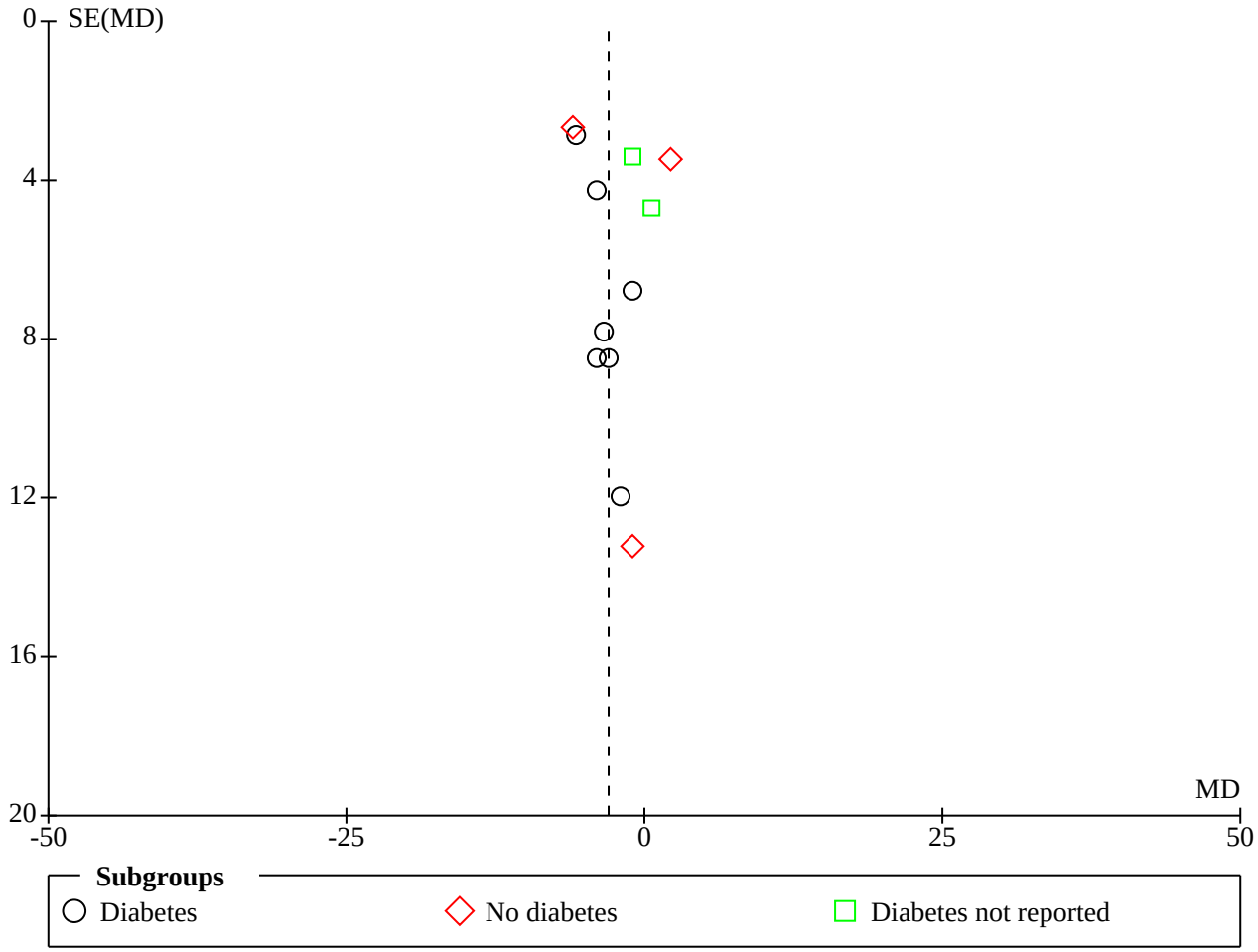
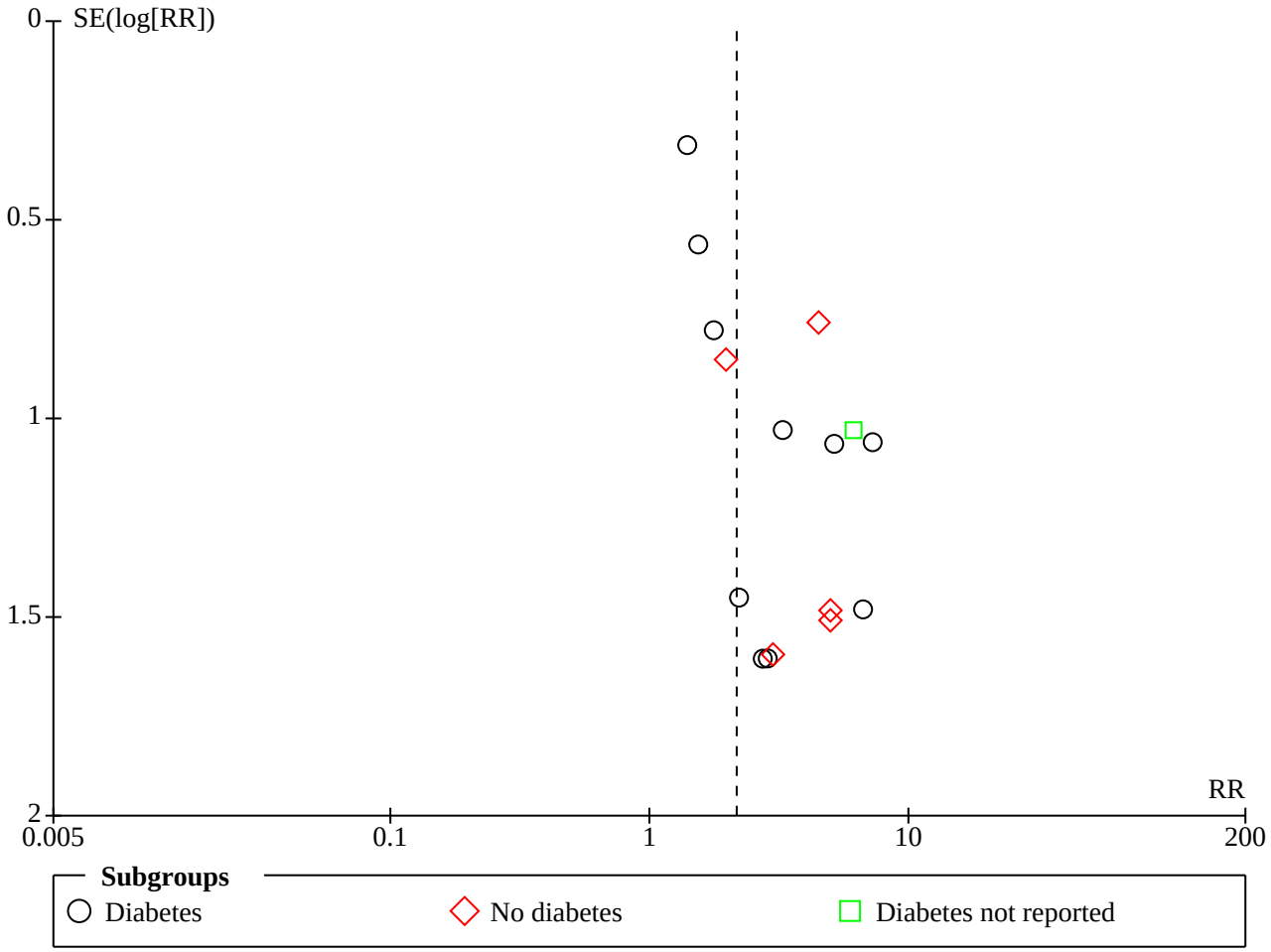


Figure 10. Funnel plot of comparison studies comparing aldosterone antagonist versus control for the study endpoint of hyperkalaemia.



DISCUSSION

Summary of main results

In this review of the evidence for aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of CKD, 44 studies involving 5637 participants were available. Studies included follow-up for generally three to 12 months. Compared to ACEI or ARB (or both), the addition of an aldosterone antagonist has uncertain effects on progression to kidney failure, major cardiovascular events, and death (any cause) while probably doubling the risk of hyperkalaemia and probably increasing risk of acute kidney injury and gynaecomastia in adults who have proteinuric CKD stages 1 to 4. Aldosterone blockade may reduce proteinuria and kidney function in addition to co-intervention with ACEi or ARB over a median treatment duration of 3.5 months and may lower systolic blood pressure but had little or no effect on diastolic blood pressure. Aldosterone antagonists appeared to lower systolic pressure to a greater extent in non-diabetic kidney disease compared to diabetic kidney disease. While aldosterone antagonists appeared to lower proteinuria in diabetic kidney disease, its anti-proteinuric effect in non-diabetic kidney disease is less certain. Compared to diuretics, non-selective aldosterone antagonists (spironolactone or canrenone) had uncertain effects on proteinuria and systolic blood pressure but may increase serum potassium. Furthermore, data comparing aldosterone antagonists to calcium channel blockers or nitrates, and data for treatment effects of selective aldosterone antagonists (eplerenone) and non-steroidal mineralocorticoid antagonists (finerenone) were sparse leading to serious imprecision in treatment estimates or a lack of sufficient data for meta-analysis.

Overall completeness and applicability of evidence

This review examined the evidence, updated to 2020, for the benefits of aldosterone antagonists in proteinuric CKD focusing on patient-centred outcomes (including kidney failure, death (any cause), and major cardiovascular events) and potential harms (including hyperkalaemia, acute kidney injury, and gynaecomastia). Similar to the previous versions of this review in 2009 and 2014, evidence for aldosterone antagonists in preventing the progression of CKD has allowed primarily the evaluation of surrogate outcomes such as proteinuria and blood pressure rather than patient-centred outcomes. The Standardised Outcomes in Nephrology (SONG) initiative aims to establish a set of core outcomes based on the shared priorities of patients, caregivers,

clinicians, researchers, and policy makers. The SONG-Glomerular Disease core outcomes are being established and will be essential in standardising outcome reporting in future studies (SONG-GD 2019). The clinical relevance of proteinuria to predict progression of CKD has been shown in multiple studies where reduction in proteinuria was associated with reduced decline in eGFR and kidney failure for both non-diabetic kidney disease (AASK 2002; REIN 1998) and diabetic kidney disease (IDNT 2004; RENAAL 2001). However, it is ultimately a surrogate outcome and it remains uncertain whether reduction in proteinuria with aldosterone antagonists in addition to ACEi or ARB reduces risk of kidney failure, death (any cause), and major cardiovascular events. Furthermore, reported measures of proteinuria in the included studies were heterogeneous necessitating the use of SMD, which is difficult to apply clinically since it summarises the intervention effect in each study relative to the standard deviation observed in each study. The use of SMD also assumes differences in standard deviations amongst the studies reflect differences in the measurement scales of proteinuria rather than differences in the study populations, which may not be true due to differences in severity of CKD, cause of CKD and co-interventions between studies. Caution should also be advised since aldosterone antagonists may increase risk of hyperkalaemia, and probably increased risks of acute kidney injury and gynaecomastia. The risk of hyperkalaemia reported in the included studies may be influenced by the dose of spironolactone used, mostly 25 mg/day or higher with no studies evaluating lower dose spironolactone (e.g. 12.5 mg/day), which could reduce proteinuria and minimise risk of hyperkalaemia in the CKD population.

Study duration was mostly between three to 12 months, which limits the ability of the current evidence to inform clinical practice on hard endpoints such as kidney failure, death (any cause) and major cardiovascular events, and on long-term safety. Few studies specified baseline kidney function and proteinuria; therefore, it is unclear whether aldosterone antagonists had different efficacy and safety based on the severity of underlying kidney disease or proteinuria. A recent phase II RCT showed spironolactone did not increase risk of hyperkalaemia in maintenance haemodialysis patients compared to placebo until dosages of 50 mg/day or higher (SPin-D 2019). However, no effect on diastolic function assessed by Doppler echocardiography was detected in this small study (SPin-D 2019) and further phase III studies are needed to evaluate the safety and efficacy of aldosterone antagonists in kidney failure.

Quality of the evidence

The evidence identified in this review for the primary efficacy and safety outcomes (kidney failure and hyperkalaemia) was of very low to low certainty. This evidence for the effect of aldosterone antagonists on preventing kidney failure was downgraded primarily due to methodological limitations in the included studies and serious imprecision in estimated treatment effects. The evidence for the increased risk of hyperkalaemia due to aldosterone antagonists in CKD was downgraded primarily due to study limitations.

Most studies enrolled few patients and were powered to observe differences in surrogate end points rather than patient-focused outcomes. Ten studies had a cross-over design (Boesby 2011; Morales 2009; Morales 2015; Nielsen 2012; Rossing 2005; Saklayen 2008; Schjoedt 2005; Smolen 2006; Tylicki 2008, Tylicki 2012), none of which reported on endpoints at the completion of each study phase to enable inclusion into the meta-analysis. The majority of studies did not adequately report study methods, such as the methods of allocation concealment and blinding of outcome assessment, sufficient to assess study quality. For most studies, the study protocol was not available to assess selective reporting of outcomes. Of the 15 studies reporting systolic blood pressure in the comparison between aldosterone antagonists and placebo or standard care, only six studies defined the method of measuring blood pressure (Boesby 2013; CRIBS II 2009; Furumatsu 2008; Guney 2009; Saklayen 2008; Tylicki 2008). Of the five studies reporting acute kidney injury, only one study specified a definition (ARTS 2012). Of the four studies reporting gynaecomastia, none provided a definition.

Potential biases in the review process

Our review has a number of strengths and weaknesses. The review examined aldosterone antagonists for their benefits on patient-centred outcomes and potential harms, and was conducted with a peer-reviewed protocol, a systematic search of electronic databases including the Cochrane Kidney and Transplant Specialised Register of studies, data extraction and analysis and study quality assessment by two independent authors, and adjudication of evidence certainty using the GRADE process. The key limitation of the review is the data provided by available studies. First, long-term data for the effects of aldosterone antagonists on major patient-centred outcomes including death, kidney failure, and major cardiovascular events were absent or sparse, with most studies primarily focused on surrogate outcomes such as proteinuria. In the cross-over studies and many other RCTs, outcomes were not reported in ways that could be extracted, which lowered confidence in the results. Whilst authors of all studies were contacted, most no longer had access to the raw data. Second, the duration of follow-up in most studies was likely sub-optimal for detecting these hard endpoints. The 10-year risk of kidney failure in 50 year old persons with an eGFR of 30 to 44 mL/min/1.73 m^2 is 11% to 21% depending on gender and only 1% to 2% with eGFR 45 to 59 mL/min/1.73 m^2 (Turin 2012), whilst the 25-year risk of kidney failure in persons with an eGFR less than 60 mL/min/1.73 m^2 and 2+ proteinuria or higher on urinalysis is 41% compared to 6% for 1+ proteinuria and 4% in the absence of proteinuria (Ishani 2006). Overall, in our systematic review of persons with CKD and variable levels of proteinuria, the median follow-up of three months in the included studies is likely sub-optimal for detecting the development of kidney failure. Third, data on stage 5 CKD were not available in the included studies. Finally, there was a significant heterogeneity between studies in treatment effects on proteinuria. Although we explored causes of heterogeneity by type of kidney disease and study duration, insufficient data were available for testing the effect of baseline kidney function and proteinuria. Treatment duration and other factors may therefore modify the treatment effects we observed.

Agreements and disagreements with other studies or reviews

In this systematic review, aldosterone antagonist therapy in addition to ACEi or ARB therapy was found to reduce proteinuria in participants with stage 1-4 proteinuric CKD, increase risk of hyperkalaemia and decline in eGFR, but had no detectable effect on kidney failure, cardiovascular events, and death, which is consistent with existing literature. One previous systematic review of aldosterone antagonists in both diabetic and non-diabetic CKD

found a reduction in proteinuria, eGFR, systolic and diastolic blood pressure, and an increased risk of hyperkalaemia (Currie 2016). Similar to our review, Currie 2016l could not conclude the effect of aldosterone antagonists on kidney failure, cardiovascular events and death, due to underreporting of these outcomes in included studies. However, apart from hyperkalaemia, other potential harms of aldosterone antagonists such as acute kidney injury and gynaecomastia were not explored. Furthermore, our review found the effect of aldosterone antagonists on diastolic blood pressure were uncertain. The discordance between the current Cochrane review and Currie 2016 is possibly explained by the inclusion of more recent trials in our review. Four other previous systematic reviews of aldosterone antagonists in diabetic CKD reported a reduction in proteinuria, and systolic and diastolic blood pressure, an increased risk of hyperkalaemia, and a reduction or unclear effect on eGFR (Hou 2015; Mavrakanas 2014; Sun 2017; Takahashi 2016). One review (Takahashi 2016) performed meta-analyses on blood pressure and serum potassium but not on the kidney outcomes such as proteinuria and eGFR, despite an adequate number of included studies, decreasing the strengths of its conclusions due to potential selective reporting bias. One review (Mavrakanas 2014) did not perform a meta-analysis due to the heterogeneous reporting of outcomes in the limited number of included studies, and did not specify risk of bias assessment by two independent authors, limiting the strength of its conclusions. None of the four reviews on diabetic CKD examined patient-centred efficacy outcomes such as kidney failure, major cardiovascular events, or death.

The results of our review also agree with existing RCTs and review articles showing an increased risk of hyperkalaemia when spironolactone is combined with ACEi or ARB (or both) in individuals with heart failure (Phillips 2007; RALES 1995). There is good evidence that ACEi or ARBs reduce progression of CKD to kidney failure requiring dialysis or transplantation by approximately 20% and have cardioprotective effects for adults with diabetic or non-diabetic CKD (RENAAL 2004; Strippoli 2005; Strippoli 2006). Some patients treated with ACEi with or without ARB exhibit aldosterone escape (Staessen 1981) and the addition of aldosterone antagonists has been shown to have anti-fibrotic and antihypertensive effects in animal and human studies (Nakhoul 2008; Tylicki 2008). However, our review was unable to conclude whether aldosterone antagonists in addition to ACEi or ARB (or both) had any effect on risk of kidney failure, major cardiovascular events, or death.

AUTHORS' CONCLUSIONS

Implications for practice

In adults with CKD who have an eGFR between 15 and 90 mL/min/1.73 m^2 and who have persistent proteinuria despite being on maximal doses of ACEi or ARB, aldosterone antagonists may reduce proteinuria, eGFR and systolic blood pressure. However, treatment effects on patient-relevant outcomes including progression to kidney failure, major cardiovascular events, and death are uncertain. Treatment using aldosterone antagonists in combination with ACEi or ARB (or both) may increase risk of hyperkalaemia and probably increases risk of acute kidney injury. Treatment using spironolactone probably increases risk of gynaecomastia. Evidence for the efficacy and safety of aldosterone antagonists compared to other interventions (diuretics, calcium channel blockers, nitrates, or ACEI or ARB (or both)) and evidence for the relative efficacy between different aldosterone antagonists are sparse. Patients and clinicians may reasonably choose not to use an aldosterone antagonist due to the uncertain benefits of treatment and identified risks of harm and adverse events.

Implications for research

Existing evidence on the effect of aldosterone antagonists on progression of CKD, cardiovascular events and death are uncertain. Whilst there is strong evidence supporting the association between reduction of proteinuria with ACEi or ARB and reduced risk of kidney failure, data supporting the benefit of further reduction in proteinuria using aldosterone antagonists in addition to ACEi or ARB on risk of kidney failure are lacking. Clinical evidence for the cardioprotective benefits of aldosterone antagonists in addition to ACEi or ARB is also sparse. Therefore, future high-quality studies with adequate follow-up that are powered to detect differences kidney failure and major cardiovascular events are necessary. The concurrent use of potassium-binding agents such as patiromer may reduce the risk of hyperkalaemia associated with aldosterone antagonists (AMBER 2019) though whether this will lead to improvements in long-term patient-level outcomes requires further study. Two ongoing studies of finerenone (FIDELIO-DKD 2019; FIGARO-DKD 2019) will provide important insights into whether non-steroidal mineralocorticoid antagonists in addition to ACEi or ARB may reduce the risk of patient-level cardiovascular and kidney endpoints without increasing the risk of hyperkalaemia.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abolghasmi 2011

Study characteristics

Abolghasmi 2011 *(Continued)*

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 12 weeks
Participants	• Country: Iran • Setting: not reported • Patients with CKD and resistant hypertension • Number: treatment group (19); control group (22) • Mean age ± SD (years): treatment group (49 ± 13.2); control group (50 ± 10.1) • Sex (M/F): treatment group (10/9); control group (12/10) • Exclusion criteria: secondary hypertension (renovascular, primary hyperaldosteronism, pheochromocytoma, Cushing)
Interventions	Treatment group • Spironolactone: 25 to 50 mg/day for 12 weeks Control group • Placebo for 12 weeks Co-interventions • Limited salt intake to < 6 g/day • ACEi/diuretic/CCB
Outcomes	• BP • Hyperkalaemia • Serum sodium and potassium • SCr • Urinary sodium
Notes	• Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly divided. No further details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Randomly divided into two groups in a double-blind fashion".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, however outcome measurement unlikely to be affected by awareness of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Abolghasmi 2011 *(Continued)*

Selective reporting (reporting bias)	High risk	The study fails to include results for key outcomes that would be expected to have been reported for such a study
Other bias	Unclear risk	Funding and other sources of bias were unclear

ARTS 2012

Study characteristics	
Methods	• Study design: double-blind, placebo-controlled, parallel-group RCT divided into two parts. • Study duration: not reported • Study follow-up: 6 weeks

Participants	• Country: 10 countries
	• Setting: multicentre (55 sites)
	• inclusion criteria
	  * Part A: patients with HFrEF with LVEF ≤ 40%) and mild CKD (GFR 60 to 90 mL/min/1.73 m^2)
	  * Part B: patients with HFrEF with LVEF ≤ 40% and moderate CKD (GFR 30 to 60 mL/min/1.73 m^2)
	• Number
	  * Part A: treatment group 1 (16); treatment group 2 (16); treatment group 3 (16); control group (16)
	  * Part B: treatment group 1 (66); treatment group 2 (67); treatment group 3 (67); treatment group 4 (65); control group 1 (63); control group 2 (65)
	• Mean age, range: Part A (66.3 years, 42 to 85); Part B (72.1 years, 40 to 89)
	• Sex (M/F): Part A (52/13); Part B (312/80)
	• Exclusion criteria: women of child-bearing potential; known hypersensitivity to the study drug (active substance or excipients) or spironolactone and respective excipients (part B only); anuria; acute kidney failure; Addison's disease; worsening heart failure requiring hospitalisation and treatment with IV diuretics in the 30 days before the screening visit for patients (NYHA class II–III) naive to aldosterone antagonist therapy or in the 6 months before the screening visit for patients (NYHA class II) who, immediately before study entry, are receiving aldosterone antagonist therapy; acute coronary syndrome or unstable coronary artery disease in the 30 days before randomisation; valvular heart disease requiring surgical intervention during the course of the study; evidence of increased ventricular vulnerability (e.g. survived ventricular fibrillation, sustained ventricular tachycardia, or firing of implantable; cardioverter-defibrillator in the 30 days before randomisation) requiring any intervention during the course of the study; history of hospitalisation for hyperkalaemia or acute kidney failure induced by previous aldosterone antagonist treatment; history of or clinically significant evidence of any severe disease other than chronic heart failure that would preclude participation in the study; clinically relevant hepatic dysfunction at screening visit indicated by one of the following: total bilirubin concentration more than twice the ULN and alanine aminotransferase levels more than three times the ULN or hepatic insufficiency classified as Child–Pugh B or C; use of any renin inhibitor or aldosterone antagonist in the 30 days before randomisation; concomitant therapy with potassium-sparing agents, high-dose acetylsalicylic acid (> 500 mg/day), or continuous treatment with non-steroidal anti-inflammatory agents; concomitant therapy with potent CYP isoenzyme 3A4 inhibitors or inducers (to be stopped ≥ 7 days before randomisation) or strong CYP2C8 inhibitors (to be stopped ≥ 48 hours before randomisation) such as gemfibrozil (investigators will be provided with a list of concomitant medications considered potent CYP3A4 inhibitors or inducers or strong CYP2C8 inhibitors); ongoing drug or alcohol abuse; concomitant regular liquorice consumption; uncontrolled hypertension at the screening visit requiring additional antihypertensive treatment during the course of the study; clinically relevant findings from the physical examination that may influence absorption, distribution, metabolism, elimination, or effects of the study drugs, or jeopardize the patient's safety during the study; poorly controlled DM with HbA1c > 8.5% at screening visit; participation in another clinical study or treatment with another investigational product in the 30 days before randomisation; any other condition or therapy that will make the patient unsuitable for this study and will not allow participation for the full planned study period; previous assignment to treatment during this study

ARTS 2012 *(Continued)*

Interventions	Part A treatment groups (1, 2, 3) • Finerenone: 2.5, 5, or 10 mg once/day for uncertain duration Part A: control group • Placebo for uncertain duration Part B: treatment groups (1, 2, 3, 4) • Finerenone (2.5, 5, or 10 mg/day, or 5 mg twice/day) for uncertain duration Part B: control group • Open-label spironolactone (25 to 50 mg) or placebo for uncertain duration Co-interventions • Not reported
Outcomes	Part A • Serum potassium concentration • Biomarkers of kidney injury • eGFR • Albuminuria Part B • changes in serum potassium concentration • Safety and tolerability • Biomarkers of cardiac and kidney function or injury • eGFR • Albuminuria • BAY 94-8862 pharmacokinetics
Notes	• Funding: Bayer Pharma AG. Editorial work by Oxford PharmaGenesis was funded by Bayer Pharma AG. • Trial registration: NCT01345656

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported in sufficient detail to perform adjudication. Some outcomes might have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias)	High risk	34/265 participants assigned to BAY 94-8862 did not complete study follow-up; 20/128 participants assigned to spironolactone and placebo did not complete

ARTS 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	The study fails to include results for key outcomes that would be expected to have been reported for such a study. Outcomes were reported according to the published protocol
Other bias	High risk	Funded by pharmaceutical company.

ARTS-DN 2015

Study characteristics	
Methods	• Study design: double-blind, placebo-controlled, parallel-group phase 2B RCT • Study duration: June 2013 to August 2014 • Study follow-up: 90 days
Participants	• Country: 23 countries • Setting: multicentre (148 sites) • Patients with type 2 DM, albuminuria (UACR ≥ 30 mg/g), and eGFR > 30 mL/min/1.73 m^2; treated with at least the minimum dose of an RAS blocker prior to the screening visit; and had serum potassium concentration ≤ 4.8 mmol/L at screening; patients with an eGFR 30 to 45 mL/min/1.73 m^2 must have been receiving treatment with a non-potassium-sparing diuretic at the screening visit and without any adjustments for 4 weeks or longer. • Number: 20 mg/day (120); 15 mg/day (125); 10 mg/day (98); 7.5 mg/day (98); 5 mg/day (100); 2.5 mg/day (92), 1.25 mg/day (96); placebo (94) • Age ± SD (years): 20 mg/day (64.70 ± 9.26); 15 mg/day (63.95 ± 8.34); 10 mg/day (64.94 ± 9.62); 7.5 mg/day (63.73 ± 10.04); 5 mg/day (63.31 ± 8.79); 2.5 mg/day (64.86 ± 9.09); 1.25 mg/day (64.91 ± 9.57); placebo (63.26 ± 8.68) • Sex (M/F): 20 mg/day (89/30); 15 mg/day (98/27); 10 mg/day (77/21); 7.5 mg/day (79/18); 5 mg/day (71/29); 2.5 mg/day (78/14); 1.25 mg/day (78/18); placebo (69/25) • Exclusion criteria: concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or a potassium-sparing diuretic that could not be discontinued for the run-in and treatment periods
Interventions	Treatment group (7 groups) • Finerenone: 1.25, 2.5, 5, 7.5, 10, 15 and 20 mg/day for 90 days Control group • Placebo for 90 days Co-interventions • RAS blocker
Outcomes	• UACR • eGFR • Adverse events • Serum potassium levels • BP
Notes	• Funder: Bayer HealthCare AG • Trial registration: NCT1874431
Risk of bias	

ARTS-DN 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Interactive voice/web response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, and the sponsor's clinical team were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No reported, although key outcomes were laboratory measures conducted centrally, and investigators were unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants except 9 were included in the analysis set. Those that were excluded related to no valid post-baseline urine albumin to creatinine ratio. Missing participants were evenly split across treatment groups
Selective reporting (reporting bias)	Low risk	Key outcomes expected for this type of study including kidney outcomes and adverse events were systematically reported
Other bias	High risk	Funded by pharmaceutical company

ARTS-HF 2015

Study characteristics	
Methods	• Study design: double-blind, active-comparator-controlled, parallel-group, phase 2b, dose-finding RCT • Study duration: June 2013 to August 2014 • Study follow-up: 90 days
Participants	• Country: 25 countries • Setting: multicentre (173 sites) • Participants at least 18 years and had worsening chronic HFrEF requiring hospitalisation and treatment with intravenous diuretics; type 2 DM and/or CKD (i.e. an estimated GFR of.30 mL/min/1.73 m^2 in patients with type 2 DM and 30 to 60 mL/min/1.73 m^2 in patients without type 2 DM), have been receiving treatment with evidence-based therapy for heart failure for at least the previous 3 months, and have a medical history of a LVEF ≤ 40% within the previous 12 months; patients receiving treatment with spironolactone, eplerenone, renin inhibitors, or potassium-sparing diuretics at presentation had to be able to discontinue those treatments for 24 hours before randomisation (48 h for spironolactone) and for the duration of the study treatment period • Number: finerenone 2.5 to 5 mg (173); finerenone 5 to 10 mg (165); finerenone 7.5 to 15 mg (169); finerenone 10 to 20 mg (170); finerenone 15 to 20 mg (165); eplerenone (224) • Age ± SD (years): eplerenone (72.4 ± 9.9); finerenone 2.5 to 5 mg 72.5 ± 9.7; finerenone 5-10 mg 71.8 ± 10.6; finerenone 7.5-15 mg 69.3 ± 9.8; finerenone 10-20 mg 71.3 ± 10.23; finerenone 15-20 mg 69.2 ± 10.2 • Sex (M/F): eplerenone (170/51); finerenone 2.5-5 mg (135/37); finerenone 5-10 mg (126/37); finerenone 7.5 to 15 mg (124/43); finerenone 10 to 20 mg (128/41); finerenone 15 to 20 mg (163/31) • Exclusion criteria: Patients with acute de novo heart failure 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, those with a left ventricular assist device or awaiting heart

ARTS-HF 2015 *(Continued)*

	transplantation, and patients who have experienced a stroke or transient ischaemic attack within 3months before screening.
Interventions	Treatment group (5 groups) • Finerenone: 2.5 to 5 mg/day; 5 to 10 mg/day; 7.5 to 15 mg/day; 10 to 20 mg/day; 15 to 20 mg/day for 90 days Control group • Eplerenone: 25 mg alternate daily to 50 mg daily for 90 days Co-interventions • Standard therapy for heart failure
Outcomes	• NT-proBNP • Cardiovascular hospitalisation • Emergency presentation for worsening chronic heart failure • Death (any cause) • Cardiovascular death • Composite of above events • Hyperkalaemia (> 5.6 mmol/L) • HRQoL • Pharmacokinetic data
Notes	• Funder: Bayer HealthCare AG • Trial registration: NCT01807221

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice/web response system
Allocation concealment (selection bias)	Low risk	Interactive voice/web response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, and the sponsor's clinical team was blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical endpoints have been adjudicated by the event committee. Blinding of outcome assessment was not reported in sufficient detail to perform adjudication
Incomplete outcome data (attrition bias) All outcomes	Low risk	45/842 allocated to finerenone were not included in full analysis; 17/224 allocated to eplerenone were not included in full analysis
Selective reporting (reporting bias)	Low risk	This study reported outcomes according to published protocol and as expected for a study of this type
Other bias	High risk	Funded by pharmaceutical company

Bianchi 2006

Study characteristics	
Methods	• Study design: open-label RCT • Study duration: not reported • Follow-up: 12 months
Participants	• Country: Italy • Setting: single centre • CKD from idiopathic GN (proteinuria >1 g/g Cr with no evidence of systemic disease) • Number: treatment group (83); control group (82) • Mean age ± SEM (years): treatment group (55 ± 1.2); control group (54.4 ± 1.2) • Sex (M/F): treatment group (50/32); control group (56/27) • Exclusion criteria: DM; renovascular and malignant hypertension; secondary glomerular diseases; malignancy; CHF; hyperkalaemia (serum potassium > 5 mEq/L); eGFR < 30 mL/min/1.73 m^2
Interventions	Treatment group • Spironolactone: 25 mg/day for 1 year Control group • Standard care for 1 year Co-interventions • ACEi or ARB, additional antihypertensive, diuretic to manage hyperkalaemia, 2 to 3 g/day sodium, protein intake 0.8 g/kg/day if eGFR < 60 mL/min/1.73 m^2
Outcomes	• Proteinuria • BP • Serum potassium • eGFR • Need for KRT • Gynaecomastia
Notes	• Funding: "This study was supported with private funding. No support was received by pharmaceutical companies." • Trial registration: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation was performed using a computer-generated system
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)	Unclear risk	Insufficient information to permit judgement

Bianchi 2006 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/83 patients in the spironolactone group and 4/82 in the control group withdrew. They were included in the analysis as intention-to-treat
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	No other sources of bias were identified

Bianchi 2010

Study characteristics	
Methods	• Study design: RCT • Study duration: January 2003 to February 2008 • Study follow-up: 36 months
Participants	• Country: Italy • Setting: single centre • Patients with idiopathic chronic GN and UPCR > 1 g/g • Number: treatment group (64); control group (64) • Mean age ± SD (years): treatment group (53.1 ± 1.1); control group (53.1 ± 1.1) • Sex (M/F): treatment group (43/21); control group (39/25) • Exclusion criteria: membranous GN, minimal change disease, secondary GN (including DM), renovascular or malignant hypertension, rapidly progressive GN, malignancies, MI or cerebrovascular accident within 6 months preceding the study, congestive heart failure, hepatic dysfunction, serum potassium level > 5 mEq/L, eGFR < 30 mL/min/ 1.73 m^2, intolerance to ACEi or ARBs, or treatment with steroids, NSAIDs, or immunosuppressive agents within 6 months preceding the study
Interventions	Treatment group • Spironolactone: 25 mg 3 times/week to 50 mg/day • Irbesartan: 300 mg/day Control group • No treatment Co-interventions • Ramipril 10 mg/day • Atorvastatin
Outcomes	• Urine protein • eGFR • BP • Adverse events • Dropouts
Notes	• Funding: not reported • Trial registration: not reported
Risk of bias	

Bianchi 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	High risk	Randomisation was performed by investigators who were aware of group assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators aware of group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	18% drop out with no description of differences in drop out between groups. No mention of analysis by ITT
Selective reporting (reporting bias)	High risk	No protocol available. The study did not report all outcomes that might be expected for this type of study
Other bias	Low risk	No other sources of bias identified

Boesby 2011

Study characteristics	
Methods	• Study design: cross-over RCT • Study duration: April 2007 to August 2009 • Follow-up: 8 weeks
Participants	• Country: Denmark • Setting: not reported • Age > 18 years; 24-hour proteinuria > 500 mg; 24-hour albuminuria > 300 mg; BP > 130/80 mmHg • Number: 40 • Age (range): 45 years (21 to 71) • Sex (M/F): 27/13 • Exclusion criteria: DKD; eGFR <20 mL/min; potassium >5.0 mEq/L; allergy to study drug; pregnancy; liver insufficiency; lithium; steroids
Interventions	Treatment group • Eplerenone: 25 to 50 mg/day for 8 weeks Control group • Standard care for 8 weeks Co-interventions • BP goal of < 130/80, if symptomatic hypotension then reductions were primarily made in non-RAS blocking agents, and in case of BP above target, non-RAS blocking agents were added

Boesby 2011 *(Continued)*

Outcomes	• 24-hour albuminuria • BP • Serum potassium • eGFR
Notes	• Cross-over study, no washout period • Funding: Danish Cardiovascular Research Academy, the Danish Kidney Association, the Danish Society of Nephrology, the Foundation of Aase Bay, the Helen and Ejnar Bjornow Foundation, the Research Council, Copenhagen University Hospital at Herlev, Director Jacob and Olga Madsen's Fund, Eva and Robert Voss Hansen's Fund and The Danish Hypertension Society LeoPharma scholarship • Trial registration: NCT00430924

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Low risk	Randomisation was done through drawing sealed opaque envelopes
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	2/42 patients were not included in analysis
Selective reporting (reporting bias)	High risk	The study did not report all outcomes that might be expected for this type of study. Data were not extractable due to cross-over study design
Other bias	Low risk	No other sources of bias were identified

Boesby 2013

Study characteristics

Methods	• Study design: open-label, parallel RCT • Study duration: April 2010 to June 2011 • Follow-up: 24 weeks
Participants	• Country: Denmark • Setting: multicentre (2 sites) • Participants aged 18 to 80 years, eGFR 15 to 59 mL/min/1.73 m^2; untreated BP > 130/80 mmHg or use of antihypertensive drugs • Number: treatment group (27); control group (27) • Mean age ± SD (years): treatment group (58.3 ± 13.4); control group (58.5 ± 12.8)

Boesby 2013 *(Continued)*

- Sex (M/F): treatment group (19/7); control group (19/6)
- Exclusion criteria: plasma potassium > 5.0 mEq/L; allergy to aldosterone antagonists; chronic liver insufficiency; ongoing treatment with CYP3A4 inhibitors, lithium or immunosuppressive agents including steroids; invalidating psychiatric disorders; other severe non-kidney disease; implantation of vascular stents in the aorta, brachial or radial arteries; non-sinus rhythm; immeasurable pulse amplitude; limb amputations; women of childbearing potential not using approved contraception; pregnancy or breastfeeding

Interventions	Treatment group • Eplerenone: 25 mg/day for first week and 50 mg/day for 23 weeks Control group • Standard care for 24 weeks Co-interventions • BP goal < 130/80 mmHg; in case of symptomatic hypotension, reductions in antihypertensive therapy were primarily made in non-RAS blocking agents and in case of BP above target, non-RAS blocking agents were added. In case of hyperkalaemia, patients were given dietary instructions and increased doses of furosemide and reviewed at extra clinics.
Outcomes	• Carotid femoral pulse wave velocity • Pulse wave analysis • Albuminuria • Office BP • Plasma potassium level • Plasma creatinine level • eGFR
Notes	• Trial funding: Danish Kidney Association, the Danish Kidney Association in Viborg, the Danish Society of Nephrology, the Research Council of Copenhagen University Hospital Herlev, The Gangsted Foundation, and the foundations of Sophus and Astrid Jacobsen, Sigurd and Addie Abrahamson, Aase Bay, Jacob and Olga Madsen, Eva and Robert Voss Hansen, and Helen and Ejnar Bjørnow. The SphygmoCorH apparatus was donated by the foundations of L. F. Foght and Frode V. Nyegaard and Toyota-Fonden, Denmark. Study medication was provided by the Department of Nephrology, Herlev Hospital • Trial registration: NCT01100203

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was done by the GCP-unit, University of Copenhagen
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation

Boesby 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	54 patients were included and 46 completed the study. Three patients were withdrawn prior to the first visit due to unexpected serious non-kidney disease. Five patients did not complete the study, four in the eplerenone group and one in the control group. Three patients in the eplerenone group were withdrawn due to serious side-effects. In the control group, one was withdrawal due to relapse of GN. There was an imbalance in study attrition based on treatment allocation and for reasons that were potentially due to the study intervention
Selective reporting (reporting bias)	High risk	The study did not report all outcomes that might be expected for this type of study
Other bias	Low risk	Public grant funding

Chen 2018b

Study characteristics	
Methods	• Study design: prospective, open-label, parallel-group RCT • Study duration: not reported • Follow-up: 72 weeks
Participants	• Country: China • Setting: inpatient or outpatient therapies in Department of Endocrinology • Participants with early DKD and mild-to-moderate hypertension, patients who met Mogensen DKD diagnosis and staging criteria, and the 2010 Chinese Guidelines for the Management of Hypertension; aged 61 to 75 years; good control of blood glucose; UAER 20 to 199 μg/min after washout before randomisation; normal range of SCr; stopping antihypertensive drugs and taking only placebo during the 2-week washout period and BP fluctuation within the range of 140 to 179 mmHg or 90 to 109 mmHg for systolic BP and diastolic BP • Number: treatment group 1 (55); treatment group 2 (54); treatment group 3 (54); treatment group 4 (55) • Mean age ± SD (years): treatment group 1 (68 ± 4); treatment group 2 (67 ± 4); treatment group 3e (67 ± 4); treatment group 4 (67 ± 5) • Sex (M/F): treatment group 1 (28/25); treatment group 2 (27/25); treatment group 3 (25/27); treatment group 4 (26/23) • Exclusion criteria: secondary hypertension; primary kidney disease; GFR < 45 mL/min/1.73 m^2; administration of ACEI, ARBs, serum uric acid synthesis-inhibiting drugs, uricosuric drugs or lipid lowering drugs for nearly 3 months; diabetic severe dysmetabolism; pregnant and lactating women; malignant tumour; severe dyslipidaemia; serum potassium < 3.5 mmol/L or > 5.5 mmol/L; serious cardiovascular and liver and other diseases
Interventions	Treatment group 1 • Low dose ARB: irbesartan 150 mg/day Treatment group 2 • High dose ARB: irbesartan 300 mg/day Treatment group 3 • Low dose ARB: irbesartan 150 mg/day • Spironolactone: 20 mg/day Treatment group 4

Chen 2018b *(Continued)*

	• High dose ARB: irbesartan 300 mg/day • Spironolactone: 20 mg/day Co-interventions • If BP was not under target level after 4-week treatment, a CCB or beta blocker was added as supplemental therapy
Outcomes	• Change in UACR • eGFR • BP • Serum uric acid • Serum potassium • Adverse events
Notes	• Funding: Shandong Province Medical and Health Technology Development Program • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table generated using statistical software
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	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in exclusion from analysis based on adverse events in the high-dose ARB and spironolactone group. Imbalance in follow up may have been related to treatment
Selective reporting (reporting bias)	Low risk	Outcomes aligned with those expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

Chrysostomou 2006

Study characteristics

Methods	• Study design: double-blind placebo-controlled RCT • Study duration: January 2002 to September 2004 • Follow-up: 3 months
Participants	• Country: Australia

Chrysostomou 2006 *(Continued)*

- Setting: single centre
- 24-hour proteinuria > 1.5 g/24 hour; SCr < 200 µmol/L; treatment with ACEi for at least 6 months
- Number: treatment group 1 (10); treatment group 2 (10); treatment group 3 (10); treatment group 4 (11)
- Mean age ± SD (years): treatment group 1 (59.2 ± 10.1); treatment group 2 (56.3 ± 8.8); treatment group 3 (65.5 ± 8.8); treatment group 4 (55.9 ± 15.4)
- Sex (M/F): treatment group 1 (7/3); treatment group 2 (8/2); treatment group 3 (7/3); treatment group 4 (6/5)
- Exclusion criteria: severe hypertension; hyperkalaemia (> 5 mEq/L); renovascular disease; serum bicarbonate < 20 mEq/L

Interventions	Treatment group 1 • Ramipril: 5 mg/day for 3 months • Irbesartan placebo for 3 months • Spironolactone placebo for 3 months Treatment group 2 (control group) • Ramipril: 5 mg/day for 3 months • Irbesartan: 150 mg/day for 3 months • Spironolactone placebo for 3 months Treatment group 3 • Ramipril: 5 mg/day for 3 months • Irbesartan placebo for 3 months • Spironolactone: 25 mg/day for 3 months Treatment group 4 (treatment group) • Ramipril: 5 mg/day for 3 months • Irbesartan: 150 mg/day for 3 months • Spironolactone: 25 mg/day for 3 months Co-interventions • Doses maintained unless hyperkalaemia occurred • Target diastolic BP of < 90 mmHg was maintained with BP lowering drugs other than ACEi, ARB, spironolactone, or non dihydropyridine agents. • When the potassium > 6 mmol/L, diuretic therapy was commenced or dosage was increased, ramipril dose was decreased, or the dosage of spironolactone or placebo was reduced to 25 mg alternate days
Outcomes	• Proteinuria • BP • Serum potassium • Need for KRT • Gynaecomastia • CrCl
Notes	• Group 2 (control) and group 4 (treatment) were used in the meta-analyses • Funding: investigator initiated • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Chrysostomou 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The randomisation process was undertaken by the Royal Melbourne Hospital Pharmacy Department. Method of randomisation not reported
Allocation concealment (selection bias)	Low risk	Clinical trial pharmacists, who were otherwise not involved in the clinical trial, performed treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in 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	Low risk	No other sources of bias were identified

Cohen 2010

Study characteristics	
Methods	• Study design: RCT • Study duration: not reported • Follow-up: 4 months
Participants	• Country: USA • Setting: not reported • CKD stages 1 to 3; proteinuria > 500 mg/day • Number: treatment group (14); control group 1 (7); control group 2 (13) • Mean age ± SD: 53.9 ± 13.6 years • Sex (M/F): 82% males • Exclusion criteria: not reported
Interventions	Treatment group • Eplerenone for 4 months Control group 1 • ACEi and ARB for 4 months Control group 2 • Isosorbide mononitrate for 4 months Co-interventions • Not reported

Cohen 2010 *(Continued)*

Outcomes	• Proteinuria
Notes	• Abstract-only publication • Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	2/7 patients in one comparator group withdrew
Selective reporting (reporting bias)	Unclear risk	The study did not report all outcomes that might be expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

CRIBS II 2009

Study characteristics

Methods	• Study design: prospective, double-blind, placebo-controlled, parallel RCT • Study duration: 2005 to 2007 • Follow-up: 36 weeks
Participants	• Country: UK • Setting: single centre • Age 18 to 80 years; stage 2 (GFR 60 to 89 mL/min/1.73 m^2 and evidence of kidney damage for 3 months) or stage 3 (GFR 30 to 59 mL/min/1.73 m^2) CKD (15); treatment with an ACEi or ARB (or both) for at least 6 months; controlled BP (mean daytime BP on ambulatory monitoring 130/85 mmHg) • Number: treatment group (56); control group (56) • Mean age ± SD (years): treatment group (54 ± 12); control group (53 ± 12) • Sex (males): treatment group (57%); control group (59%) • Exclusion criteria: a history or other evidence of angina, MI, heart failure, cerebral or peripheral vascular disease; DM; previous hyperkalaemia; valvular heart disease; atrial fibrillation; renovascular disease; anaemia (Hb < 12 g/dL)

CRIBS II 2009 *(Continued)*

Interventions	Treatment group • Spironolactone: 25 mg/day (4 weeks open-label run-in, then randomisation to further 36 weeks of treatment) Control group • Placebo Co-interventions • Patients with potassium 5.5 to 5.9 mmol/L received spironolactone on alternate days • Maximally tolerated use of ACEi and/or ARB, BP control < 130/85 mmHg
Outcomes	• LVM/arterial stiffness • Aortic distensibility • BP • Albuminuria
Notes	• Funding: British Heart Foundation project grant • Trial registration: NCT00291720

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/112 patients withdrew from the study
Selective reporting (reporting bias)	High risk	The study did not report all outcomes that might be expected for this type of study
Other bias	Low risk	No other sources of bias were identified

Epstein 2002

Study characteristics

Methods	• Study design: double-blind parallel RCT • Study duration: not reported

Epstein 2002 *(Continued)*

	• Follow-up: 24 weeks
Participants	• Country: USA • Setting: single centre • Type 2 DM with mild to moderate hypertension (diastolic BP > 95 mmHg and < 110 mmHg; systolic BP < 180 mmHg); microalbuminuria (UACR < 50 mg/g) • Number: treatment group (67); control group (74) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Eplerenone: 200 mg/day for 24 weeks • Enalapril: 40 mg/day for 24 weeks Control group • Eplerenone: 200 mg/day for 24 weeks • Enalapril: 10 mg/day for 24 weeks Co-interventions • If BP remained uncontrolled (diastolic BP ≥ 90 mmHg), hydrochlorothiazide 12.5 mg was added and further up-titrated to 25 mg if necessary
Outcomes	• Serum potassium • Need for KRT • BP
Notes	• Abstract-only publication • Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
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

Epstein 2002 *(Continued)*

Selective reporting (reporting bias)	High risk	The study did not report all outcomes that might be expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

Epstein 2006

Study characteristics	
Methods	• Study design: double-blind, placebo-controlled, parallel RCT • Study duration: not reported • Follow-up: 12 weeks
Participants	• Country: USA • Setting: multicentre (43 sites) • Type 2 DM with albuminuria (UACR > 50 mg/g) • Number: treatment group (177); control group (91) • Median age (years): treatment group (58); control group (60) • Sex (M/F): treatment group (116/61); control group (50/41) • Exclusion criteria: severe hypertension; CrCl <70 mL/min; orthostatic hypotension
Interventions	Treatment group 1 • Eplerenone: 50 mg/day for 12 weeks • Enalapril: 20 mg/day for 12 weeks Treatment group 2 • Eplerenone 100 mg/day for 12 weeks • Enalapril: 20 mg/day for 12 weeks Control group • Placebo for 12 weeks • Enalapril: 20 mg/day for 12 weeks Co-interventions • Amlodipine if BP uncontrolled at 4 weeks
Outcomes	• UAER • BP • Serum potassium • Need for KRT • Adverse events • eGFR • HbA1c
Notes	• Funding: financial support for this study was provided by Pharmacia, Inc. (currently Pfizer Inc.), Skokie, IL. Editorial support was provided by Jennifer L. Alexander, MSc, at Medesta Publication Group and was funded by Pfizer Inc • Trial registration: not reported
Risk of bias	

Epstein 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/91 patients in the control group, 8/91 and 9/86 in the EPL 50 and 100 mg groups respectively, withdrew. The overall percentage of withdrawal was 13%. These patients were analysed on an ITT basis
Selective reporting (reporting bias)	Low risk	Outcomes aligned with those expected for this type of study
Other bias	High risk	Study funded by Pfizer Inc

Esteghamati 2013

Study characteristics	
Methods	• Study design: 0pen-label, parallel, RCT • Study duration: April to December 2010 • Study follow-up: 18 months
Participants	• Country: Iran • Setting: single centre • Participants with type 2 DM according to American Diabetes Association criteria; UAE ≥ 30 mg/24 hours in 2 of 3 24-hour urine sample collections; taking combination of an ACEi (enalapril) and an ARB (losartan) with recommended doses for at least the past year • Number: treatment group (74); control group (62) • Mean age ± SD (years): treatment group (57.80 ± 8.91); control group (58.33 ± 9.33) • Sex (M/F): treatment group (51/23); control group (40/22) • Exclusion criteria: non-diabetic kidney disease, known cardiovascular or liver disease, CKD stages ≥ 4 and serum potassium concentration ≥ 5.5 mmol/:
Interventions	Treatment group • Spironolactone 25 mg/day for 18 months • Losartan: 50 to 100 mg/day for 18 months Control group • Enalapril 30 to 40 mg/day for 18 months • Losartan: 50 to 100 mg/day for 18 months

Esteghamati 2013 *(Continued)*

	Co-interventions • Education about salt intake • No dose adjustment for anti-hypertensive medications was done during the treatment period
Outcomes	• BP • UAE • eGFR • Serum potassium • Hyperkalaemia
Notes	• Funding: not reported. • Trial registration: NCT01667614

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation software, not further defined
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	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	3/74 discontinued in treatment arm directly due to treatment side-effects. No participants lost excluded in control arm due to side effects. Marked loss to follow up at 18 months (22/74 in treatment arm and 17/62 in control arm)
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	Other sources of bias and funding source unclear

EVALUATE 2010

Study characteristics

Methods	• Study design: double-blind, placebo-controlled RCT • Study duration: 1 April 2009 to 31 March 2012 • Study follow-up: 52 weeks
Participants	• Country: Japan • Setting: multicentre (59 sites) • Aged 20 to 79 years, were hypertensive with systolic BP of 130 to 179 mmHg or diastolic BP of 80 to 99 mmHg; pre-treatment UACR 30 to 599 mg/g; eGFR ≥ 50 mL/min/1.73 m^2; received an ACEi, an ARB, or both for at least 8 weeks

EVALUATE 2010 *(Continued)*

- Number: treatment group (170); control group (166)
- Mean age ± SD (years): treatment group (58.6 ± 13.0); control group (58.6 ± 13.8)
- Sex (M/F): treatment group (114/48); control group (100/52)
- Exclusion criteria: hypertensive emergencies that required IV administration of antihypertensive agents; serum potassium concentration ≥ 5.0 mmol/L; DM (fasting blood glucose concentration > 126 mg/dL or treatment with anti-diabetic drugs); severe liver damage; severe heart failure (NYHA class ≥ III); severe arrhythmia) angina; MI or cerebrovascular disease within 6 months before registration; pregnancy, possibility of pregnancy, or a desire to become pregnant; a history of severe adverse effects from mineralocorticoid receptor antagonists, ACEi, ARB; administration of a mineralocorticoid receptor antagonist less than 8 weeks before registration; taking contraindicated drugs; treatment with NSAIDs

Interventions	Treatment group • Eplerenone: 50 mg/day for 52 weeks Control group • Placebo for 52 weeks Co-interventions • If BP was 130/80 mmHg or more, the addition of antihypertensive medication (apart from mineralocorticoid receptor antagonist, ACEi, or ARB) was allowed
Outcomes	• UACR • eGFR • Urinary L-FABP • Estimated 24-hour urinary sodium excretion • Cerebrovascular and cardiovascular events
Notes	• Funding: Pfizer • Trial registration: UMIN000001803

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised computer-generated allocation procedure
Allocation concealment (selection bias)	Low risk	Web-based allocation system used by UMIN. Block size was concealed to investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	DBcaps capsules were used to mask the test drugs (eplerenone and placebo). Encapsulated study drugs were prepared and packed centrally by the pharmacy of the University of Tokyo and distributed to participating hospitals. The study investigators, patients, data collection and management personnel and statisticians were all masked to treatment assignment throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study investigators, patients, data collection and management personnel and statisticians were all masked to treatment assignment throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/170 lost to follow up in the treatment group for safety analysis and 14/166 lost to follow up in the control group

EVALUATE 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol is available and all the study prespecified primary and secondary outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	Funded by pharmaceutical company.

Fogari 2014

Study characteristics

Methods	• Study design: open-label, blind (masked) end-point, parallel RCT • Study duration: September 2010 to December 2012 • Study follow-up: 24 weeks
Participants	• Country: Italy • Setting: single centre • Participants with systolic BP ≥ 140 and < 180 mmHg and/or diastolic BP ≥ 95 < 110 mmHg; well-controlled type 2 DM (HbA1c < 7%) and microalbuminuria defined as a 24-hour excretion rate > 60 and < 300 mg • Number: treatment group (60); control group (60) • Mean age ± SD (years): treatment group (64.8 ± 9.3); control group (65.1 ± 8.9) • Sex (M/F): treatment group (33/27); control group (31/29) • Exclusion criteria: secondary hypertension; history of heart failure or a LVEF ≤ 50%; history of angina, stroke, transient Ischaemic attack, coronary artery bypass surgery, or MI; concurrent known symptomatic arrhythmia; liver dysfunction; SCr > 1.5 mg/dL; and known hypersensitivity to study drugs
Interventions	Treatment group • Canrenone: 25 mg/day for 24 weeks Control group • Hydrochlorothiazide: 12.5 mg/day for 24 weeks Co-interventions • Doses were doubled in patients who had a BP > 130/80 mmHg after 6 weeks • No other concomitant therapy was allowed except oral hypoglycaemia agents when required
Outcomes	• BP • UAE • Fasting plasma glucose • HbA1c • Cr • Serum potassium • Adverse events
Notes	• Funding: not reported • Trial registration: The trial was not registered in a clinical trial registry

Risk of bias

Bias	Authors' judgement	Support for judgement

Fogari 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Low risk	Blinded endpoint evaluation
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/60 patients in the treatment group discontinued therapy while 5/60 patients in the control group discontinued therapy
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	No payment received for manuscript preparation

Furumatsu 2008

Study characteristics	
Methods	• Study design: open-label, prospective RCT • Study duration: 2002 to 2004 • Follow-up: 12 months
Participants	• Country: Japan • Setting: multicentre (2 sites) • CKD (SCr < 3.0 mg/dL or calculated CrCl > 30 mL/min/1.73 m^2); controlled BP < 130/80 mmHg; persistent proteinuria (UPE > 0.5 g/day) • Number: treatment group (15); control group (15) • Mean age ± SD (years): treatment group (49.8 ± 2.7); control group (53.9 ± 2.7) • Sex (M/F): treatment group (10/5); control group (9/6) • Exclusion criteria: DM (HbA1c > 5.8%); severe kidney failure (SCr > 3.0 mg/dL); uncontrolled hyperkalaemia (serum potassium concentration > 5.0 mEq/L); proteinuria > 5.0 g/g Cr; renovascular hypertension or malignant hypertension
Interventions	Treatment group • Spironolactone: 25 mg/day for 1 year • Enalapril: 5 mg/day for 1 year • Losartan: 50 mg/day for 1 year Control group • Furosemide if Cr ≥ 1.8 mg/dL for 1 year • Trichlormethiazide if Cr < 1.8 mg/dL for 1 year • Enalapril: 5 mg/day for 1 year • Losartan: 50 mg/day for 1 year

Furumatsu 2008 *(Continued)*

	Co-interventions
	• Diet therapies were maintained
	• No drug was changed except that in some cases potassium binder or sodium bicarbonate were added
	  * Addition of potassium binder was permitted with the potassium level > 5.0 mEq/L
	  * Sodium bicarbonate was also allowed when the bicarbonate < 20 mEq/L

Outcomes	• Proteinuria • BP • Serum potassium • SCr • eGFR • Gynaecomastia
Notes	• Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient in the spironolactone and one in the control group were 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	Low risk	No other sources of bias identified

Guney 2009

Study characteristics

Methods	• Study design: preliminary prospective RCT • Study duration: not reported. • Follow-up: 6 months
Participants	• Country: Turkey • Setting: single centre

Guney 2009 *(Continued)*

	• Aged 20 to 70 years; controlled BP < 130/80 mmHg; CKD (SCr < 3.0 mg/dL or eGFR > 30 mL/min/1.73 m^2; persistent proteinuria as defined by UPCR > 0.5 mg/mg and daily treatment with ACEI or ARB (or both) for 6 months or more • Number: treatment group (15); control group (15) • Mean age ± SD (years): treatment group (45.9 ± 11.2); control group (39.1 ± 13.0) • Sex (M/F): treatment group (9/3); control group (8/4) • Exclusion criteria: DM; UTI; need for treatment with corticosteroids, NSAIDs, or immunosuppressive drugs; hyperkalaemia (serum potassium concentration > 5.5 mEq/L); proteinuria > 10 g/day; hypoalbuminaemia < 2.8 mg/dL; pregnancy
Interventions	Treatment group • Spironolactone: 25 mg/day for 6 months Control group • No treatment for 6 months Co-interventions • Standard therapy including ACEi or ARB
Outcomes	• Proteinuria • eGFR • BP • Plasma aldosterone • Hyperkalaemia
Notes	• Funding: Ali Raif Drug Industry A.C. for providing TGF-b1 and aldosterone kits • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	6/30 participants did not complete the 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
Other bias	Low risk	No other sources of bias were identified

Hamid 2017a

Study characteristics	
Methods	• Study design: RCT • Study duration: not reported • Study follow-up: not reported
Participants	• Country: Iran • Setting: single centre • Patients with hypertension, DM, receiving enalapril due to DKD • Number: 90 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone (duration not reported) Control group • Hydrochlorothiazide (duration not reported) Co-intervention • Enalapril
Outcomes	• UAE • BP • Serum potassium
Notes	• Abstract-only publication • Funding: not reported • Trial registration: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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)	Unclear risk	Insufficient information to permit judgement.

Hamid 2017a *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Protocol not available and study did not report all outcomes expected for a study of this type.
Other bias	Unclear risk	Insufficient information to permit judgement

Hase 2013

Study characteristics

Methods	• Study design: open-label, parallel, active-control RCT • Study duration: not reported • Study follow-up: 24 weeks
Participants	• Country: Japan • Setting: single centre • Japanese women and men with type 2 DM, aged 40 to 79 years, UACR from first morning urine ≥ 100 mg/g on 2 consecutive measures within 2 months, and use of ACEi or ARB for at least 6 months • Number: treatment group (18); control group (15) • Mean age ± SD (years): treatment group (65 ± 7); control group)62 ± 9) • Sex (M/F): treatment group (12/6); control group (12:3) • Exclusion criteria: clinically significant heart, liver, infectious or malignant disease; SCr ≥ 2.0 mg/dL, or if serum potassium ≥ 5.0 mEq/L or < 3.5 mEq/L
Interventions	Treatment group: • Spironolactone: 25 mg/day for 24 weeks Control group • Trichlormethiazide: 2 mg/day for 24 weeks Co-interventions • Antihypertensive medication
Outcomes	• UACR • SCr • eGFR • Serum potassium • HbA1c • BP
Notes	• Funding: not reported • Trial registration: UMIN-CTR (no. UMIN000008914)

Risk of bias

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

Hase 2013 *(Continued)*

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	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	33/35 participants completed treatment
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	No other sources of bias and funding source unclear

Haykal 2007

Study characteristics	
Methods	• Study design: parallel-group RCT • Study duration: not reported • Follow-up: 12 weeks
Participants	• Country: Ukraine • Setting: not reported • CKD stage 1-3; non-nephrotic proteinuria • Number: treatment group (12); control group (10) • Mean age ± SD: 23.4 ± 2.1 years • Sex (M/F): 14/8 • Exclusion criteria: not reported
Interventions	Treatment group • Eplerenone: 25 to 50 mg/day • Quinapril: 20 mg/day for 28 weeks Control group • Quinapril: 20 mg/day for 28 weeks Co-interventions • not reported
Outcomes	• Proteinuria • eGFR • BP
Notes	• Abstract-only publication

Haykal 2007 *(Continued)*

- Funding: not reported
- Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	3/15 patients in both treatment and control groups withdrew
Selective reporting (reporting bias)	High risk	Study did not report all expected outcomes for a study of this type. No pre-published protocol
Other bias	Unclear risk	Insufficient information to permit judgement

Horestani 2012

Study characteristics

Methods	• Study design: RCT • Study duration: not reported • Follow-up: 3 months
Participants	• Country: Iran • Setting: single centre • Participants with type 2 DM; aged > 40 years; proteinuria ≥150 mg/day; GFR ≥ 30 mL/min; serum potassium < 5 mmol/L • Number: treatment group 1 (20); treatment group 2 (20); treatment group 3 (20) • Mean age ± SD (years): treatment group 1 (56.2 ± 6.3); treatment group 2 (58.9 ± 9.3); treatment group 3 (55.4 ± 8.9) • Sex (M/F): 26/34 • Exclusion criteria: non-cooperation during the study; NYHA class 3 and 4 heart failure; history of hypothyroidism; change of dose of ARBs or ACEi during the study; serum potassium ≥ 5.5 during the study; use of pentoxifylline; and any significant or acute complication of drugs
Interventions	Treatment group 1 • Spironolactone: 50 mg/day for 3 months

Horestani 2012 *(Continued)*

	Treatment group 2 • Spironolactone: 50 mg/day for 3 months • Hydrochlorothiazide: 25 mg/day for 3 months Treatment group 3 • Hydrochlorothiazide: 25 mg/day for 3 months Co-interventions • All patients used renoprotective drugs (ACEi or ARB) and dosage of these drugs was not changed during the study
Outcomes	• Blood sugar level • HbA1c • Lipid profile • SCr • eGFR • Serum calcium, phosphorus • Serum potassium • BP
Notes	• Funding: Deputy director of research at Shahrekord University of Medical Sciences, Shahrekord Iran • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Blinding of outcome assessment not reported, although outcomes unlikely to be affected by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	High risk	Participants were excluded after randomisation if their antihypertensive treatment was changed

Ito 2019a

Study characteristics	
Methods	• Study design: prospective double-blind, parallel RCT • Study duration: January 2015 to June 2016 • Follow-up: 12 weeks
Participants	• Country: Japan • Setting: 71 sites in Japan • Type 2 DM with or without hypertension; UACR 45 to 300 mg/g despite 3 months of maximally tolerated ACEi or ARB; aged 20 to 70 years, eGFR >30 mL/min/1.73 m^2 • Number: treatment group (285); control group (73) • Mean age ± SD (years): treatment group (65 ± 9); control group (66 ± 10) • Sex (M/F): treatment group (222/63); control group (57/16) • Exclusion criteria: aldosterone agonist use; type 1 diabetes or non-diabetic kidney disease; HbA1c > 8.4%, secondary glucose intolerance, nephrotic syndrome, secondary hypertension or malignant hypertension; sitting systolic BP of > 160 or < 110 mmHg and sitting diastolic BP of > 100 or < 50 mmHg measured at the second and third visits; serum potassium < 3.5 or > 5.1 mEq/L in participants with eGFR of > 45 mL/min/1.73 m^2; and a serum potassium < 3.5 or > 4.8 mEq/L in participants with eGFR of 30 to 45 mL/min/1.73 m^2
Interventions	Treatment group • Esaxerenone: 0.625 to 5 mg/day for 12 weeks Control group • Placebo Co-interventions • Maximally tolerated ACEi or ARB
Outcomes	• Albuminuria • Regression to normoalbuminuria and reduction in UACR by > 30% from baseline • Reduction in UACR > 30% or 50% despite UACR > 300 mg/g at study end • BP • SCr and eGFR • Serum aldosterone and renin • Serum potassium • > 50% increase in SCr
Notes	• Funding: Daiichi-Sankyo pharmaceutical company • Trial registration: NCT02345057

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Dynamic allocation (minimisation method) but randomisation method not described
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

Ito 2019a *(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% drop out rate without ITT analysis
Selective reporting (reporting bias)	High risk	No cardiovascular outcomes
Other bias	High risk	Multiple authors received personal fees from Daiichi-Sankyo and 2 authors were employees of Daiichi-Sankyo

Kato 2015

Study characteristics	
Methods	• Study design: prospective, open-label, parallel RCT • Study duration: August 2012 to May 2013 • Follow-up: 8 weeks
Participants	• Country: Japan • Setting: multicentre (4 sites) • Type 2 DM at least 5 years before enrolment, and diabetic kidney disease; UACR 100 to 2000 mg/g despite ACEi or ARB; aged 30 to 70 years; eGFR >30 mL/min/1.73 m^2 • Number: treatment group (26); control group (26) • Mean age ± SD (years): treatment group (61.0 ± 9.2); control group (59.4 ± 10.8) • Sex (M/F): spironolactone group (18/8); control group (19/7) • Exclusion criteria: aldosterone agonist use; type 1 diabetes or non-diabetic kidney disease; impaired glucose tolerance secondary to exocrine pancreatic disease, endocrine disease, liver disease, or infection; systolic BP > 180 mmHg or diastolic BP > 110 mmHg; confirmed or suspected bilateral renal artery stenosis or stenosis of solitary renal artery; cerebrovascular disease or cardiovascular disease within 3 months and NYHA functional class III and IV heart failure; malignancy; rapid progression of kidney disease; history of orthostatic hypotension; liver dysfunction as indicated aspartate transaminase and alanine transaminase > 100 IU/L; serum potassium > 5.0 mEq/L; serious adverse event caused by aldosterone blockers; history of rapidly declining kidney function after aldosterone antagonist; pregnancy or planning pregnancy or breast feeding
Interventions	Treatment group • Spironolactone: 25 mg/day for 8 weeks Control group • Standard care for 8 weeks Co-interventions • Change in type of antihypertensive was not allowed
Outcomes	• Albuminuria • BP • eGFR

Kato 2015 *(Continued)*

	• Cystatin C • BP • Serum potassium • Serum aldosterone • Highly-sensitive C-reactive protein • Urine biomarkers
Notes	• Funding: Nagoya University Graduate School of Medicine • Trial registration: UMIN-CTR: UMIN000008016

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low 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	3/52 did not complete the 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
Other bias	Unclear risk	No other sources of bias were identified. Funding by University which also receives payment from pharmaceutical company

Koroshi 2010

Study characteristics

Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up: 72 weeks
Participants	• Country: Albania • Setting: single centre • Diabetes and kidney disease; arterial hypertension; proteinuria (> 300 mg/day) • Number: 62 • Mean age ± SD (years): not reported • Sex (M/F): not reported

Koroshi 2010 *(Continued)*

	• Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 50 mg/day for 72 weeks Control group 1 • Placebo for 72 weeks Control group 2 • Losartan: 100 mg/day for 72 weeks Co-interventions • Enalapril: 20 mg/day
Outcomes	• Proteinuria • BP • CrCl • Hyperkalaemia
Notes	• Abstract-only publication • Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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)	High risk	The study did not report all expected outcomes for this type of study.
Other bias	Unclear risk	Insufficient information to permit judgement

Lv 2009a

Study characteristics	
Methods	• Study design: prospective, open-label, pilot, parallel RCT • Study duration: not reported • Follow-up: 9 months
Participants	• Country: China • Setting: not reported • IgA nephropathy, eGFR > 30 mL/min; proteinuria > 0.5 g/day • Number: treatment group (16); control group (16) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 20 mg/day for 9 months • ACEi or ARB for 9 months Control group • ACEi or ARB for 9 months Co-interventions • Not reported
Outcomes	• Proteinuria • eGFR (monthly rate of decrease) • BP • Serum potassium • Mammoplasia
Notes	• Abstract-only publication • Funding: not reported • Trial registration: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Lv 2009a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	No protocol was available. The study reported many of the outcomes that would be expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

Mehdi 2009

Study characteristics	
Methods	• Study design: prospective double-blind placebo-controlled parallel RCT • Study duration: August 2003 to March 2007 • Follow-up: 52 weeks
Participants	• Country: USA • Setting: single centre • Men and women, aged 20 to 65 years; type 1 or type 2 DM; seated systolic BP > 130 mmHg, proteinuria (UACR) > 300 mg/g despite treatment with an ACEi or ARB • Number: treatment group (27); control group 1 (27); control group 2 (26) • Mean age ± SD (years): treatment group (52 ± 9); control group 1 (49 ± 9); control group 2 (52 ± 9) • Sex (M/F): treatment group (13/14); control group 1 (12/15); control group 2 (13/13) • Exclusion criteria: BMI > 45; SCr > 3.0 mg/dL; serum potassium > 5.5 mEq/L; HbA1c > 11%; recent MI or stroke within preceding 12 months, heart failure; known adverse reaction to losartan or spironolactone; need for dialysis with 12 months
Interventions	Treatment group • Spironolactone: 12.5 to 25 mg/day for 48 weeks Control group 1 • Placebo for 48 weeks Control group 2 • Losartan: 50 to 100 mg/day for 48 weeks Co-interventions • ACEi or ARB; add-on antihypertensive medications, including diuretics, and blockers, central acting agonists, and vasodilators, were used to achieve and maintain a goal systolic BP < 130 mmHg
Outcomes	• Albuminuria • BP • CrCl • 24-hour urinary sodium • 24-hour urinary potassium • Normalised protein catabolic rate • Kidney failure • Death (any cause)

Mehdi 2009 *(Continued)*

Notes	• Funding: National Institute of Diabetes Digestive and Kidney Diseases (2-R01 DK6301001) and the National Center for Research Resources General Clinical Research Center (M01-RR-00633 and CTSA UL1-RR-024982) • Trial registration: NCT00381134

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation stratified by diabetes type was programmed to determine treatment assignment
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	Not reported. Adjudication of some outcomes may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	10/27 patients assigned to spironolactone, 6/27 assigned to placebo and 9/27 assigned to losartan withdrew
Selective reporting (reporting bias)	Low risk	All defined outcomes expected for this type of study have been reported
Other bias	Low risk	No other apparent sources of bias were identified

Morales 2009

Study characteristics

Methods	• Study design: prospective cross-over RCT • Study duration: not reported • Follow-up: 6 weeks
Participants	• Country: Spain • Setting: single centre • Obese patients with proteinuria > 0.5 g/day; BMI > 30; eGFR > 15 mL/min • Number: treatment group (12); control group 1 (12); control group 2 (12) • Mean age ± SD: 57 ± 14.13 years • Sex (M/F): 7/5 • Exclusion criteria: rapid deterioration in kidney function, poor control of BP (MAP > 100 mmHg), requiring > 3 antihypertensives for BP control, immunosuppression.
Interventions	Treatment group • Eplerenone: 25 mg/day for 6 weeks Control group 1

Morales 2009 *(Continued)*

	• Lisinopril: 20 mg/day for 6 weeks Control group 2 • Lisinopril 10 mg/day for 6 weeks • Candesartan: 16 mg/day for 6 weeks
Outcomes	• Proteinuria • MAP • BMI • SCr • eGFR • Serum potassium • Plasma aldosterone • Plasma renin activity
Notes	• Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Randomisation was carried out by means of envelopes containing the order of treatment which the patients was to receive. Unclear whether sealed, opaque, or sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the patients completed the study
Selective reporting (reporting bias)	High risk	All defined outcomes have been reported. Data were not extractable due to crossover study design
Other bias	Unclear risk	No other sources of potential bias were identified

Morales 2015

Study characteristics

Methods	• Study design: open-label, cross-over RCT • Study duration: not reported

Morales 2015 *(Continued)*

	• Follow-up: 4 weeks
Participants	• Country: Spain • Setting: single centre • Men and women > 18 years; chronic diabetes or non-diabetes nephropathies; UACR > 300 mg/g; stable kidney function during the last 3 months; GFR > 30 mL/min/1.73 m^2, treatment with ACEi or ARBs in stable dosages during the last 3 months • Number: 21 • Mean age ± SD: 55.9 ± 10.9 years • Sex (M/F): 14/7 • Exclusion: poorly controlled BP; history of cardiovascular events (stroke, Ischaemic heart disease); treatment with NSAIDS, corticosteroids, or other immunosuppressants; history of renovascular disease; obstructive uropathy; autoimmune disease; cancer; pregnancy or currently breastfeeding; allergies or intolerance to hydrochlorothiazide, spironolactone, or amiloride
Interventions	Treatment group • Spironolactone: 25 mg/day for 4 weeks Control group 1 • Hydrochlorothiazide: 50 mg/day for 4 weeks Control group 2 • Hydrochlorothiazide: 50 mg/day for 4 weeks • Amiloride 5 mg/day for 4 weeks Co-interventions • Enalapril: dose kept fixed at 40 mg/day • Standard medication maintained without changes
Outcomes	• Albuminuria (reduction in UACR, % who achieved > 30% and >50% reduction) • eGFR • BP • Plasma sodium • Serum potassium • Uric acid levels • Renin and aldosterone levels • Adverse events
Notes	• Funding: Ministerio de Sanidad y Politica Social; FIS; AITER, Association for the Research and Treatment of Kidney Disease • Trial registration: EudraCT No: 2011-001929-24

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised assignment list was generated by a computer
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement.

Morales 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	21 of 29 selected patients were randomised
Selective reporting (reporting bias)	High risk	No protocol was pre-published. The study appeared to report all outcomes expected for this type of study. Data were not extractable due to crossover study design
Other bias	Low risk	No other sources of bias were identified and public grant funding

Nielsen 2012

Study characteristics	
Methods	• Study design: double-blind, placebo-controlled, cross-over RCT • Study duration: not reported • Follow-up: 60 days
Participants	• Country: Denmark • Setting: single centre • Type I DM with albuminuria • Number: 21 • Mean age ± SD: 58.3 ± 10.1 years • Sex (M/F): 14/7 • Exclusion criteria: Macroalbuminuria (> 300 mg/24 hours) at any time before inclusion or at randomisation; plasma potassium > 4.7 mmol/L; pregnancy; breastfeeding; lack of safe contraception in women; abuse of alcohol or medicine; allergy to ACEi, ARB, or spironolactone; BP > 160/100 mmHg; HbA1c > 86 mmol/mol (HbA1c > 10%); treatment with aldosterone antagonists
Interventions	Treatment group • Spironolactone: 25 mg/day for 60 days Control group • Placebo for 60 days Co-interventions • Standard therapy (including ACEi or ARB)
Outcomes	• Albuminuria • BP • GFR • Hyperkalaemia

Nielsen 2012 *(Continued)*

	• Markers of tubular damage (liver-type fatty acid binding protein, neutrophil gelatinase associated lipocalin, kidney injury molecule-1)
Notes	• Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE "randomisation was ensured with computer-generated envelopes with an unknown block size and frequency"
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	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	High risk	All defined outcomes expected for this type of study have been reported. Data were not extractable due to cross-over study design
Other bias	Low risk	No other potential sources of risk were identified

Ogawa 2006a

Study characteristics

Methods	• Study design: prospective RCT • Study duration: not reported • Follow-up: 12 months
Participants	• Country: Japan • Setting: single centre • ACR > 30 mg/g; type 2 DM, plasma B-type natriuretic peptide >100 pg/mL, treated with imidapril • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (63.5 ± 5.5); control group (61.2 ± 6.4) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 25 mg/day for 12 months Control group

Ogawa 2006a *(Continued)*

	• Furosemide: 20 mg/day for 12 months Co-interventions • Imidapril: 5 mg/day
Outcomes	• Albuminuria • B-type natriuretic peptide • Plasma aldosterone • Plasma renin activity • BP
Notes	• Funding: not reported • Trial registration: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear 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	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	There was no pre-published protocol. The study did not report all expected outcomes
Other bias	Unclear risk	No other potential sources of bias

Rossing 2005

Study characteristics

Methods	• Study design: double-blind, cross-over RCT • Study duration: not reported • Follow-up: 8 weeks
Participants	• Country: Denmark • Setting: single centre • Type 2 DM with kidney disease defined as albuminuria > 300 mg/day on maximum recommended dose of ACEi or ARB (or both)

Rossing 2005 *(Continued)*

- Number: 20
- Mean age ± SS: 58 ± 10 years
- Sex (M/F): 17/3
- Exclusion criteria: non-diabetic CKD; eGFR < 30 mL/min; serum potassium > 4.5 mEq/L

Interventions	Treatment group • Spironolactone: 25 mg/day for 8 weeks Control group • Matching placebo for 8 weeks Co-interventions • The study medication was given in the morning and was added to the patient's previous antihypertensive treatment. In addition to ACEi and ARB treatment, all patients received diuretics in individualised doses before entry into the study to treat and prevent fluid retention and hyperkalaemia. After inclusion previous antihypertensive medication including diuretics was kept unchanged throughout the study
Outcomes	• CrCl • BP • Serum potassium • Need for KRT
Notes	• Funding: supported by Danish Diabetes Association • Trial registration: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	QUOTE "Randomisation was concealed with computer-generated 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	Insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 patient withdrew
Selective reporting (reporting bias)	High risk	All defined outcomes have been reported. Data were not extractable due to cross-over study design
Other bias	Low risk	No other sources of potential bias were identified

Saklayen 2008

Study characteristics	
Methods	• Study design: cross-over RCT • Study duration: not reported • Follow-up: 3 months
Participants	• Country: USA • Setting: single centre • Diabetic CKD; treated with ACEi or ARB • Number: 34 • Mean age: 64 years • Sex (M/F): 34/0 • Exclusion criteria: SCr >2.0 mg/dL; potassium >5.0 mEq/L
Interventions	Treatment group • Spironolactone: 25 to 50 mg/day for 3 months Control group • Placebo for 3 months Co-interventions • ACEi or ARB
Outcomes	• BP • Proteinuria • GFR
Notes	• Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators and the study nurse remained blind regarding the assignment until the code was broken at the end of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/30 randomised patients withdrew and were not included in the final analysis (no ITT)

Saklayen 2008 *(Continued)*

Selective reporting (reporting bias)	High risk	There was no pre-published protocol. The study did not report all expected outcomes. Data were not extractable due to cross-over study design
Other bias	Unclear risk	No other sources of bias

Schjoedt 2005

Study characteristics

Methods	• Study design: double-blind, placebo-controlled, cross-over RCT • Study duration: not reported. • Follow-up: 8 weeks
Participants	• Country: Denmark • Setting: single centre • Type 1 DM with albuminuria (> 300 mg/day) despite ACEi or ARB (or both) treatment • Number: 20 • Mean age ± SD: 45 ± 7 years • Sex (M/F): 15/5 • Exclusion criteria: eGFR <30 mL/min; serum potassium >4.5 mEq/L; known renal artery stenosis
Interventions	Treatment group • Spironolactone: 25 mg/day for 8 weeks Control group • Matching placebo for 8 weeks Co-interventions • Diuretic treatment
Outcomes	• Proteinuria • CrCl • BP • Serum potassium • Need for KRT
Notes	• Funding: supported by The Danish Diabetes Association • Trial registration: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE "Randomization was concealed with computer generated envelopes"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

Schjoedt 2005 *(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	Low risk	20/22 patients completing the study were included in the final analysis
Selective reporting (reporting bias)	High risk	There was no pre-published protocol. The study reported all expected outcomes for this type of study. Data were not extractable due to cross-over study design
Other bias	Low risk	No other sources of bias were identified

Smolen 2006

Study characteristics	
Methods	• Study design: cross-over RCT • Study duration: not reported • Follow-up: 8 weeks
Participants	• Country: Poland • Setting: not reported • GN; persistent non-nephrotic proteinuria; hypertension • Number: 16 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 25 mg/day for 8 weeks Control group • Hydrochlorothiazide: 25 mg/day for 8 weeks Co-interventions • Not reported
Outcomes	• Proteinuria • BP • GFR • Potassium • Plasma renin activity
Notes	• Abstract-only publication • Funding: not reported • Trial registration: not applicable
Risk of bias	

Smolen 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Low risk	Blinding of outcome assessment was not reported but outcomes unlikely influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No pre-published protocol was identified. The study did not report all expected outcomes for this type of study. Data were not extractable due to cross-over study design
Other bias	Unclear risk	Insufficient information to permit judgement

Takebayashi 2006

Study characteristics	
Methods	• Study design: parallel-group RCT • Study duration: June 2004 to June 2005 • Follow-up: 12 weeks
Participants	• Country: Japan • Setting: outpatients • DM; ACR >30 mg/g • Number: treatment group (23); control group (14) • Mean age ± SD (years): treatment group (60.1 ± 8.0); control group (56.5 ± 13.4) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 50 mg/day for 12 weeks Control group • Amlodipine: 2.5 mg/day for 12 weeks Co-interventions • No change in administration of any drug occurred for any patient during the 12-week investigational period

Takebayashi 2006 *(Continued)*

Outcomes	• Albuminuria • BP • Plasma aldosterone • Plasma renin activity
Notes	• Funding: not reported • Trial registration: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	2/25 patients in the spironolactone group were excluded from the analysis due to symptoms of common cold. 1/15 patient in the control group was excluded due to poor compliance
Selective reporting (reporting bias)	High risk	No pre-published protocol was identified. The study did not report all expected outcomes for this type of study
Other bias	Unclear risk	No other sources of bias were identified

Tokunaga 2008a

Study characteristics

Methods	• Study design: parallel-group RCT • Study duration: not reported • Follow-up: 17.1 ± 11.5 months
Participants	• Country: Japan • Setting: not reported • Patients receiving ARB with CKD stages 3-4 • Number: treatment group (32); control group (32) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group

Tokunaga 2008a *(Continued)*

	• Spironolactone: dose not reported for 17.1 months Control group • Standard care for 17.1 months Co-interventions • ARB
Outcomes	• Doubling SCr • Proteinuria • Potassium • Kidney failure
Notes	• Abstract-only publication • Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Unclear risk	not reported. Outcomes adjudication was possibly influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	No pre-published protocol was identified. The study reported expected outcomes for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

Tylicki 2008

Study characteristics

Methods	• Study design: open-label, cross-over RCT • Study duration: March 2005 to February 2006 • Follow-up: 24 weeks
Participants	• Country: Poland

Tylicki 2008 *(Continued)*

- Setting: single centre
- Non-diabetic proteinuric CKD; normal or slightly impaired stable kidney function (SCr < 1.7 mg/dL (< 150 µmol/L; eGFR <45 mL/min (< 0.75 mL/s)); stable proteinuria > 0.3 g/24 hour; hypertension
- Number: 18
- Mean age ± SD: 42 ± 1.9 years
- Sex (M/F): 11/7
- Exclusion criteria: nephrotic syndrome

Interventions	Treatment group • Spironolactone: 25 mg/day for 8 weeks Control group • Standard care for 8 weeks Co-interventions • Cilazapril was continued or newly administered to patients who had not received this agent previously. A maximal recommended dose of 5 mg once/day in the morning was set. • Patients also were administered hydrochlorothiazide in a dose of 12.5 mg once/day and telmisartan, 80 mg once/day in the morning • There was no washout period between antihypertensive agents used previously and the study treatment involving cilazapril and telmisartan • To achieve the target office trough BP (BP) of 130/80 mmHg or less, adjuvant antihypertensive treatment with doxazosin was used, if necessary. When the target BP was achieved, patients received such adjusted therapy (background therapy) until the end of the run-in period, but not less than 6 weeks
Outcomes	• Proteinuria • BP • Serum potassium • SCr • eGFR • Gynaecomastia
Notes	• Funding: The study was supported by a grant from the Polish Committee for Scientific Research (KBN) through the Medical University of Gdansk (ST-4) • Trial registration: NCT00528385

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE "Allocation was performed independent of the research team person according to a computer-generated randomisation list"
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	Unclear risk	not reported. Outcomes adjudication was possibly influenced by knowledge of treatment allocation

Tylicki 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All the patients completed the study
Selective reporting (reporting bias)	Low risk	No pre-published protocol was identified. The study reported expected outcomes for this type of study
Other bias	Low risk	No other sources of bias were identified

Tylicki 2012

Study characteristics	
Methods	• Study design: prospective, double-blind, cross-over RCT • Study duration: not reported • Follow-up: 8 weeks
Participants	• Country: Poland • Setting: multicentre (2 sites) • Aged 18 to 65 years, non-diabetic proteinuric CKD stage 1-3, stable proteinuria above 500 mg/24 hours in last 6 months (no variations above 500 mg/24 hours); hypertension treated with at least one agent or hypertension no treated so far with BP above 140/90 mmHg; no steroids or other immunosuppressive treatment for a minimum of six months before the study • Number: 18 • Mean age ± SD: 39.3 ± 2.7 years • Sex (M/F): 14/4 • Exclusion criteria: unstable coronary heart disease or decompensated congestive heart failure in the previous 6 months, with an episode of malignant hypertension or stroke in the history, diabetics and eGFR < 30 mL/min/1.73 m^2
Interventions	Treatment group • Eplerenone: 50 mg/day for 8 weeks Control group • Aliskiren: 300 mg/day for 8 weeks Control group • Telmisartan: 80 mg/day for 8 weeks Co-interventions • Telmisartan: 80 mg/day
Outcomes	• Systolic and diastolic BP • Albuminuria • Estimated CrCl • Sodium and protein dietary intake • Adverse effects
Notes	• Funding: not reported • Trial registration: NCT01541267

Tylicki 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
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	Not reported. Outcomes adjudication was possibly influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	Low risk	No pre-published protocol was identified. The study reported expected outcomes for this type of study
Other bias	Unclear risk	No other sources of bias were identified

van den Meiracker 2006

Study characteristics

Methods	• Study design: prospective, double-blind, placebo-controlled, parallel RCT • Study duration: not reported • Follow-up: 12 months
Participants	• Country: The Netherlands • Setting: single centre • Type 2 DM with macroalbuminuria (24-h UAE > 300 mg or an UACR > 20 mg/mmol) despite use of an ACEi or ARB • Number: treatment group (24); control group (29) • Mean age, range (years): treatment group (55.2, 38 to 78); control group (55.2, 29 to 75) • Sex (M/F): treatment group (16/7); control group (17/12) • Exclusion criteria: SCr > 265 mmol/L; serum potassium > 5.0 mmol/L; CKD other than DKD; nephrotic syndrome
Interventions	Treatment group • Spironolactone: 25 to 50 mg/day for 12 months Control group • Placebo for 12 months Co-interventions

van den Meiracker 2006 *(Continued)*

	• Apart from antidiabetic medication, antihypertensive medications were kept constant throughout the course of the study
Outcomes	• Serum potassium • Need for KRT • Gynaecomastia
Notes	• Funding: not reported • Trial registration: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE "Eligible participants were randomised for spironolactone or placebo using a computerized randomisation list"
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	Not reported. Outcomes adjudication was possibly influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	5/29 patients in the spironolactone group and 2/30 in the control group withdrew. Apparently, they were not included in the final analysis
Selective reporting (reporting bias)	High risk	No pre-published protocol was identified. The study did not report all expected outcomes for this type of study
Other bias	Low risk	No other sources of bias were identified

Wang 2013g

Study characteristics

Methods	• Study design: prospective, parallel RCT • Study duration: June 2009 and April 2013 • Follow-up: 16 weeks
Participants	• Country: China • Setting: single centre • No history of hormone or immunosuppressive agent administration or withdrawal of these drugs for ≥ 3 months; a history of ACEi and/or ARB treatment for ≥ 6 months; stable BP < 140/90 mmHg; urine protein > 0.5 g/24 hour; plasma albumin >35 g/L; SCR < 133 μmol/L; eGFR > 30 mL/min/1.73 m^2 • Number: treatment group (106); control group (102) • Mean age ± SD (years): treatment group (33.7 ± 8.3); control group (34.6 ± 10.2) • Sex (M/F): treatment group (61/45); control group (57/45)

Wang 2013g *(Continued)*

	• Exclusion criteria: failure to attend further consultation on time; serum potassium >5.0 mmol/L; side-effects, such as mammoplasia and spargosis
Interventions	Treatment group • Spironolactone: 20 mg/day for 16 weeks Control group • Standard therapy for 16 weeks Co-interventions • ACEi and/or ARB
Outcomes	• UPE • SCr • eGFR • Serum potassium • Plasma aldosterone • BP
Notes	• Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12/221 were excluded after randomisation due to adverse effects, failure to attend follow-up. not reported which treatment group
Selective reporting (reporting bias)	High risk	No pre-published protocol was identified. The study did not report all expected outcomes for this type of study
Other bias	Unclear risk	No other sources of bias were identified

Zheng 2011

Study characteristics

Zheng 2011 *(Continued)*

Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up: 3 months
Participants	• Country: China • Setting: not reported • Patients with diabetic CKD (duration of diabetes 8 to 18 years); UPE > 300 mg/24 hour; SCr < 150 mol/L; fasting plasma glucose < 10 mmol/L • Number: treatment group (20); control group (20) • Mean age ± SD: 58 ± 5.7 years • Sex (M/F): 22/18 • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 20 mg/day for 3 months Control group • Standard therapy for 3 months Co-interventions • Benazepril: 10 mg/day
Outcomes	• Proteinuria • SCr • Serum potassium
Notes	• Funding: not reported • Trial registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as randomised; method of randomisation not reported
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	Low risk	Not reported. Outcomes adjudication was unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients apparently completed the study
Selective reporting (reporting bias)	High risk	No pre-published protocol was identified. The study did not report all expected outcomes for this type of study

Zheng 2011 *(Continued)*

Other bias	Unclear risk	No other sources of bias were identified and funding source unclear

Ziaee 2013

Study characteristics	
Methods	• Study design: pilot RCT • Study duration: December 2010 to September 2011 • Follow-up: 12 weeks
Participants	• Country: Iran • Setting: single centre • Aged 18 to 80 years, microalbuminuria due to diabetic CKD confirmed with 24-hour urine sample, 3 months treatment with ACEi, type 2 DN • Number: treatment group (29); control group (31) • Mean age ± SD (years): treatment group (53.03 ± 5.25); control group (53.10 ± 4.93) • Sex (M/F): treatment group (17/12); control group (20/11) • Exclusion criteria: SCr > 2 mg/dL; serum potassium > 5.5 mmol/L; cardiac ejection fraction < 35%; systolic BP < 90 mmHg or symptomatic hypotension; any contraindication to study drug
Interventions	Treatment group: • Spironolactone: 25 mg/day for 12 weeks Control group • Standard care for 12 weeks Co-interventions • Enalapril: 25 mg twice/day
Outcomes	• BP • Serum and urine creatinine • Serum and urine albumin • Serum potassium
Notes	• Funding: Metabolic Diseases Research Center, Qazvin University of Medical Sciences • Trial registration: not reported

Risk of bias

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

Ziaee 2013 *(Continued)*

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	No pre-published protocol was identified. The study did not report all expected outcomes for this type of study
Other bias	Low risk	No other sources of bias were identified and public grant funding.

ACR - albumin creatinine ratio; ACEi - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; BMI - body mass index; BP - blood pressure; CCB - calcium channel blocker; CKD - chronic kidney disease; CHF - chronic heart failure; CrCl - creatinine clearance; DKD - diabetic kidney disease; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; EPL - eplerenone; Hb - haemoglobin; HbA1c - haemoglobin A1c (glycated); GN - glomerulonephritis; HFrEF - heart failure and reduced ejection fraction; HRQoL- health-related quality of life; IV - intravenous; KRT - kidney replacement therapy; L-FABP - urinary L-type fatty acid-binding protein; LVEF - left ventricular ejection fraction; LVM - left ventricular mass; M/F - male/female; MAP - mean arterial pressure; MI - myocardial infarction; NSAIDs - non-steroidal anti-inflammatory drugs; NT-proBNP - N terminal pro-brain natriuretic peptide; NYHA - New York Heart Association; RAS - renin-angiotensin system; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; SEM - standard error of the mean; SPL - spironolactone; UACR - urinary albumin creatinine ratio; UAE - urinary albumin excretion; UAER - urinary albumin excretion ratio; UPCR - urinary protein creatinine ratio; UPE - urinary protein excretion; UTI - urinary tract infection

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

Study	Reason for exclusion
ATHENA-HF 2019	Treatment duration only 96 hours
Barr 1995	Wrong population: heart failure patients without proteinuria or CKD
Berry 2007	Wrong population: heart failure patients without proteinuria or CKD
Blanchard 2015	Wrong population: only patients with Gitelman syndrome
EMPHASIS-HF 2010	Wrong population: heart failure patients; not reported whether CKD and proteinuria was present
Epstein 1998	Wrong population: hypertensive patients; not reported whether CKD was present
Essaian 2007	Wrong population: HD patients
Hollenberg 2003a	Wrong population: hypertensive patients; not reported whether CKD was present
Karalliedde 2006	Wrong population: diabetic patients; not reported whether CKD and proteinuria was present
Makhlough 2014	Wrong intervention: both groups used aldosterone antagonists. Only difference between groups was the use of ARB
Medeiros 2017	Wrong population: children with chronic allograft nephropathy
Oxlund 2015	Wrong study design: experimental study; no outcomes of interest
Preston 2009	Wrong intervention: potassium was administered to patients

Study	Reason for exclusion
PRIORITY 2014	Wrong population: diabetic patients with no proteinuria
Rachmani 2004	Study retracted QUOTE: "*Diabetic Medicine* has been advised by the Chief Executive Officer of the Mair Medical Center that the above study, done in collaboration with the Sackler University of Tel Aviv, has raised concerns over ethical conduct and security of findings. Specifically, a local investigatory committee found that ethical permission was only given approximately 3 months after Diabetic Medicine accepted the paper for publication. In addition, whilst the investigatory committee believed that the research had been undertaken, they were unable to access research records and thus confirm the results, even though the study was conducted as recently as 2001. In these circumstances, *Diabetic Medicine* regrets publication of the article, and suggests that its readers treat its findings with caution. The senior author has been advised of our wish to have the article retracted and has made a statement of confidence in the findings."
RALES 1995	Wrong population: heart failure patients; not reported whether CKD was present
Schjoedt 2006	12 of 20 participants were also reported in Schjoedt 2005 and Rossing 2005
Schjoedt 2009	Wrong study design: experimental study; no outcomes of interest
Schmidt 2005	Wrong population: healthy subjects and hypertensive patients without a clear diagnosis of CKD
Schmidt 2005a	No outcomes of interest
Schmidt 2008	Wrong population: CKD not present
STOP-CKD 2014	Study terminated early due to futility with no outcomes reported
Swift 2006	Wrong population: only patients with Liddle syndrome
Taheri HD 2009	Wrong population: HD patients
TOPCAT 2014	Wrong population: heart failure patients; not reported whether CKD and proteinuria was present
Toto 2005	Wrong intervention: no aldosterone antagonists has been used
Viswanathan 2013	Wrong population: diabetic patients; not reported whether CKD and proteinuria was present; no outcome of interest

CKD - chronic kidney disease; HD - haemodialysis

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT00315016

Methods	Interventional randomised phase II study
Participants	Inclusion criteria • Documented DKD with albuminuria > 0.020 g/L, stable kidney function (i.e. increase of SCr < 25%/6 months); CrCl > 40 mL/min/1.73 m^2, in spite of maximum ACEi (40 mg fosinopril/day) • BP < 140/90 mm Hg (at baseline) • Serum potassium < 5.0 mmol/L (at baseline)

NCT00315016 *(Continued)*

	Exclusion criteria • Use of NSAIDs or immunosuppressive drugs • Use of ARB, intolerance for ACEi • Use of diuretics that increase potassium such as triamterene, spironolactone or eplerenone • Pregnancy • Rash or cough on one on the drugs • Severe heart disease or instable angina
Interventions	• Eplerenone (dose not reported) • Fosinopril (dose not reported) • Placebo
Outcomes	• Proteinuria • BP • Serum potassium • Hb • Quality of Life • Plasma aldosterone, renin • Plasma angiotensin and bradykinin
Notes	• Recruitment status: completed • Last update posted: 17 April 2006 • No results published 24 August 2020

SPIRO-CKD 2017

Methods	Interventional randomised phase IV study
Participants	Inclusion criteria • Stage 2 and 3 CKD (eGFR 30 to 59 mL/min/1.73 m^2 or eGFR of 60 to 89 mL/min/1.73 m^2 plus albuminuria or a structural abnormality of the kidney) without known cardiovascular disease or DM • On ARB or ACEi • No hospital admission within 3 months and no recent (< 6 months) acute MI • Male or females of childbearing potential must agree to contraception Exclusion criteria • DM • Recent (< 6 months) acute MI or other major adverse cardiovascular event • Left ventricular systolic dysfunction (ejection fraction < 50%) or severe valvular heart disease or evidence of heart failure • Regular NSAID use • Pregnancy or breastfeeding • Hyperkalaemia (≥ 5.0 mmol/L) • Alcohol or drug abuse
Interventions	• Spironolactone 25 mg/day • Chlorthalidone 25mg/day • Duration of treatment: 40 weeks
Outcomes	• Change in left ventricular mass on cardiac MRI

SPIRO-CKD 2017 *(Continued)*	• Change between baseline and 40 week in arterial stiffness measured by carotid-femoral pulse wave velocity, blood pressure, urinary albumin-creatinine ratio, left ventricular volumes and systolic function, plasma NT-pro-BNP, and eGFR • Incidence of hyperkalaemia
Notes	• Recruitment completed 31 December 2016 • No results published: 24 August 2020

ACE- angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BP - blood pressure; CrCl - creatinine clearance; DKD - diabetic kidney disease; DM - diabetes mellitus; Hb - haemoglobin; MI - myocardial infarction; NSAIDs - nonsteroidal anti-inflammatory drug/s; SCr - serum creatinine

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

BARACK D 2014

Study name	Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D)
Methods	Interventional, randomised, open label (but with blinding of outcome assessment) phase IV trial
Participants	Inclusion criteria • Adults (aged 18 years or above) • CKD stage 3b (eGFR 30 to 44 mL/min/1.73 m^2 using MDRD equation on at least 2 occasions) • If female of child-bearing potential, willing to ensure effective contraception during the trial period Exclusion criteria • Pregnancy, lactating or planning pregnancy • Type 1 DM • Heart failure with left ventricular ejection fraction < 40% • MI within last 6 months • Alcohol or drug abuse • Serum potassium at baseline > 5 mmol/L • Addisonian crisis and/or on fludrocortisone • Symptomatic hypotension or baseline systolic BP < 100 mmHg • Recent acute kidney injury or admission for kidney failure • ACR > 70 mg/mmol
Interventions	• Spironolactone: 25 mg/day • Control: routine care • Duration: 36 months
Outcomes	• Time to first death • Onset or hospitalisation of heart disease (coronary heart disease, arrhythmia, new atrial fibrillation, sudden death, failed sudden death) • Stroke • Heart failure • Change in BP, BNP, urine ACR, eGFR, or quality of life • Rates of hypotension, transient ischaemic attack, hyperkalaemia, adverse effects
Starting date	Not reported
Contact information	Richard Hobbs, richard.hobbs@phc.ox.ac.uk, University of Oxford

BARACK D 2014 *(Continued)*

Notes	Currently recruiting

FIDELIO-DKD 2019

Study name	Design and baseline characteristics of the finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial
Methods	Double-blind placebo-controlled RCT
Participants	Inclusion criteria • Type 2 DM • DKD with albuminuria UACR ≥ 30 mg/g (≥ 3.4 mg/mmol) but < 300mg/g (< 33.9 mg/mmol) and eGFR ≥ 25 but < 60mL/min/1.73m^2 OR UACR ≥ 300 mg/g (≥ 33.9 mg/mmol) and eGFR ≥ 25 but < 75mL/min/1.73m^2 • ACEi or ARB ≥ 4 weeks before run-in • Serum potassium ≤ 4.8 mEq/L • ≥ 18 years of age Exclusion criteria • Non-diabetic kidney disease including clinically relevant renal artery stenosis • UACR > 5,000 mg/g (> 565 mg/mmol) • Uncontrolled hypertension ≥ 170/110 mmHg (run in visit) or ≥ 160/100 mmHg (at screening) • Systolic BP < 90 mmHg (run in visit or at screening) • Chronic heart failure with reduced ejection fraction NYHA II-IV • Stroke, transient ischaemic cerebral attack, acute coronary syndrome, or hospitalisation for worsening heart failure, in the 30 days before the screening visit • Dialysis for acute kidney injury within 12 weeks of run in visit • Kidney transplant scheduled within next 12 months • HbA1c > 12% • Addison's disease • Child-Pugh C liver cirrhosis
Interventions	• Finerenone: 10 to 20 mg/day • Placebo • Duration: 53 months
Outcomes	• Composite cardiovascular death and non-fatal cardiovascular events (MI, stroke, hospitalisation for heart failure) • Composite kidney failure, sustained decrease eGFR ≥ 40% from baseline for at least 4 weeks or kidney death • Death (any cause) • Hospitalisation (any cause) • Composite kidney failure, sustained decrease eGFR ≥ 57% from baseline for at least 4 weeks or kidney death • Albuminuria at month 4
Starting date	September 2015
Contact information	Bayer
Notes	Estimated primary completion date: July 2021

FIGARO-DKD 2019

Study name	A randomised, double-blind, placebo-controlled, parallel-group, multicenter, event-driven phase 3 study to investigate efficacy and safety of finerenone on the reduction of cardiovascular morbidity and mortality in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease in addition to standard of care (FIGARO-DKD)
Methods	Double-blind placebo-controlled RCT
Participants	Inclusion criteria • Type 2 DM • DKD with albuminuria • Maximally tolerated ACEi or ARB • Serum potassium ≤ 4.9 mEq/L • ≥ 18 years of age Exclusion criteria • Non-diabetic kidney disease including clinically relevant renal artery stenosis • Uncontrolled hypertension ≥ 170/110 mmHg (run in visit) or ≥ 160/100 mmHg (at screening) • Chronic heart failure with reduced ejection fraction NYHA II-IV • Dialysis for acute kidney failure within 12 weeks of run in visit • Kidney transplant scheduled within next 12 months • HbA1c > 12%
Interventions	• Finerenone: 10 to 20 mg/day • Placebo • Duration: 53 months
Outcomes	• Composite cardiovascular death and non-fatal cardiovascular events (myocardial infarction, stroke, hospitalisation for heart failure) • Composite kidney failure, sustained decrease eGFR ≥ 40% from baseline for at least 4 weeks or kidney death • Death (any cause) • Hospitalisation (any cause) • Composite kidney failure, sustained decrease eGFR ≥ 57% from baseline for at least 4 weeks or kidney death • Albuminuria at month 4
Starting date	September 2015
Contact information	Bayer Study Director
Notes	Estimated primary completion date: July 2021

NCT00870402

Study name	Aldosterone in diabetic nephropathy (ALDODN)
Methods	Interventional, double blind phase IV RCT
Participants	Inclusion criteria

NCT00870402 *(Continued)*	• Diabetic subjects with maximum 10 years after diagnosis • DKD with albuminuria • Normal kidney function • Diastolic dysfunction • Taking an ACEi or ARB drug family previously Exclusion criteria • Diabetics subjects with macroangiopathy • Acute coronary syndrome in the 3 months before • Hyperkalaemia > 5.5 mEq/L • Pregnancy
Interventions	• Spironolactone: 25 mg/day • Placebo • Duration: 9 months
Outcomes	• Reduction of albuminuria • Reduction of diastolic dysfunction
Starting date	March 2009
Contact information	Francisco G Espinoza, fespinoz@mi.cl, Universidad Los Andes
Notes	Estimated primary completion date: December 2009. No recent updates on the trial status

ACR - albumin creatinine ratio; BNP - brain natriuretic peptide; BP - blood pressure; CKD - chronic kidney disease; CrCl - creatinine clearance; DKD - diabetic kidney disease; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; HbA1c - haemoglobin A1c (glycolated); MDRD - modification of diet in renal disease; MI - myocardial infarction; NYHA - New York Heart Association; RAS - renin-angiotensin system; RCT - randomised controlled trial; SCr - serum creatinine; UACR - urinary albumin creatinine ratio

DATA AND ANALYSES

Comparison 1. Aldosterone antagonist versus placebo/standard care (all studies)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Kidney failure	2	84	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 27.65]
1.1.1 Diabetes	1	54	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 70.53]
1.1.2 No diabetes	1	30	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.26]
1.2 Hyperkalaemia	17	3001	Risk Ratio (M-H, Random, 95% CI)	2.17 [1.47, 3.22]
1.2.1 Diabetes	10	2122	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.20, 2.91]
1.2.2 No diabetes	6	687	Risk Ratio (M-H, Random, 95% CI)	3.43 [1.35, 8.72]
1.2.3 Diabetes not reported	1	192	Risk Ratio (M-H, Random, 95% CI)	6.14 [0.82, 46.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Subgroup analysis: hyperkalaemia - number of RAS inhibitors used	13	1977	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.42, 3.46]
1.3.1 Aldosterone antagonist plus 1 RAS inhibitor	11	1828	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.28, 3.28]
1.3.2 Aldosterone antagonist plus 2 RAS inhibitors	4	149	Risk Ratio (M-H, Random, 95% CI)	4.30 [1.12, 16.51]
1.4 Hyperkalaemia data from cross-over studies	1		Other data	No numeric data
1.5 Death	3	421	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.10, 3.50]
1.5.1 Diabetes	2	107	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.03, 2.46]
1.5.2 No diabetes	1	314	Risk Ratio (M-H, Random, 95% CI)	2.82 [0.12, 68.60]
1.6 Cardiovascular events	3	1067	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.33, 3.99]
1.6.1 Diabetes	2	875	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.57, 8.55]
1.6.2 No diabetes	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6.3 Diabetes not reported	1	192	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.11, 2.47]
1.7 Myocardial infarction	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7.1 Diabetes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7.2 No diabetes	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.8 Stroke	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 Diabetes	3	1233	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.12, 3.44]
1.8.2 No diabetes	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.9 Proteinuria	14	1193	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-0.82, -0.20]
1.9.1 Diabetes	7	572	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.64, -0.27]
1.9.2 No diabetes	5	367	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-1.57, 0.21]
1.9.3 Diabetes not reported	2	254	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.49, 0.01]
1.10 Proteinuria: descriptive outcome data	13		Other data	No numeric data

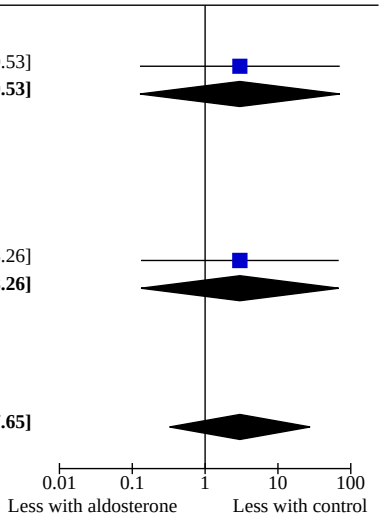
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11 Proteinuria data from cross-over studies	2		Other data	No numeric data
1.12 eGFR [mL/min/1.73 m^2]	13	1165	Mean Difference (IV, Random, 95% CI)	-3.00 [-5.51, -0.49]
1.12.1 Diabetes	8	610	Mean Difference (IV, Random, 95% CI)	-4.43 [-8.35, -0.51]
1.12.2 No diabetes	3	301	Mean Difference (IV, Random, 95% CI)	-2.26 [-8.69, 4.18]
1.12.3 Diabetes not reported	2	254	Mean Difference (IV, Random, 95% CI)	-0.45 [-5.85, 4.95]
1.13 eGFR: descriptive outcome data	6		Other data	No numeric data
1.14 eGFR data from cross-over studies	1		Other data	No numeric data
1.15 Doubling serum creatinine	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.1 Diabetes	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.2 No diabetes	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.16 Systolic BP	14	911	Mean Difference (IV, Random, 95% CI)	-4.98 [-8.22, -1.75]
1.16.1 Diabetes	6	249	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.80, -0.31]
1.16.2 No diabetes	5	367	Mean Difference (IV, Random, 95% CI)	-3.35 [-5.06, -1.65]
1.16.3 Diabetes not reported	3	295	Mean Difference (IV, Random, 95% CI)	-12.07 [-29.27, 5.12]
1.17 Diastolic BP	13	875	Mean Difference (IV, Random, 95% CI)	-1.04 [-2.82, 0.73]
1.17.1 Diabetes	6	249	Mean Difference (IV, Random, 95% CI)	-0.26 [-1.95, 1.44]
1.17.2 No diabetes	4	331	Mean Difference (IV, Random, 95% CI)	-1.62 [-2.86, -0.38]
1.17.3 Diabetes not reported	3	295	Mean Difference (IV, Random, 95% CI)	-1.52 [-10.75, 7.71]
1.18 Blood pressure: descriptive outcome data	9		Other data	No numeric data
1.19 Blood pressure data from cross-over studies	2		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.20 Serum potassium	17	1326	Mean Difference (IV, Random, 95% CI)	0.19 [0.10, 0.29]
1.20.1 Diabetes	9	664	Mean Difference (IV, Random, 95% CI)	0.21 [0.14, 0.28]
1.20.2 No diabetes	5	367	Mean Difference (IV, Random, 95% CI)	0.30 [0.10, 0.50]
1.20.3 Diabetes not reported	3	295	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.21, 0.15]
1.21 Potassium: descriptive outcome data	6		Other data	No numeric data
1.22 Acute kidney injury	5	1446	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.99, 3.79]
1.22.1 Diabetes	2	1179	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.26, 3.69]
1.22.2 No diabetes	1	24	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 67.06]
1.22.3 Diabetes not reported	2	243	Risk Ratio (M-H, Random, 95% CI)	2.42 [1.08, 5.39]
1.23 Gynaecomastia	4	281	Risk Ratio (M-H, Random, 95% CI)	5.14 [1.14, 23.23]
1.23.1 Diabetes	1	54	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 70.53]
1.23.2 No diabetes	3	227	Risk Ratio (M-H, Random, 95% CI)	6.02 [1.08, 33.57]
1.24 Subgroup analysis: proteinuria - duration of follow-up	13	1153	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.83, -0.17]
1.24.1 Less than 6 months	9	822	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.54, -0.24]
1.24.2 At least 6 months	4	331	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-1.68, 0.50]
1.25 Subgroup analysis: systolic BP - duration of follow-up	14	911	Mean Difference (IV, Random, 95% CI)	-4.98 [-8.22, -1.75]
1.25.1 Less than 6 months	10	580	Mean Difference (IV, Random, 95% CI)	-5.65 [-10.96, -0.33]
1.25.2 At least 6 months	4	331	Mean Difference (IV, Random, 95% CI)	-3.62 [-6.09, -1.15]
1.26 Subgroup analysis: diastolic BP - duration of follow-up	13	884	Mean Difference (IV, Random, 95% CI)	-1.04 [-2.81, 0.73]
1.26.1 Less than 6 months	9	553	Mean Difference (IV, Random, 95% CI)	-0.98 [-3.71, 1.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.26.2 At least 6 months	4	331	Mean Difference (IV, Random, 95% CI)	-1.62 [-2.86, -0.38]
1.27 Subgroup analysis: serum potassium - duration of follow-up	16	1285	Mean Difference (IV, Random, 95% CI)	0.22 [0.13, 0.31]
1.27.1 Less than 6 months	12	954	Mean Difference (IV, Random, 95% CI)	0.16 [0.10, 0.22]
1.27.2 At least 6 months	4	331	Mean Difference (IV, Random, 95% CI)	0.35 [0.04, 0.65]

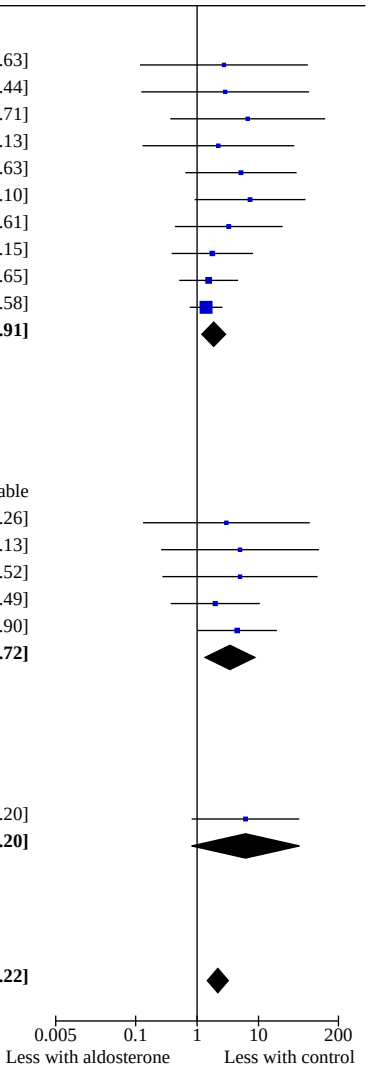
Analysis 1.1. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 1: Kidney failure

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Diabetes						
Mehdi 2009	1	27	0	27	49.5%	3.00 [0.13 , 70.53]
Subtotal (95% CI)		**27**		**27**	**49.5%**	**3.00 [0.13 , 70.53]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.1.2 No diabetes						
Guney 2009	1	15	0	15	50.5%	3.00 [0.13 , 68.26]
Subtotal (95% CI)		**15**		**15**	**50.5%**	**3.00 [0.13 , 68.26]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**42**		**42**	**100.0%**	**3.00 [0.33 , 27.65]**
Total events:	2		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



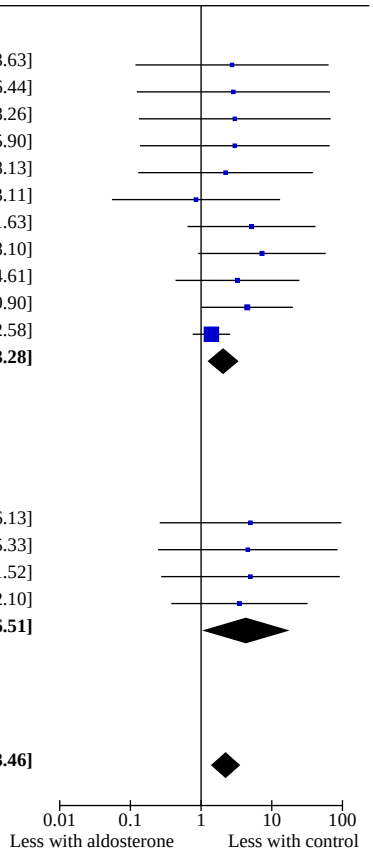
Analysis 1.2. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 2: Hyperkalaemia

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Diabetes						
Schjoedt 2005	1	22	0	20	1.6%	2.74 [0.12 , 63.63]
Rossing 2005	1	21	0	20	1.6%	2.86 [0.12 , 66.44]
Chrysostomou 2006	3	21	0	20	1.8%	6.68 [0.37 , 121.71]
ARTS-DN 2015	8	727	0	94	1.9%	2.22 [0.13 , 38.13]
van den Meiracker 2006	5	29	1	30	3.6%	5.17 [0.64 , 41.63]
Chen 2018b	7	101	1	105	3.6%	7.28 [0.91 , 58.10]
Ito 2019a	13	286	1	72	3.8%	3.27 [0.44 , 24.61]
Epstein 2002	8	167	2	74	6.6%	1.77 [0.39 , 8.15]
Epstein 2006	12	171	4	88	12.7%	1.54 [0.51 , 4.65]
Mehdi 2009	14	27	10	27	41.3%	1.40 [0.76 , 2.58]
Subtotal (95% CI)		**1572**		**550**	**78.5%**	**1.86 [1.20 , 2.91]**
Total events:	72		19			
Heterogeneity: Tau² = 0.00; Chi² = 5.24, df = 9 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.75 (P = 0.006)						
1.2.2 No diabetes						
EVALUATE 2010	0	169	0	163		Not estimable
Guney 2009	1	15	0	15	1.6%	3.00 [0.13 , 68.26]
Furumatsu 2008	2	15	0	15	1.8%	5.00 [0.26 , 96.13]
Tylicki 2008	2	9	0	9	1.8%	5.00 [0.27 , 91.52]
Bianchi 2006	4	83	2	82	5.5%	1.98 [0.37 , 10.49]
CRIBS II 2009	9	56	2	56	7.0%	4.50 [1.02 , 19.90]
Subtotal (95% CI)		**347**		**340**	**17.7%**	**3.43 [1.35 , 8.72]**
Total events:	18		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 4 (P = 0.95); I² = 0%						
Test for overall effect: Z = 2.58 (P = 0.010)						
1.2.3 Diabetes not reported						
ARTS 2012	12	127	1	65	3.8%	6.14 [0.82 , 46.20]
Subtotal (95% CI)		**127**		**65**	**3.8%**	**6.14 [0.82 , 46.20]**
Total events:	12		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
Total (95% CI)		**2046**		**955**	**100.0%**	**2.17 [1.47 , 3.22]**
Total events:	102		24			
Heterogeneity: Tau² = 0.00; Chi² = 8.60, df = 15 (P = 0.90); I² = 0%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
Test for subgroup differences: Chi² = 2.39, df = 2 (P = 0.30), I² = 16.3%						



Analysis 1.3. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 3: Subgroup analysis: hyperkalaemia - number of RAS inhibitors used

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Aldosterone antagonist plus 1 RAS inhibitor						
Schjoedt 2005	1	22	0	20	2.0%	2.74 [0.12 , 63.63]
Rossing 2005	1	21	0	20	2.0%	2.86 [0.12 , 66.44]
Guney 2009	1	15	0	15	2.0%	3.00 [0.13 , 68.26]
Chrysostomou 2006	1	10	0	10	2.1%	3.00 [0.14 , 65.90]
ARTS-DN 2015	8	727	0	94	2.4%	2.22 [0.13 , 38.13]
Bianchi 2006	1	46	1	39	2.6%	0.85 [0.05 , 13.11]
van den Meiracker 2006	5	29	1	30	4.6%	5.17 [0.64 , 41.63]
Chen 2018b	7	101	1	105	4.6%	7.28 [0.91 , 58.10]
Ito 2019a	13	286	1	72	4.9%	3.27 [0.44 , 24.61]
CRIBS II 2009	9	56	2	56	9.0%	4.50 [1.02 , 19.90]
Mehdi 2009	14	27	10	27	52.9%	1.40 [0.76 , 2.58]
Subtotal (95% CI)		**1340**		**488**	**89.1%**	**2.05 [1.28 , 3.28]**
Total events:	61		16			
Heterogeneity: Tau² = 0.00; Chi² = 6.29, df = 10 (P = 0.79); I² = 0%						
Test for overall effect: Z = 2.98 (P = 0.003)						
1.3.2 Aldosterone antagonist plus 2 RAS inhibitors						
Furumatsu 2008	2	15	0	15	2.3%	5.00 [0.26 , 96.13]
Chrysostomou 2006	2	11	0	10	2.3%	4.58 [0.25 , 85.33]
Tylicki 2008	2	9	0	9	2.3%	5.00 [0.27 , 91.52]
Bianchi 2006	3	37	1	43	4.0%	3.49 [0.38 , 32.10]
Subtotal (95% CI)		**72**		**77**	**10.9%**	**4.30 [1.12 , 16.51]**
Total events:	9		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 3 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						
Total (95% CI)		**1412**		**565**	**100.0%**	**2.22 [1.42 , 3.46]**
Total events:	70		17			
Heterogeneity: Tau² = 0.00; Chi² = 7.45, df = 14 (P = 0.92); I² = 0%						
Test for overall effect: Z = 3.51 (P = 0.0004)						
Test for subgroup differences: Chi² = 1.04, df = 1 (P = 0.31), I² = 4.1%						



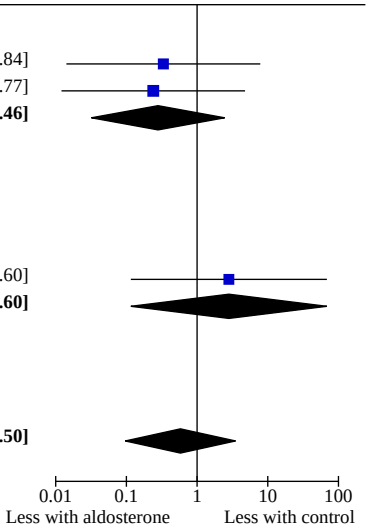
Analysis 1.4. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 4: Hyperkalaemia data from cross-over studies

Hyperkalaemia data from cross-over studies

Study	Comparison	Description of outcome
Nielsen 2012	Spironolactone versus placebo	Two patients had severe hyperkalaemia (plasma potassium = 5.7 mmol/L). Four patients experienced light to moderate hyperkalaemia (plasma potassium = 5.0 to 5.4 mmol/L). Hyperkalaemia was mainly observed 2 weeks after the start of spironolactone treatment

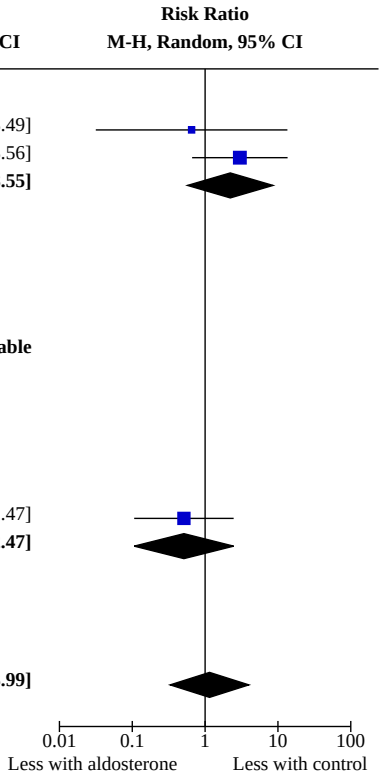
Analysis 1.5. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 5: Death

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Diabetes						
Mehdi 2009	0	27	1	27	32.3%	0.33 [0.01 , 7.84]
van den Meiracker 2006	0	24	2	29	36.1%	0.24 [0.01 , 4.77]
Subtotal (95% CI)		**51**		**56**	**68.4%**	**0.28 [0.03 , 2.46]**
Total events:	0		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.5.2 No diabetes						
EVALUATE 2010	1	162	0	152	31.6%	2.82 [0.12 , 68.60]
Subtotal (95% CI)		**162**		**152**	**31.6%**	**2.82 [0.12 , 68.60]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.53)						
Total (95% CI)		**213**		**208**	**100.0%**	**0.58 [0.10 , 3.50]**
Total events:	1		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.39, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.55)						
Test for subgroup differences: Chi² = 1.37, df = 1 (P = 0.24), I² = 27.1%						



Analysis 1.6. Comparison 1: Aldosterone antagonist versus placebo/ standard care (all studies), Outcome 6: Cardiovascular events

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Diabetes						
ARTS-DN 2015	2	727	0	94	14.8%	0.65 [0.03 , 13.49]
Mehdi 2009	6	27	2	27	43.7%	3.00 [0.66 , 13.56]
Subtotal (95% CI)		**754**		**121**	**58.6%**	**2.22 [0.57 , 8.55]**
Total events:	8		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.6.2 No diabetes						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.3 Diabetes not reported						
ARTS 2012 (1)	3	127	3	65	41.4%	0.51 [0.11 , 2.47]
Subtotal (95% CI)		**127**		**65**	**41.4%**	**0.51 [0.11 , 2.47]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**881**		**186**	**100.0%**	**1.15 [0.33 , 3.99]**
Total events:	11		5			
Heterogeneity: Tau² = 0.33; Chi² = 2.71, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 47.9%						

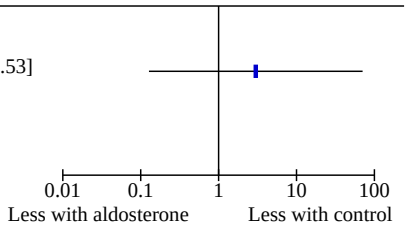


Footnotes

(1) Heart failure

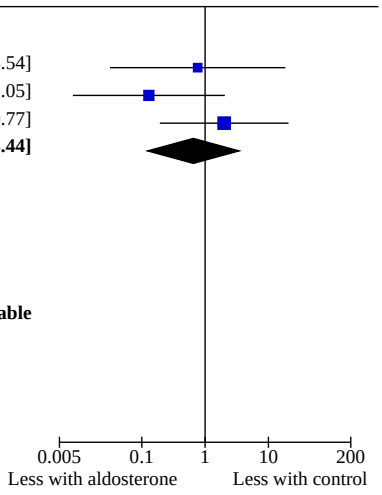
Analysis 1.7. Comparison 1: Aldosterone antagonist versus placebo/ standard care (all studies), Outcome 7: Myocardial infarction

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Risk Ratio M-H, Random, 95% CI
1.7.1 Diabetes					
Mehdi 2009	1	27	0	27	3.00 [0.13 , 70.53]
1.7.2 No diabetes					

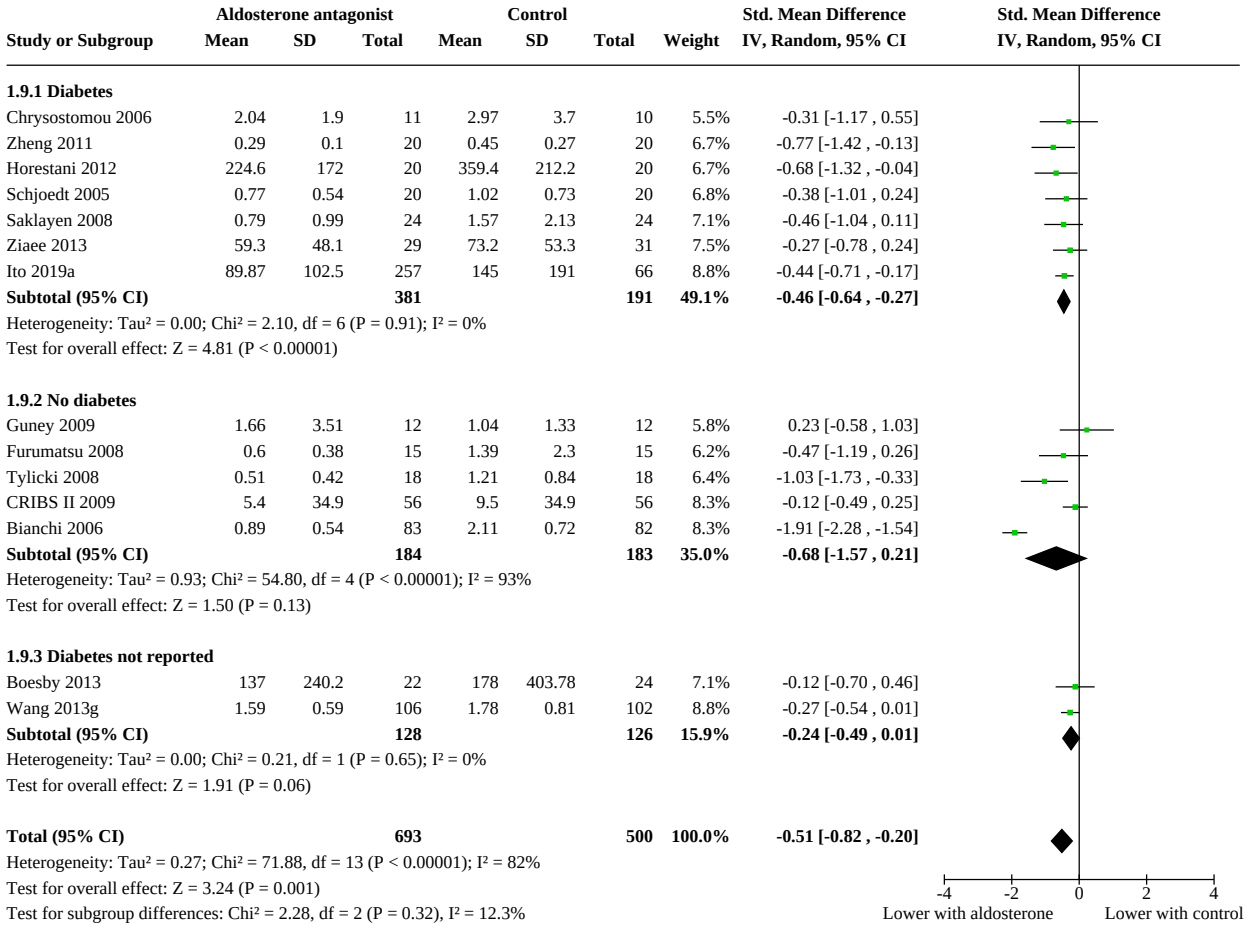


Analysis 1.8. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 8: Stroke

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Diabetes						
Ito 2019a	1	286	0	72	24.8%	0.76 [0.03 , 18.54]
ARTS-DN 2015	1	727	1	94	32.2%	0.13 [0.01 , 2.05]
Mehdi 2009	2	27	1	27	43.0%	2.00 [0.19 , 20.77]
Subtotal (95% CI)		**1040**		**193**	**100.0%**	**0.65 [0.12 , 3.44]**
Total events:	4		2			
Heterogeneity: Tau² = 0.25; Chi² = 2.26, df = 2 (P = 0.32); I² = 11%						
Test for overall effect: Z = 0.50 (P = 0.61)						
1.8.2 No diabetes						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 1.9. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 9: Proteinuria



Analysis 1.10. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 10: Proteinuria: descriptive outcome data

Proteinuria: descriptive outcome data

Study	Comparison	Description of outcome
ARTS 2012	Finerenone or spironolactone versus placebo	Mean UACR decreased in all BAY 94-8862 dose groups (geometric mean ratio versus baseline UACR 0.77 for 2.5 mg/day, 0.69 for 5 mg/day, 0.72 for 10 mg/day and 0.86 for 5 mg twice/day) and in the spironolactone group (geometric mean ratio versus baseline UACR 0.61), compared with a small increase in the placebo group (geometric mean ratio versus baseline UACR 1.04). No P value or CI reported
ARTS-DN 2015	Finerenone plus ACEi or ARB versus ACEi or ARB alone	The mean placebo-corrected ratios of UACR at day 90 versus baseline in the finerenone 7.5, 10, 15, and 20 mg/day groups were 0.79 (90% CI, 0.68 to 0.91; P = .004), 0.76 (90% CI, 0.65 to 0.88; P = 0.001), 0.67 (90% CI, 0.58 to 0.77; P < 0.001), and 0.62 (90% CI, 0.54 to 0.72; P < 0.001), respectively
Chen 2018b	Spironolactone plus irbesartan (low or high dose) versus irbesartan (low or high dose)	At 72 weeks, UAER significant decreased in the spironolactone + high dose irbesartan group (-30 μg/min) and spironolactone + low dose irbesartan group (-23 μg/min) compared to low dose irbesartan group (-15 μg/min) (P < 0.05). However, UAER was significantly reduced in high dose irbesartan (-30 μg/min) compared to spironolactone + low dose irbesartan (-23 μg/min) (P < 0.05)

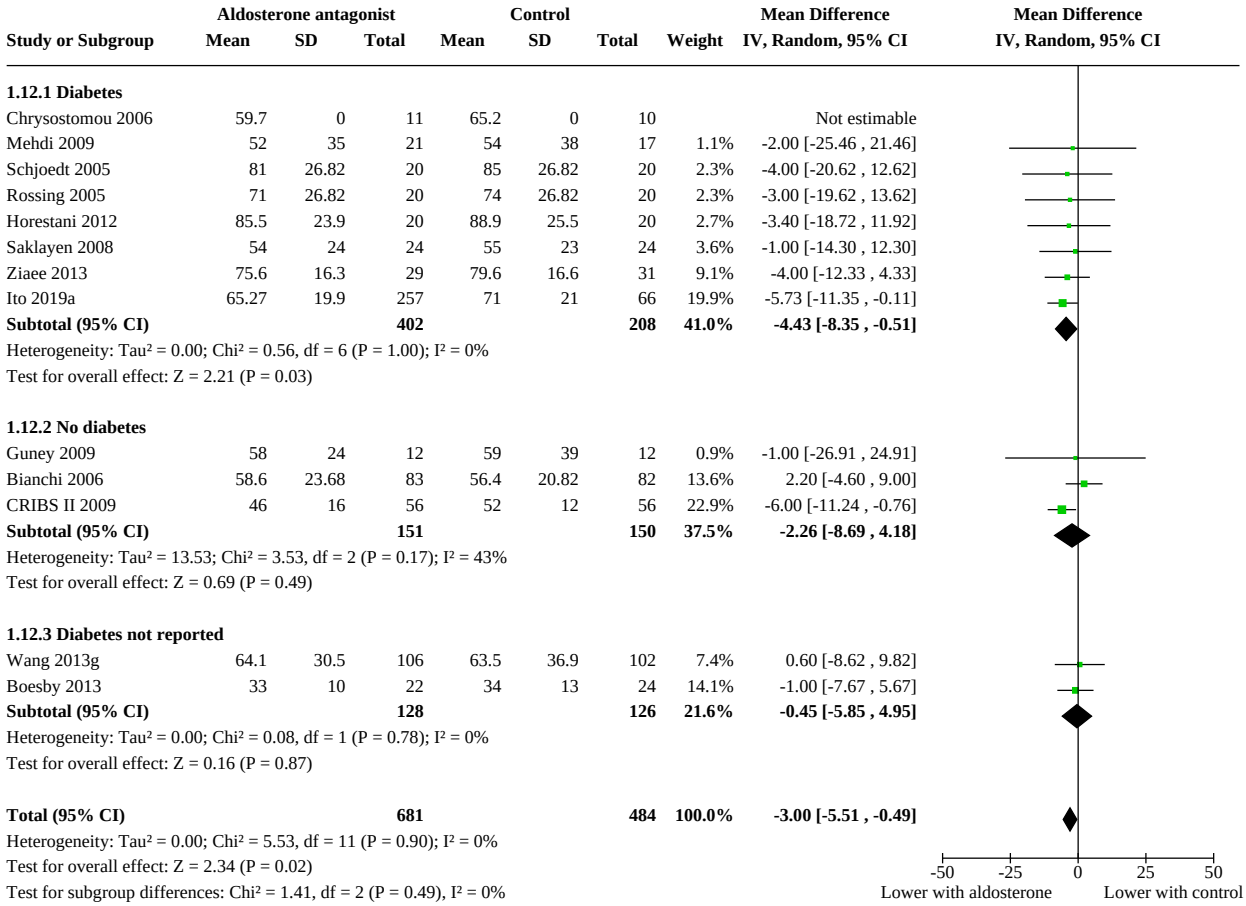
Cohen 2010	Eplerenone plus ACEi or ARB versus ACEi plus ARB	Urine protein excretion was reduced by 1.04 ± 0.4 g/24 h in the eplerenone and by 0.32 ± 0.2 g/24 h in the ACEi plus ARB group
Epstein 2002	Eplerenone plus ACEi versus ACEi	UAE was reduced by 74% in the eplerenone and by 45% in the control group
Epstein 2006	Eplerenone plus ACEi versus ACEi	Eplerenone treatment significantly reduced albuminuria from baseline as early as week 4 and continued throughout weeks 8 and 12. ACEi treatment did not result in any significant decrease from baseline in albuminuria
EVALUATE 2010	Eplerenone plus ACEi and/or ARB versus ACEi and/or ARB	UACR reduced significantly more with eplerenone (-17.3 mg/g) than placebo (+10.3 mg/g) (P = 0.0222)
Haykal 2007	Eplerenone plus ACEi versus ACEi	Eplerenone treatment reduced proteinuria after 4 weeks. The effect continued throughout weeks 8 and 12 (P < 0.001)
Kato 2015	Spironolactone plus ACEi or ARB versus ACEi or ARB	At week 8, spironolactone reduced proteinuria compared to control (UACR -519.7 ± 129.4 mg/g) (P = 0.001)
Koroshi 2010	Spironolactone + ACEi versus ACEi	In comparison with the placebo group, proteinuria decreased by 42.3% (95% CI, P = 0.004) in the group assigned to spironolactone
Lv 2009a	Spironolactone + ACEi or ARB versus ACEi or ARB alone	After 9 months therapy, proteinuria decreased significantly (1.25 ± 0.61 g/day at baseline, 0.85 ± 0.56 g/day at the 3rd month, 0.81 ± 0.61 g/day at the 6th month, and 0.64 ± 0.42 g/day, at the 9th month, P < 0.05) in patients treated with spironolactone, while it didn't change in control group
Mehdi 2009	Spironolactone + ACEi versus ARB	During the 48 weeks of treatment, albuminuria (UACR) decreased significantly from baseline in the ARB (P = 0.001) and spironolactone (P < 0.0001) groups but not in the placebo group (P = 0.08). At 48 weeks, the percentage change from the baseline was 24.6% (95% CI 54.8% to 25.9%) in those assigned to placebo, 38.2% (95% CI 59.3% to 5.9%) in those assigned to ARB, and 51.6% (95% CI 70.2% to 21.4%) in those assigned to spironolactone
Tokunaga 2008a	Spironolactone + ARB versus ARB alone	Spironolactone reduced proteinuria from 1.70 ± 1.12 g/g to 1.11 ± 1.13 g/g Cr (P < 0.05)

Analysis 1.11. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 11: Proteinuria data from cross-over studies

Proteinuria data from cross-over studies

Study	Comparison	Description of outcome
Boesby 2011	Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both)	Albuminuria was significantly lower during the add-on eplerenone period as compared with the control period with a 22% (95% CI 14 to 28, P < 0.001), lower excretion. The mean 24 hour excretion was 1481 mg (95% CI 1192 to 1840) during the control period and 1163 mg (95% CI 921 to 1468) during add-on eplerenone. No significant carry-over, P = 0.3 or time effect, P = 0.3, was detected for the UAE
Nielsen 2012	Spironolactone versus placebo	During spironolactone treatment, urinary albumin excretion was reduced by 60% (21% to 80%) from 90 mg/24 h to 35 mg/24 h when compared with placebo (P = 0.01)

Analysis 1.12. Comparison 1: Aldosterone antagonist versus placebo/ standard care (all studies), Outcome 12: eGFR [mL/min/1.73 m²]



Analysis 1.13. Comparison 1: Aldosterone antagonist versus placebo/ standard care (all studies), Outcome 13: eGFR: descriptive outcome data

eGFR: descriptive outcome data

Study	Comparison	Description of outcome
ARTS 2012	Finerenone or spironolactone versus placebo	There was a decrease in eGFR in all finerenone groups (mean change from baseline eGFR ranging -0.85 to -2.69 mL/min/1.73 m^2) and the spironolactone group (-6.70 mL/min/1.73 m^2), compared with a small increase in the placebo group (0.87 mL/min/1.73 m^2). However, the decrease in the spironolactone group was significantly greater than in all finerenone groups (P = 0.0002 to 0.0133)
ARTS-DN 2015	Finerenone plus ACEi or ARB versus ACEi or ARB alone	There was absolute decrease in eGFR in all finerenone groups (mean change from baseline eGFR ranging -1.9 to -3.9 mL/min/1.73 m^2) as well as placebo (-1.5 mL/min/1.73 m^2). No P value was reported
Chen 2018b	Spironolactone plus irbesartan (low or high dose) versus irbesartan (low or high dose)	At 72 weeks, eGFR was lower in the spironolactone + high dose irbesartan group (-3.8 mL/min/1.73 m^2) compared to low dose irbesartan (-0.3 mL/min/1.73 m^2) and high dose irbesartan group (-1.5 mL/min/1.73 m^2) (P < 0.05), but not significantly different in the spironolactone + low dose irbesartan group (-0.6 mL/min/1.73 m^2)
EVALUATE 2010	Eplerenone plus ACEi and/or ARB versus ACEi and/or ARB	eGFR was significantly lower with eplerenone (-4.6 mL/min/1.73 m^2) than placebo (+0.47 mL/min/1.73 m^2) (P = 0.0041)

Kato 2015	Spironolactone plus ACEi or ARB versus ACEi or ARB	At week 8, there was no difference in eGFR between spironolactone and control (-3.2 ± 9.7 mL/min/1.73 m^2) (P = 0.052)
Lv 2009a	Spironolactone + ACEi or ARB versus ACEi or ARB alone	By the end of the 9th month, the monthly rate of decrease of eGFR was similar in the two groups (-0.66 mL/min/1.73 m^2 in spironolactone group versus -0.94 mL/min/1.73 m^2 in control group, P = 0.28)

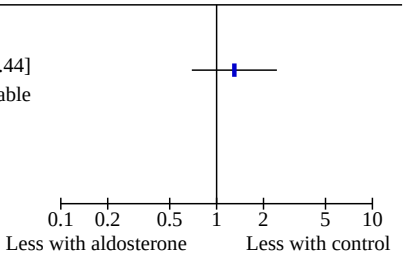
Analysis 1.14. Comparison 1: Aldosterone antagonist versus placebo/ standard care (all studies), Outcome 14: eGFR data from cross-over studies

eGFR data from cross-over studies

Study	Comparison	Description of outcome
Nielsen 2012	Spironolactone versus placebo	Significant decline in GFR from 78 mL/min/1.73 m^2 to 72 mL/min/1.73 m^2 (P = 0.003) during spironolactone treatment

Analysis 1.15. Comparison 1: Aldosterone antagonist versus placebo/ standard care (all studies), Outcome 15: Doubling serum creatinine

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Risk Ratio M-H, Random, 95% CI
1.15.1 Diabetes					
Mehdi 2009	13	27	10	27	1.30 [0.69 , 2.44]
ARTS-DN 2015 (1)	0	727	0	94	Not estimable
1.15.2 No diabetes					

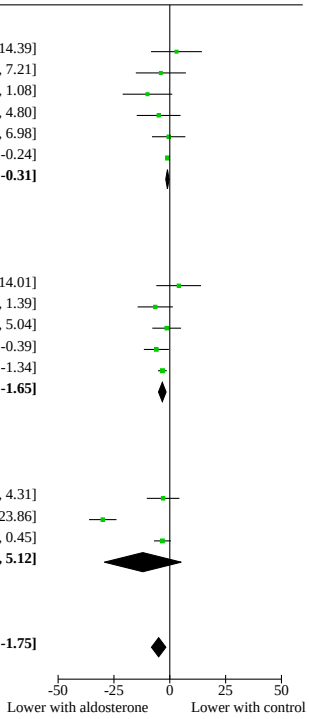


Footnotes

(1) eGFR decrease # 57%

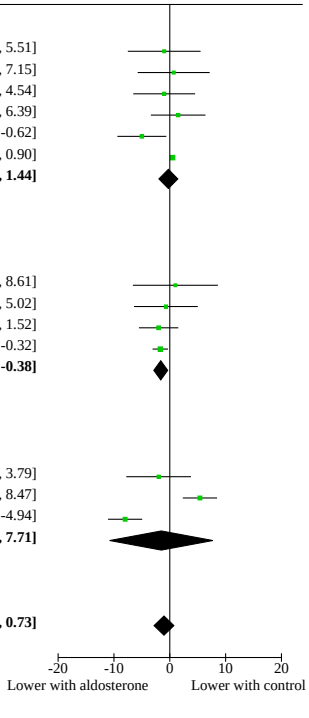
Analysis 1.16. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 16: Systolic BP

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
1.16.1 Diabetes								
Chrysostomou 2006	127	15.4	11	124	11.06	10	4.6%	3.00 [-8.39 , 14.39]
Saklayen 2008	141	16	24	145	23	24	4.7%	-4.00 [-15.21 , 7.21]
Rossing 2005	132	17.88	20	142	17.88	20	4.8%	-10.00 [-21.08 , 1.08]
Schjoedt 2005	131	17.88	20	136	13.41	20	5.5%	-5.00 [-14.80 , 4.80]
Horestani 2012	132.5	12.6	20	133	11.5	20	6.9%	-0.50 [-7.98 , 6.98]
Ziaee 2013	117.2	1.5	29	118.2	1.5	31	10.8%	-1.00 [-1.76 , -0.24]
Subtotal (95% CI)			**124**			**125**	**37.3%**	**-1.06 [-1.80 , -0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 3.92, df = 5 (P = 0.56); I² = 0%								
Test for overall effect: Z = 2.76 (P = 0.006)								
1.16.2 No diabetes								
Guney 2009	115	12	12	111	13	12	5.3%	4.00 [-6.01 , 14.01]
Furumatsu 2008	119.4	11.22	15	125.9	10.83	15	6.6%	-6.50 [-14.39 , 1.39]
Tylicki 2008	114.72	10.64	18	116.11	8.98	18	7.6%	-1.39 [-7.82 , 5.04]
CRIBS II 2009	119	13	56	125	17	56	8.2%	-6.00 [-11.61 , -0.39]
Bianchi 2006	126.9	7.28	83	130.2	5.43	82	10.5%	-3.30 [-5.26 , -1.34]
Subtotal (95% CI)			**184**			**183**	**38.3%**	**-3.35 [-5.06 , -1.65]**
Heterogeneity: Tau² = 0.00; Chi² = 3.90, df = 4 (P = 0.42); I² = 0%								
Test for overall effect: Z = 3.85 (P = 0.0001)								
1.16.3 Diabetes not reported								
Boesby 2013	122	10	22	125	15	24	7.0%	-3.00 [-10.31 , 4.31]
Abolghasmi 2011	135	10	19	165	10	22	7.8%	-30.00 [-36.14 , -23.86]
Wang 2013g	117.6	12.7	106	120.9	14.8	102	9.5%	-3.30 [-7.05 , 0.45]
Subtotal (95% CI)			**147**			**148**	**24.4%**	**-12.07 [-29.27 , 5.12]**
Heterogeneity: Tau² = 221.77; Chi² = 56.35, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.38 (P = 0.17)								
Total (95% CI)			**455**			**456**	**100.0%**	**-4.98 [-8.22 , -1.75]**
Heterogeneity: Tau² = 24.96; Chi² = 96.58, df = 13 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.02 (P = 0.003)								
Test for subgroup differences: Chi² = 7.31, df = 2 (P = 0.03), I² = 72.6%								



Analysis 1.17. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 17: Diastolic BP

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
1.17.1 Diabetes								
Saklayen 2008	77	12	24	78	11	24	4.8%	-1.00 [-7.51 , 5.51]
Chrysostomou 2006	72.7	7.1	11	72	7.9	10	4.9%	0.70 [-5.75 , 7.15]
Schjoedt 2005	71	8.94	20	72	8.94	20	5.9%	-1.00 [-6.54 , 4.54]
Horestani 2012	81.5	8.6	20	80	7.1	20	6.7%	1.50 [-3.39 , 6.39]
Rossing 2005	71	8.94	20	76	4.47	20	7.5%	-5.00 [-9.38 , -0.62]
Ziaee 2013	70.6	0.68	29	70.1	0.88	31	13.7%	0.50 [0.10 , 0.90]
Subtotal (95% CI)			**124**			**125**	**43.6%**	**-0.26 [-1.95 , 1.44]**
Heterogeneity: Tau² = 1.25; Chi² = 6.64, df = 5 (P = 0.25); I² = 25%								
Test for overall effect: Z = 0.30 (P = 0.77)								
1.17.2 No diabetes								
Guney 2009	74	9	12	73	10	12	3.9%	1.00 [-6.61 , 8.61]
Furumatsu 2008	77.6	8.9	15	78.3	6.96	15	5.7%	-0.70 [-6.42 , 5.02]
CRIBS II 2009	71	10	56	73	9	56	8.9%	-2.00 [-5.52 , 1.52]
Bianchi 2006	75.6	4.55	83	77.3	4.52	82	12.7%	-1.70 [-3.08 , -0.32]
Subtotal (95% CI)			**166**			**165**	**31.3%**	**-1.62 [-2.86 , -0.38]**
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 3 (P = 0.89); I² = 0%								
Test for overall effect: Z = 2.56 (P = 0.01)								
1.17.3 Diabetes not reported								
Boesby 2013	72	9	22	74	11	24	5.6%	-2.00 [-7.79 , 3.79]
Wang 2013g	70.4	10.1	106	65	12.3	102	9.8%	5.40 [2.33 , 8.47]
Abolghasmi 2011	83	2	19	91	7	22	9.8%	-8.00 [-11.06 , -4.94]
Subtotal (95% CI)			**147**			**148**	**25.2%**	**-1.52 [-10.75 , 7.71]**
Heterogeneity: Tau² = 62.13; Chi² = 36.82, df = 2 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 0.32 (P = 0.75)								
Total (95% CI)			**437**			**438**	**100.0%**	**-1.04 [-2.82 , 0.73]**
Heterogeneity: Tau² = 5.94; Chi² = 56.28, df = 12 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 1.15 (P = 0.25)								
Test for subgroup differences: Chi² = 1.63, df = 2 (P = 0.44), I² = 0%								



Analysis 1.18. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 18: Blood pressure: descriptive outcome data

Blood pressure: descriptive outcome data

Study	Comparison	Description of outcome
ARTS 2012	Finerenone or spironolactone versus placebo	Spironolactone significantly decreased systolic BP (-10.1 mmHg) at day 29 ± 2 compared with either placebo (-3.1 mmHg, P = 0.0104) or all doses of finerenone (range -1.9 to -4.2 mmHg, P = 0.0023 to 0.0255)
ARTS-DN 2015	Finerenone plus ACEi or ARB versus ACEi or ARB alone	Systolic BP from baseline to day 90 decreased in all finerenone groups (placebo corrected least squares mean differences range from −2.8 to −5.1 mmHg). Decreases only significant in 15 mg daily and 20 mg daily groups
Chen 2018b	Spironolactone plus irbesartan (low or high dose) versus irbesartan (low or high dose)	At 72 weeks, there was no difference between systolic of diastolic BP between the spironolactone + high dose irbesartan group (change in systolic BP -24 mmHg, diastolic BP -14 mmHg) or spironolactone + low dose irbesartan (change in systolic BP -24 mmHg, diastolic BP -13 mmHg), compared to low dose irbesartan (change in systolic BP -23 mmHg, diastolic BP -13 mmHg) and high dose irbesartan group (change in systolic BP -24 mmHg, diastolic BP -14 mmHg)
Cohen 2010	Eplerenone plus ACEi or ARB versus ACEi plus ARB	Systolic BP was reduced by 9.7 ± 6.4 mmHg in the eplerenone group and by 13.4 ± 14.9 mmHg in the ACEi plus ARB group
Epstein 2002	Eplerenone plus ACEi versus ACEi	Systolic BP was reduced by 21.8% and 20.4% in the eplerenone and control group respectively. Diastolic BP was reduced by 16.2% and 15% in the eplerenone and control group respectively
Epstein 2006	Eplerenone plus ACEi versus ACEi	Both systolic and diastolic BP decreased at weeks 4, 8, and 12 in eplerenone and control groups. There were no significant differences in BP reduction between groups
EVALUATE 2010	Eplerenone plus ACEi and/or ARB versus ACEi and/or ARB	Systolic BP was lower with eplerenone (128.8 mmHg) than placebo (132.2 mmHg) (P = 0.0035). Diastolic BP was also lower with eplerenone (76.7 mmHg) than placebo (78.4 mmHg) (P < 0.0370)
Haykal 2007	Eplerenone plus ACEi versus ACEi	Both systolic and diastolic BP decreased in the two groups at weeks 4, 8 and 12 (P < 0.001). BP reduction was slightly higher in eplerenone group
Kato 2015	Spironolactone plus ACEi or ARB versus ACEi or ARB	At week 8, there was no difference in blood pressure between spironolactone (systolic BP -2.68 ± 25.3 mmHg, diastolic BP -3.44 ± 14.3 mmHg) and control (no change but exact values not reported) (P value not reported)

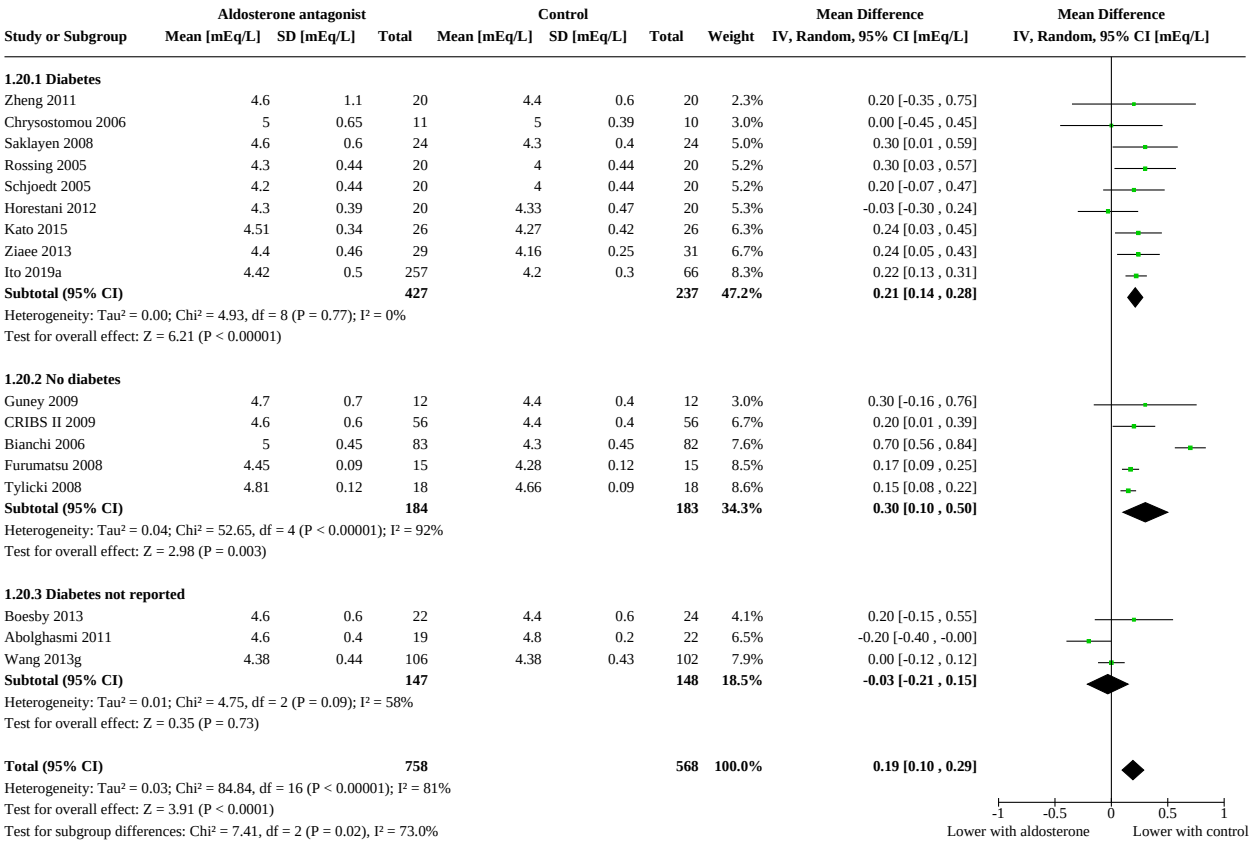
Analysis 1.19. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 19: Blood pressure data from cross-over studies

Blood pressure data from cross-over studies

Study	Comparison	Description of outcome
Boesby 2011	Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both) alone	Systolic and diastolic BP was significantly lower during add-on eplerenone treatment when compared to the control period. There was a significant reduction of systolic BP after 2 weeks of eplerenone treatment (P = 0.003). The diastolic BP was significantly reduced after 4 weeks of eplerenone treatment (P = 0.002), and there was a significant difference in diastolic BP between the treatment period and control period at the same time point (P = 0.004).There were no significant differences between diastolic BP at the end of the 2 periods. There were no significant carry-over, P = 0.4 and P = 0.9, or time effects, P = 0.5 and P = 0.2 for systolic BP or diastolic BP

Nielsen 2012	Spironolactone versus placebo	No significant changes in diastolic and systolic BP after the placebo or spironolactone period

Analysis 1.20. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 20: Serum potassium



Analysis 1.21. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 21: Potassium: descriptive outcome data

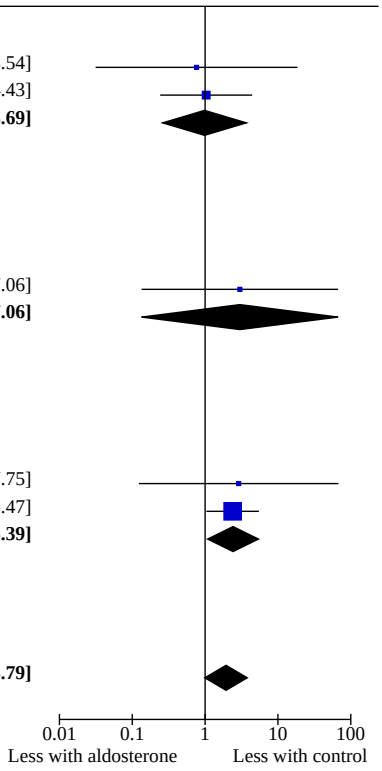
Potassium: descriptive outcome data

Study	Comparison	Description of outcome
ARTS 2012	Finerenone or spironolactone versus placebo	By day 29 ± 2, finerenone 10 mg/day and 5 mg twice/day showed significantly greater mean increases in serum potassium concentration from baseline than placebo (P = 0.02 and P = 0.0003, respectively) Finerenone: 5mg/day and 2.5 mg/day groups were not significantly different from placebo
ARTS-DN 2015	Finerenone plus ACEi or ARB versus ACEi or ARB alone	Potassium non-significantly increased in all finerenone groups (absolute mean change from baseline to day 90 range 0.07 to 0.23) and non-significantly decreased with placebo (-0.004)
Chen 2018b	Spironolactone plus irbesartan (low or high dose) versus irbesartan (low or high dose)	At 72 weeks, potassium was higher in the spironolactone + high dose irbesartan group (+ 0.5 mmol/L) compared to low dose irbesartan (+ 0.11 mmol/L) and high dose irbesartan group (+ 0.29 mmol/L) (P < 0.05). Potassium was higher in the spironolactone + low dose irbesartan group (+ 0.27 mmol/L) compared to low dose irbesartan (+ 0.11 mmol/L) (P < 0.05)

EVALUATE 2010	Eplerenone plus ACEi and/or ARB versus ACEi and/or ARB	Potassium increased from baseline more with eplerenone (+0.17 mmol/L) than placebo (+0.02 mmol/L) (P = 0.0043)
Lv 2009a	Spironolactone + ACEi or ARB versus ACEi or ARB alone	Spironolactone caused an increase in serum potassium after 9 months of treatment (from 3.8 ± 0.4 mEq/L to 4.1 ± 0.3 mEq/L, P = 0.029)
Tokunaga 2008a	Spironolactone + ARB versus ARB alone	Spironolactone produced a significant increase in serum potassium levels (from 4.31 ± 0.53 mmol/L to 4.67 ± 0.68 mmol/L, P < 0.05)

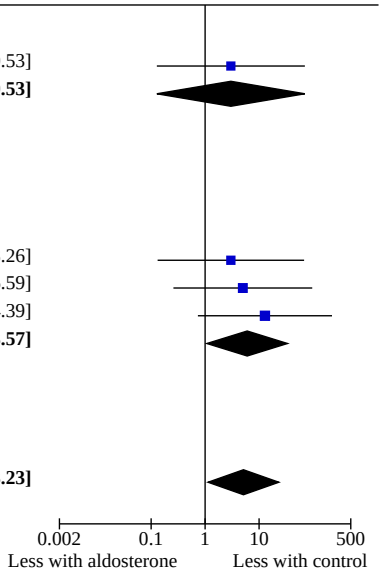
Analysis 1.22. Comparison 1: Aldosterone antagonist versus placebo/ standard care (all studies), Outcome 22: Acute kidney injury

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.22.1 Diabetes						
Ito 2019a	1	286	0	72	4.4%	0.76 [0.03 , 18.54]
ARTS-DN 2015	16	727	2	94	21.2%	1.03 [0.24 , 4.43]
Subtotal (95% CI)		**1013**		**166**	**25.6%**	**0.98 [0.26 , 3.69]**
Total events:	17		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.22.2 No diabetes						
Guney 2009	1	12	0	12	4.6%	3.00 [0.13 , 67.06]
Subtotal (95% CI)		**12**		**12**	**4.6%**	**3.00 [0.13 , 67.06]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.22.3 Diabetes not reported						
Boesby 2013	1	26	0	25	4.5%	2.89 [0.12 , 67.75]
ARTS 2012	28	127	6	65	65.2%	2.39 [1.04 , 5.47]
Subtotal (95% CI)		**153**		**90**	**69.7%**	**2.42 [1.08 , 5.39]**
Total events:	29		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 2.16 (P = 0.03)						
Total (95% CI)		**1178**		**268**	**100.0%**	**1.94 [0.99 , 3.79]**
Total events:	47		8			
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 4 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.94 (P = 0.05)						
Test for subgroup differences: Chi² = 1.38, df = 2 (P = 0.50), I² = 0%						



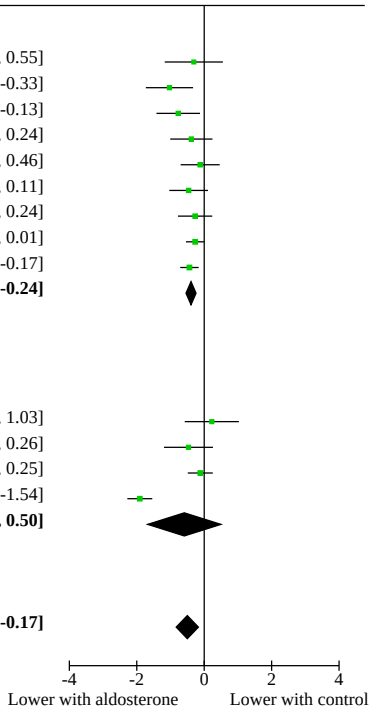
Analysis 1.23. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 23: Gynaecomastia

Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 Diabetes						
Mehdi 2009	1	27	0	27	22.8%	3.00 [0.13 , 70.53]
Subtotal (95% CI)		**27**		**27**	**22.8%**	**3.00 [0.13 , 70.53]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.23.2 No diabetes						
Furumatsu 2008	1	15	0	15	23.3%	3.00 [0.13 , 68.26]
Lv 2009a	2	16	0	16	26.0%	5.00 [0.26 , 96.59]
Bianchi 2006	6	83	0	82	27.8%	12.85 [0.74 , 224.39]
Subtotal (95% CI)		**114**		**113**	**77.2%**	**6.02 [1.08 , 33.57]**
Total events:	9		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Total (95% CI)		**141**		**140**	**100.0%**	**5.14 [1.14 , 23.23]**
Total events:	10		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.70), I² = 0%						



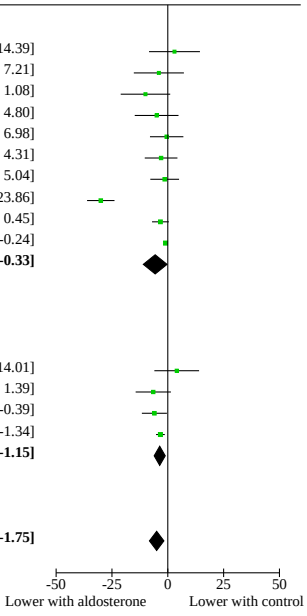
Analysis 1.24. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 24: Subgroup analysis: proteinuria - duration of follow-up

Study or Subgroup	Aldosterone antagonist Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.24.1 Less than 6 months								
Chrysostomou 2006	2.04	1.9	11	2.97	3.7	10	5.9%	-0.31 [-1.17 , 0.55]
Tylicki 2008	0.51	0.42	18	1.21	0.84	18	6.9%	-1.03 [-1.73 , -0.33]
Zheng 2011	0.29	0.1	20	0.45	0.27	20	7.2%	-0.77 [-1.42 , -0.13]
Schjoedt 2005	0.77	0.54	20	1.02	0.73	20	7.3%	-0.38 [-1.01 , 0.24]
Boesby 2013	137	240.2	22	178	403.78	24	7.6%	-0.12 [-0.70 , 0.46]
Saklayen 2008	0.79	0.99	24	1.57	2.13	24	7.7%	-0.46 [-1.04 , 0.11]
Ziaee 2013	59.3	48.1	29	73.2	53.3	31	8.1%	-0.27 [-0.78 , 0.24]
Wang 2013g	1.59	0.59	106	1.78	0.81	102	9.3%	-0.27 [-0.54 , 0.01]
Ito 2019a	89.87	102.5	257	145	191	66	9.3%	-0.44 [-0.71 , -0.17]
Subtotal (95% CI)			**507**			**315**	**69.3%**	**-0.39 [-0.54 , -0.24]**
Heterogeneity: Tau² = 0.00; Chi² = 6.58, df = 8 (P = 0.58); I² = 0%								
Test for overall effect: Z = 5.15 (P < 0.00001)								
1.24.2 At least 6 months								
Guney 2009	1.66	3.51	12	1.04	1.33	12	6.3%	0.23 [-0.58 , 1.03]
Furumatsu 2008	0.6	0.38	15	1.39	2.3	15	6.7%	-0.47 [-1.19 , 0.26]
CRIBS II 2009	5.4	34.9	56	9.5	34.9	56	8.9%	-0.12 [-0.49 , 0.25]
Bianchi 2006	0.89	0.54	83	2.11	0.72	82	8.9%	-1.91 [-2.28 , -1.54]
Subtotal (95% CI)			**166**			**165**	**30.7%**	**-0.59 [-1.68 , 0.50]**
Heterogeneity: Tau² = 1.14; Chi² = 54.57, df = 3 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Total (95% CI)			**673**			**480**	**100.0%**	**-0.50 [-0.83 , -0.17]**
Heterogeneity: Tau² = 0.28; Chi² = 71.65, df = 12 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 2.98 (P = 0.003)								
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%								



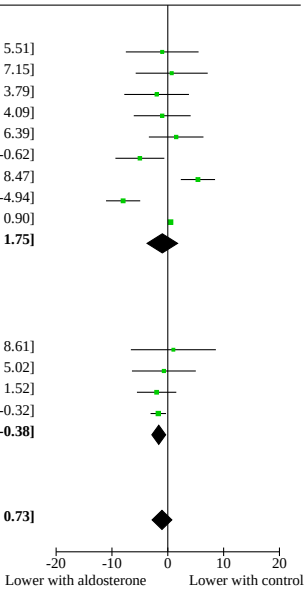
Analysis 1.25. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 25: Subgroup analysis: systolic BP - duration of follow-up

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
1.25.1 Less than 6 months								
Chrysostomou 2006	127	15.4	11	124	11.06	10	4.6%	3.00 [-8.39 , 14.39]
Saklayen 2008	141	16	24	145	23	24	4.7%	-4.00 [-15.21 , 7.21]
Rossing 2005	132	17.88	20	142	17.88	20	4.8%	-10.00 [-21.08 , 1.08]
Schjoedt 2005	131	17.88	20	136	13.41	20	5.5%	-5.00 [-14.80 , 4.80]
Horestani 2012	132.5	12.6	20	133	11.5	20	6.9%	-0.50 [-7.98 , 6.98]
Boesby 2013	122	10	22	125	15	24	7.0%	-3.00 [-10.31 , 4.31]
Tylicki 2008	114.72	10.64	18	116.11	8.98	18	7.6%	-1.39 [-7.82 , 5.04]
Abolghasmi 2011	135	10	19	165	10	22	7.8%	-30.00 [-36.14 , -23.86]
Wang 2013g	117.6	12.7	106	120.9	14.8	102	9.5%	-3.30 [-7.05 , 0.45]
Ziaee 2013	117.2	1.5	29	118.2	1.5	31	10.8%	-1.00 [-1.76 , -0.24]
Subtotal (95% CI)			**289**			**291**	**69.3%**	**-5.65 [-10.96 , -0.33]**
Heterogeneity: Tau² = 57.61; Chi² = 89.10, df = 9 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 2.08 (P = 0.04)								
1.25.2 At least 6 months								
Guney 2009	115	12	12	111	13	12	5.3%	4.00 [-6.01 , 14.01]
Furumatsu 2008	119.4	11.22	15	125.9	10.83	15	6.6%	-6.50 [-14.39 , 1.39]
CRIBS II 2009	119	13	56	125	17	56	8.2%	-6.00 [-11.61 , -0.39]
Bianchi 2006	126.9	7.28	83	130.2	5.43	82	10.5%	-3.30 [-5.26 , -1.34]
Subtotal (95% CI)			**166**			**165**	**30.7%**	**-3.62 [-6.09 , -1.15]**
Heterogeneity: Tau² = 1.33; Chi² = 3.52, df = 3 (P = 0.32); I² = 15%								
Test for overall effect: Z = 2.87 (P = 0.004)								
Total (95% CI)			**455**			**456**	**100.0%**	**-4.98 [-8.22 , -1.75]**
Heterogeneity: Tau² = 24.96; Chi² = 96.58, df = 13 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.02 (P = 0.003)								
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%								

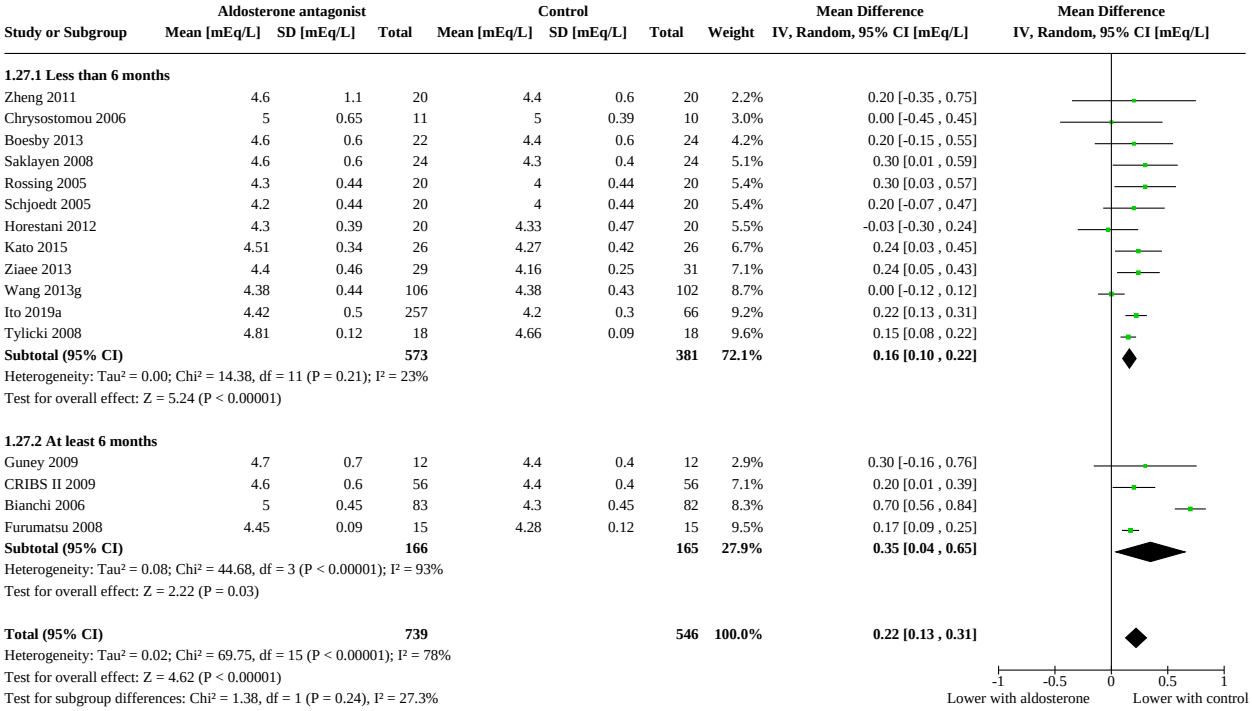


Analysis 1.26. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 26: Subgroup analysis: diastolic BP - duration of follow-up

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
1.26.1 Less than 6 months								
Saklayen 2008	77	12	24	78	11	24	4.8%	-1.00 [-7.51 , 5.51]
Chrysostomou 2006	72.7	7.1	11	72	7.9	10	4.9%	0.70 [-5.75 , 7.15]
Boesby 2013	72	9	22	74	11	24	5.6%	-2.00 [-7.79 , 3.79]
Schjoedt 2005	71	8.94	20	72	8.94	29	6.4%	-1.00 [-6.09 , 4.09]
Horestani 2012	81.5	8.6	20	80	7.1	20	6.7%	1.50 [-3.39 , 6.39]
Rossing 2005	71	8.94	20	76	4.47	20	7.5%	-5.00 [-9.38 , -0.62]
Wang 2013g	70.4	10.1	106	65	12.3	102	9.7%	5.40 [2.33 , 8.47]
Abolghasmi 2011	83	2	19	91	7	22	9.7%	-8.00 [-11.06 , -4.94]
Ziaee 2013	70.6	0.68	29	70.1	0.88	31	13.7%	0.50 [0.10 , 0.90]
Subtotal (95% CI)			**271**			**282**	**68.9%**	**-0.98 [-3.71 , 1.75]**
Heterogeneity: Tau² = 12.31; Chi² = 46.57, df = 8 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 0.70 (P = 0.48)								
1.26.2 At least 6 months								
Guney 2009	74	9	12	73	10	12	3.9%	1.00 [-6.61 , 8.61]
Furumatsu 2008	77.6	8.9	15	78.3	6.96	15	5.6%	-0.70 [-6.42 , 5.02]
CRIBS II 2009	71	10	56	73	9	56	8.9%	-2.00 [-5.52 , 1.52]
Bianchi 2006	75.6	4.55	83	77.3	4.52	82	12.7%	-1.70 [-3.08 , -0.32]
Subtotal (95% CI)			**166**			**165**	**31.1%**	**-1.62 [-2.86 , -0.38]**
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 3 (P = 0.89); I² = 0%								
Test for overall effect: Z = 2.56 (P = 0.01)								
Total (95% CI)			**437**			**447**	**100.0%**	**-1.04 [-2.81 , 0.73]**
Heterogeneity: Tau² = 5.91; Chi² = 56.32, df = 12 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 1.15 (P = 0.25)								
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%								



Analysis 1.27. Comparison 1: Aldosterone antagonist versus placebo/standard care (all studies), Outcome 27: Subgroup analysis: serum potassium - duration of follow-up

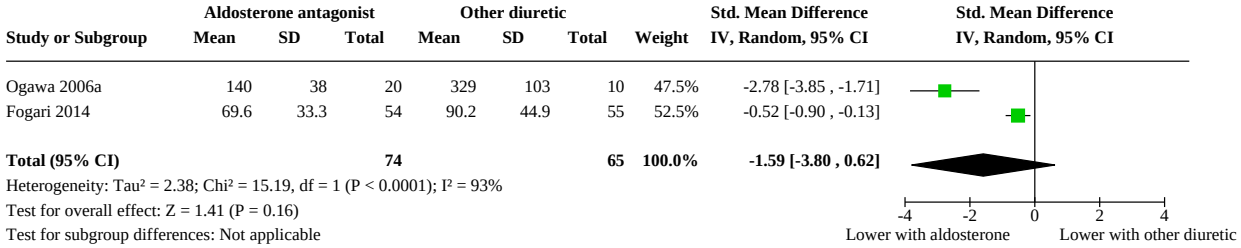


Comparison 2. Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Proteinuria	2	139	Std. Mean Difference (IV, Random, 95% CI)	-1.59 [-3.80, 0.62]
2.2 Proteinuria: descriptive outcome data	2		Other data	No numeric data
2.3 Proteinuria data from cross-over studies	1		Other data	No numeric data
2.4 eGFR [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.5 GFR: descriptive outcome data	1		Other data	No numeric data
2.6 eGFR data from cross-over studies	1		Other data	No numeric data
2.7 Diastolic BP	3	151	Mean Difference (IV, Random, 95% CI)	-1.56 [-3.52, 0.41]
2.8 Systolic BP	3	151	Mean Difference (IV, Random, 95% CI)	-3.79 [-14.36, 6.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9 Blood pressure: descriptive outcome data	1		Other data	No numeric data
2.10 Blood pressure data from cross-over studies	1		Other data	No numeric data
2.11 Serum potassium	2	121	Mean Difference (IV, Random, 95% CI)	0.31 [0.17, 0.45]
2.12 Potassium: descriptive outcome data	1		Other data	No numeric data
2.13 Potassium data from cross-over studies	1		Other data	No numeric data
2.14 Fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 1: Proteinuria



Analysis 2.2. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 2: Proteinuria: descriptive outcome data

Proteinuria: descriptive outcome data

Study	Comparison	Description of outcome
Hase 2013	Spironolactone plus ACEi or ARB versus trichlormethiazide plus ACEi or ARB	At week 24, UAER decreased in both spironolactone group (-57.6% from baseline) and trichlormethiazide group (-48.4% from baseline) but there was no between group difference
Morales 2015	Spironolactone plus ACEi versus hydrochlorothiazide plus ACEi	At week 4, 24 h urine protein decreased in both spironolactone group (median proteinuria 1.7 g to 1.5 g) and hydrochlorothiazide group (median proteinuria 1.7 g to 1.3 g) but there was no between group difference

Analysis 2.3. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 3: Proteinuria data from cross-over studies

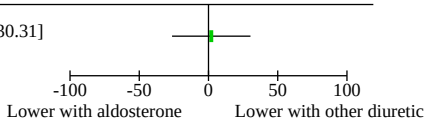
Proteinuria data from cross-over studies

Study	Comparison	Descriptive outcome data

Smolen 2006	Spironolactone verus hydrochlorothiazide	At the start of treatment with spironolactone or hydrochlorothiazide, PCR was 1.65 ± 1.39 and 1.46 ± 1.28 g/g, respectively. After 8 weeks of treatment with spironolactone proteinuria was significantly reduced to 0.99 ± 1.03 g/g (P = 0.03; a decrease of 0.66 ± 0.64 g/g) but not after hydrochlorothiazide (1.28 ± 1.18 g/g; P = 0.35, a decrease of 0.18 ± 0.83 g/g)

Analysis 2.4. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 4: eGFR [mL/min/1.73 m²]

Study or Subgroup	Aldosterone antagonist Mean	SD	Total	Other diuretic Mean	SD	Total	Mean Difference IV, Random, 95% CI
Morales 2015	62	26	6	60	24	6	2.00 [-26.31 , 30.31]



Analysis 2.5. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 5: GFR: descriptive outcome data

GFR: descriptive outcome data

Study	Comparison	Description of outcome
Hase 2013	Spironolactone plus ACEi or ARB versus trichlormethiazide plus ACEi or ARB	At week 24, eGFR decreased in both spironolactone group (-9.3 mL/min/1.73 m² from baseline) and trichlormethiazide group (-9.4 mL/min/1.73 m² from baseline) but there was no between group difference

Analysis 2.6. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 6: eGFR data from cross-over studies

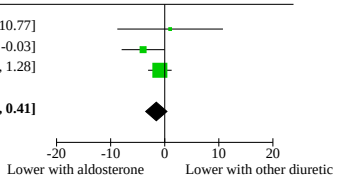
eGFR data from cross-over studies

Study	Comparison	Descriptive outcome data
Smolen 2006	Spironolactone versus hydrochlorothiazide	Mean baseline GFR was 94 ± 25 mL/min in the spironolactone and 95 ± 28 mL/min in the hydrochlorothiazide group. After treatment the GFR remained similar in the two groups (91 ± 28 mL/min versus 93 ± 29 mL/min respectively)

Analysis 2.7. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 7: Diastolic BP

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Other diuretic Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
Morales 2015	72	10	6	71	7	6	4.0%	1.00 [-8.77 , 10.77]
Ogawa 2006a	72	8	20	76	3	10	23.6%	-4.00 [-7.97 , -0.03]
Fogari 2014	72.9	5.7	54	73.8	5.9	55	72.4%	-0.90 [-3.08 , 1.28]
Total (95% CI)			**80**			**71**	**100.0%**	**-1.56 [-3.52 , 0.41]**

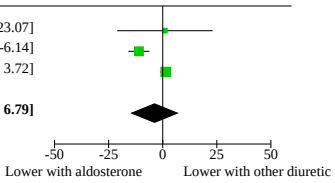
Heterogeneity: Tau² = 0.15; Chi² = 2.07, df = 2 (P = 0.36); I² = 3%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 8: Systolic BP

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Other diuretic Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
Morales 2015	125	20	6	124	19	6	15.2%	1.00 [-21.07 , 23.07]
Ogawa 2006a	127	5	20	138	7	10	41.0%	-11.00 [-15.86 , -6.14]
Fogari 2014	123.4	6.1	54	122.1	6.8	55	43.8%	1.30 [-1.12 , 3.72]
Total (95% CI)			**80**			**71**	**100.0%**	**-3.79 [-14.36 , 6.79]**

Heterogeneity: Tau² = 64.84; Chi² = 19.74, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 9: Blood pressure: descriptive outcome data

Blood pressure: descriptive outcome data

Study	Comparison	Description of outcome
Hase 2013	Spironolactone plus ACEi or ARB versus trichlormethiazide plus ACEi or ARB	At week 24, systolic BP decreased in both spironolactone group (-12 mmHg from baseline) and trichlormethiazide group (-10 mmHg from baseline) but there was no between group difference. Diastolic BP also decreased in both spironolactone group (-7 mmHg from baseline) and trichlormethiazide group (-3 mmHg from baseline) and there was no between group difference

Analysis 2.10. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 10: Blood pressure data from cross-over studies

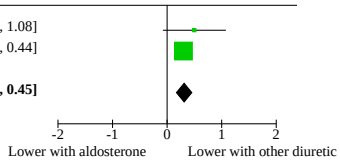
Blood pressure data from cross-over studies

Study	Comparison	Descriptive outcome data
Smolen 2006	Spironolactone verus hydrochlorothiazide	Mean 24 h BP was similar at the start of treatment with spironolactone or hydrochlorothiazide (95.7 ± 10.2 and 95.6 ± 9.1 mmHg, respectively). Both drugs did not significantly influence the 24 h BP (post-treatment values were 95.6 ± 10.4 and 96.4 ± 12.1 mmHg, respectively)

Analysis 2.11. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 11: Serum potassium

Study or Subgroup	Aldosterone antagonist Mean [mEq/L]	SD [mEq/L]	Total	Other diuretic Mean [mEq/L]	SD [mEq/L]	Total	Weight	Mean Difference IV, Random, 95% CI [mEq/L]
Morales 2015	5	0.6	6	4.5	0.4	6	5.9%	0.50 [-0.08 , 1.08]
Fogari 2014	4.6	0.41	54	4.3	0.36	55	94.1%	0.30 [0.16 , 0.44]
Total (95% CI)			**60**			**61**	**100.0%**	**0.31 [0.17 , 0.45]**

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.35 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 12: Potassium: descriptive outcome data

Potassium: descriptive outcome data

Study	Comparison	Description of outcome
Hase 2013	Spironolactone plus ACEi or ARB versus trichlormethiazide plus ACEi or ARB	At week 24, serum potassium increased in the spironolactone group (+ 0.3 mmol/L from baseline)

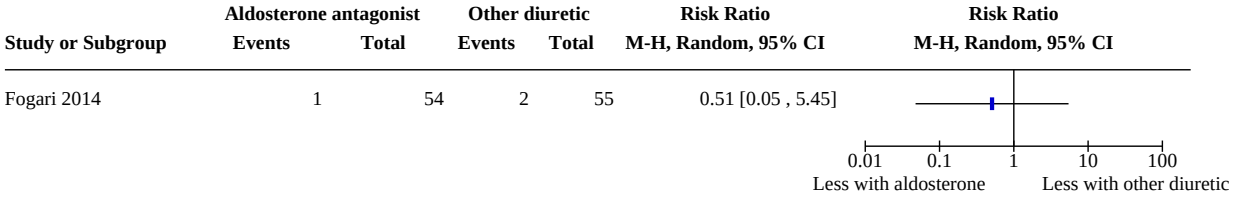
	but remained unchanged in the trichlormethiazide group (P = 0.035)

Analysis 2.13. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 13: Potassium data from cross-over studies

Potassium data from cross-over studies

Study	Comparison	Descriptive outcome data
Smolen 2006	Spironolactone verus hydrochlorothiazide	Serum potassium concentration was 4.23 ± 0.39 and 4.29 ± 0.37 mmol/L, in the spironolactone and hydrochlorothiazide group, respectively. It tended to increase in the spironolactone group after treatment (0.29 ± 0.39 mmol/L, P = 0.01) while it remained stable in the hydrochlorothiazide group (-0.13 ± 0.4 mmol/L, P = 0.18)

Analysis 2.14. Comparison 2: Aldosterone antagonist plus RAS inhibitor versus other diuretic plus RAS inhibitor, Outcome 14: Fatigue



Comparison 3. Spironolactone versus calcium channel blockers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Proteinuria: descriptive outcome data	1		Other data	No numeric data
3.2 Systolic BP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.3 Diastolic BP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.4 Serum potassium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

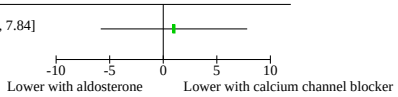
Analysis 3.1. Comparison 3: Spironolactone versus calcium channel blockers, Outcome 1: Proteinuria: descriptive outcome data

Proteinuria: descriptive outcome data

Study	Comparison	Description of outcome
Takebayashi 2006	Spironolactone versus amlodipine	Spironolactone reduced UAE from 543.7 mg/g Cr (170 to 1146) to 376.7 mg/g Cr (135 to 794) (P = 0.003). UAE did not change in amlodipine group (P = 0.38)

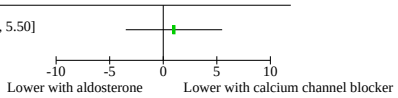
Analysis 3.2. Comparison 3: Spironolactone versus calcium channel blockers, Outcome 2: Systolic BP

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Calcium channel blocker Mean [mmHg]	SD [mmHg]	Total	Mean Difference IV, Random, 95% CI [mmHg]	Mean Difference IV, Random, 95% CI [mmHg]
Takebayashi 2006	129	9	23	128	11	14	1.00 [-5.84 , 7.84]	



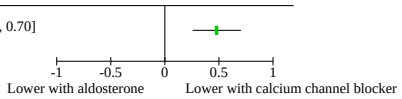
Analysis 3.3. Comparison 3: Spironolactone versus calcium channel blockers, Outcome 3: Diastolic BP

Study or Subgroup	Aldosterone antagonist Mean [mmHg]	SD [mmHg]	Total	Calcium channel blocker Mean [mmHg]	SD [mmHg]	Total	Mean Difference IV, Random, 95% CI [mmHg]	Mean Difference IV, Random, 95% CI [mmHg]
Takebayashi 2006	70	4	23	69	8	14	1.00 [-3.50 , 5.50]	



Analysis 3.4. Comparison 3: Spironolactone versus calcium channel blockers, Outcome 4: Serum potassium

Study or Subgroup	Aldosterone antagonist Mean [mEq/L]	SD [mEq/L]	Total	Calcium channel blocker Mean [mEq/L]	SD [mEq/L]	Total	Mean Difference IV, Random, 95% CI [mEq/L]	Mean Difference IV, Random, 95% CI [mEq/L]
Takebayashi 2006	4.51	0.45	23	4.03	0.24	14	0.48 [0.26 , 0.70]	



Comparison 4. Eplerenone versus ACEi

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Hyperkalaemia data from cross-over studies	1		Other data	No numeric data
4.2 Proteinuria data from cross-over studies	1		Other data	No numeric data

Analysis 4.1. Comparison 4: Eplerenone versus ACEi, Outcome 1: Hyperkalaemia data from cross-over studies

Hyperkalaemia data from cross-over studies

Study	Comparison	Description of outcome
Morales 2009	Eplerenone versus ACEi	The number of patients in which serum potassium was above 5.5 mEq/L after treatment was 2/12 (16%) with ACEi (lisinopril) while none of the patients treated with eplerenone reached this level of potassium

Analysis 4.2. Comparison 4: Eplerenone versus ACEi, Outcome 2: Proteinuria data from cross-over studies

Proteinuria data from cross-over studies

Study	Comparison	Descriptive outcome data
Morales 2009	Eplerenone versus ACEi	ACEi (lisinopril) induced a reduction in proteinuria (11.3 ± 34.8%) which was not statistically significant with respect to baseline values (P = 0.158), while that induced by eplerenone (28.4 ± 31.6%) was significant with respect to baseline values (comparison P = 0.034) and to the lisinopril group (P = 0.034)

Comparison 5. Eplerenone versus ACEi plus ARB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Hyperkalaemia data from cross-over studies	1		Other data	No numeric data
5.2 Proteinuria data from cross-over studies	1		Other data	No numeric data

Analysis 5.1. Comparison 5: Eplerenone versus ACEi plus ARB, Outcome 1: Hyperkalaemia data from cross-over studies

Hyperkalaemia data from cross-over studies

Study	Comparison	Description of outcome
Morales 2009	Eplerenone versus ACEi plus ARB	The number of patients in which serum potassium was above 5.5 mEq/L after treatment was 2/12 (16%) with ACEi plus ARBs (lisinopril plus candesartan) while none of the patients treated with eplerenone reached this level of potassium

Analysis 5.2. Comparison 5: Eplerenone versus ACEi plus ARB, Outcome 2: Proteinuria data from cross-over studies

Proteinuria data from cross-over studies

Study	Comparison	Description of outcome
Morales 2009	Eplerenone versus ACEi plus ARB	Both eplerenone and the combination of ACEi plus ARB (lisinopril and candesartan) obtained a significant reduction of proteinuria from baseline (26.9 ± 30.6% and 28.4 ± 31.6%, P = 0.045 and P = 0.034 respectively)

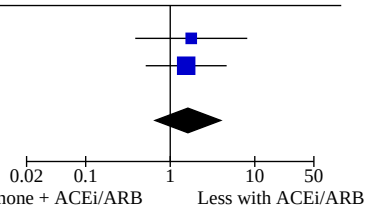
Comparison 6. Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Hyperkalaemia	2	500	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.66, 3.95]
6.2 Proteinuria: descriptive outcome data	4		Other data	No numeric data
6.3 Proteinuria data from cross-over studies	2		Other data	No numeric data
6.4 eGFR: data from cross-over studies	1		Other data	No numeric data
6.5 Blood pressure: descriptive outcome data	4		Other data	No numeric data
6.6 Blood pressure data from cross-over studies	2		Other data	No numeric data
6.7 Serum potassium: data from cross-over studies	1		Other data	No numeric data

Analysis 6.1. Comparison 6: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both), Outcome 1: Hyperkalaemia

Study or Subgroup	Eplerenone + ACEi/ARB Events	Total	ACEi/ARB Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Epstein 2002	8	167	2	74	34.3%	1.77 [0.39 , 8.15]
Epstein 2006	12	171	4	88	65.7%	1.54 [0.51 , 4.65]
Total (95% CI)		**338**		**162**	**100.0%**	**1.62 [0.66 , 3.95]**
Total events:	20		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both), Outcome 2: Proteinuria: descriptive outcome data

Proteinuria: descriptive outcome data

Study	Comparison	Description of outcome
Cohen 2010	Eplerenone plus ACEi or ARB versus ACEi plus ARB	Urine protein excretion was reduced by 1.04 ± 0.4 g/24 h in the eplerenone and by 0.32 ± 0.2 g/24 h in the ACEi plus ARB group
Epstein 2002	Eplerenone plus ACEi versus ACEi	UAE was reduced by 74% in the eplerenone and by 45% in the control group
Epstein 2006	Eplerenone plus ACEi versus ACEi	Eplerenone treatment significantly reduced albuminuria from baseline as early as week 4 and continued throughout weeks 8 and 12. ACEi treatment did not result in any significant decrease from baseline in albuminuria
Haykal 2007	Eplerenone plus ACEi versus ACEi	Eplerenone treatment reduced proteinuria after 4 weeks. The effect continued throughout weeks 8 and 12 (P < 0.001)

Analysis 6.3. Comparison 6: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both), Outcome 3: Proteinuria data from cross-over studies

Proteinuria data from cross-over studies

Study	Comparison	Description of outcome
Boesby 2011	Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both)	Albuminuria was significantly lower during the add-on eplerenone period as compared with the control period with a 22% (95% CI 14 to 28, P < 0.001), lower excretion. The mean 24 h excretion was 1481 mg (95% CI 1192 to 1840) during the control period and 1163 mg (95% CI 921 to 1468) during add-on eplerenone. No significant carry-over, P = 0.3 or time effect, P = 0.3, was detected for the UAE
Tylicki 2012	Eplerenone plus telmisartan 80 mg daily versus telmisartan 160 mg daily	During the 24 week study period, albuminuria was higher in the eplerenone plus telmisartan 80 mg/day group versus telmisartan 160 mg/day group (mean UACR 707 mg/g (95% CI 502-1204)) versus 525 mg/g (95% CI 318 to 763)) though statistical significance was not reported

Analysis 6.4. Comparison 6: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both), Outcome 4: eGFR: data from cross-over studies

eGFR: data from cross-over studies

Study	Comparison	Description of outcome
Tylicki 2012	Eplerenone plus telmisartan 80 mg daily versus telmisartan 160 mg daily	During the 24 week study period, there was no difference between eplerenone plus telmisartan 80 mg daily group versus telmisartan 160 mg daily in creatinine clearance (97.3 ± 8.1 mL/min versus 97.9 ± 8.3 mL/min)

Analysis 6.5. Comparison 6: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both), Outcome 5: Blood pressure: descriptive outcome data

Blood pressure: descriptive outcome data

Study	Comparison	Description of outcome
Cohen 2010	Eplerenone plus ACEi or ARB versus ACEi plus ARB	Systolic BP was reduced by 9.7 ± 6.4 mmHg in the eplerenone group and by 13.4 ± 14.9 mmHg in the ACEi plus ARB group
Epstein 2002	Eplerenone plus ACEi versus ACEi	Systolic BP was reduced by 21.8% and 20.4% in the eplerenone and control group respectively. Diastolic BP was reduced by 16.2% and 15% in the eplerenone and control group respectively
Epstein 2006	Eplerenone plus ACEi versus ACEi	Both systolic and diastolic BP decreased in at weeks 4, 8, and 12 in eplerenone and control groups. There were no significant differences in BP reduction between groups
Haykal 2007	Eplerenone plus ACEi versus ACEi	Both systolic and diastolic BP decreased in the two groups at weeks 4, 8 and 12 (P < 0.001). BP reduction was slightly higher in eplerenone group

Analysis 6.6. Comparison 6: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both), Outcome 6: Blood pressure data from cross-over studies

Blood pressure data from cross-over studies

Study	Comparison	Description of outcome
Boesby 2011	Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both) alone	Systolic and diastolic BP was significantly lower during add-on eplerenone treatment when compared to the control period. There was a significant reduction of systolic BP after 2 weeks of eplerenone treatment (P = 0.003). The diastolic BP was significantly reduced after 4 weeks of eplerenone treatment (P = 0.002), and there was a significant difference in diastolic BP between the treatment period and control period at the same time point (P = 0.004).There were no significant differences between diastolic BP at the end of the 2 periods. There were no significant carry-over, P = 0.4 and P = 0.9, or time effects, P = 0.5 and P = 0.2 for systolic BP or diastolic BP
Tylicki 2012	Eplerenone plus telmisartan 80 mg daily versus telmisartan 160 mg daily	During the 24 week study period, there was no difference between eplerenone plus telmisartan 80 mg daily group versus telmisartan 160 mg daily for both systolic BP (121.5 ± 2.6 mmHg versus 120.6 ± 2.4 mmHg) and diastolic BP (76.6 ± 1.9 mmHg versus 75.8 ± 2.0 mmHg)

Analysis 6.7. Comparison 6: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both), Outcome 7: Serum potassium: data from cross-over studies

Serum potassium: data from cross-over studies

Study	Comparison	Description of outcome
Tylicki 2012	Eplerenone plus telmisartan 80 mg daily versus telmisartan 160 mg daily	During the 24 week study period, there was no difference between eplerenone plus telmisartan 80 mg/day group versus telmisartan 160 mg/day in serum potassium (4.28 ± 0.08 mmol/L versus 4.45 ± 0.01 mmol/L)

Comparison 7. Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both) plus nitrate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Proteinuria: descriptive outcome data	1		Other data	No numeric data
7.2 Systolic BP: descriptive outcome data	1		Other data	No numeric data

Analysis 7.1. Comparison 7: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both) plus nitrate, Outcome 1: Proteinuria: descriptive outcome data

Proteinuria: descriptive outcome data

Study	Comparison	Description of outcome
Cohen 2010	Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both) plus isosorbide	Urine protein excretion was reduced by 1.04 ± 0.4 g/24 h in the eplerenone group but increased in the ACEi/ARB plus isosorbide group by 0.2 ± 0.3 g/24 h

Analysis 7.2. Comparison 7: Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both) plus nitrate, Outcome 2: Systolic BP: descriptive outcome data

Systolic BP: descriptive outcome data

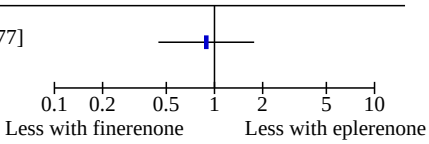
Study	Comparison	Description of outcome
Cohen 2010	Eplerenone plus ACEi or ARB (or both) versus ACEi or ARB (or both) plus isosorbide	Systolic blood pressure was reduced by 9.7 ± 6.4 mm Hg in the eplerenone group and by 1.0 ± 5.4 mm Hg in the ACEi/ARB plus isosorbide group

Comparison 8. Finerenone versus eplerenone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Hyperkalaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.3 eGFR: descriptive outcome data	1		Other data	No numeric data
8.4 Doubling serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.5 Blood pressure: descriptive outcome data	1		Other data	No numeric data

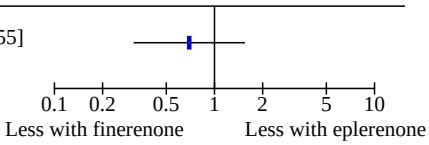
Analysis 8.1. Comparison 8: Finerenone versus eplerenone, Outcome 1: Hyperkalaemia

Study or Subgroup	Finerenone Events	Finerenone Total	Eplerenone Events	Eplerenone Total	Risk Ratio M-H, Random, 95% CI
ARTS-HF 2015	34	811	10	212	0.89 [0.45 , 1.77]



Analysis 8.2. Comparison 8: Finerenone versus eplerenone, Outcome 2: Death

Study or Subgroup	Finerenone Events	Finerenone Total	Eplerenone Events	Eplerenone Total	Risk Ratio M-H, Random, 95% CI
ARTS-HF 2015 (1)	21	834	8	221	0.70 [0.31 , 1.55]



Footnotes

(1) Cardiovascular death

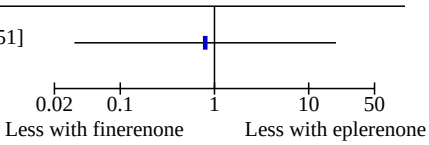
Analysis 8.3. Comparison 8: Finerenone versus eplerenone, Outcome 3: eGFR: descriptive outcome data

eGFR: descriptive outcome data

Study	Comparison	Description of outcome
ARTS-HF 2015	Finerenone versus eplerenone	At day 90, there was no significant change in eGFR from baseline in finerenone groups (mean change in eGFR range -2.4 to 1.3 mL/min/1.73 m^2) versus eplerenone (mean change in eGFR -1.1 mL/min/1.73 m^2)

Analysis 8.4. Comparison 8: Finerenone versus eplerenone, Outcome 4: Doubling serum creatinine

Study or Subgroup	Finerenone Events	Finerenone Total	Eplerenone Events	Eplerenone Total	Risk Ratio M-H, Random, 95% CI
ARTS-HF 2015 (1)	1	834	0	221	0.80 [0.03 , 19.51]



Footnotes

(1) Reported as eGFR >57% (equivalent to doubling of serum creatinine)

Analysis 8.5. Comparison 8: Finerenone versus eplerenone, Outcome 5: Blood pressure: descriptive outcome data

Blood pressure: descriptive outcome data

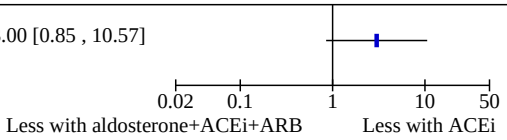
Study	Comparison	Description of outcome
ARTS-HF 2015	Finerenone versus eplerenone	In patients with worsening heart failure with reduced ejection fraction, there was no difference between the systolic BP in the finerenone groups (LS mean change in systolic BP from baseline range -0.8 to -2.7 mmHg) compared to eplerenone group (LS mean change in systolic BP from baseline -2.4 mmHg)

Comparison 9. Spironolactone plus ACEi and ARB versus ACEi

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Hyperkalaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2 Proteinuria	1		Other data	No numeric data
9.3 eGFR [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.4 Systolic BP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.5 Diastolic BP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.6 Serum potassium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.7 Gynaecomastia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Spironolactone plus ACEi and ARB versus ACEi, Outcome 1: Hyperkalaemia

	Aldosterone+ACEi+ARB		ACEi		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Bianchi 2010	9	64	3	64	3.00 [0.85 , 10.57]	



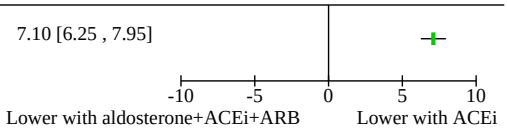
Analysis 9.2. Comparison 9: Spironolactone plus ACEi and ARB versus ACEi, Outcome 2: Proteinuria

Proteinuria

Study	Comparison	Description of outcome
Bianchi 2010	Spironolactone, ramipril, irbesartan (intensive group) versus spironolactone, ramipril (conventional group)	At month 36, proteinuria was significantly lower in the intensive group (end of study median proteinuria 0.45 g/g Cr, IQR 0.14 to 1.51) compared to conventional group (end of study median proteinuria 1.23 g/g Cr, IQR 0.36 to 3.42)

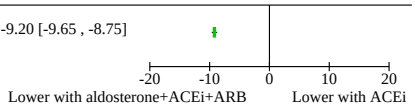
Analysis 9.3. Comparison 9: Spironolactone plus ACEi and ARB versus ACEi, Outcome 3: eGFR [mL/min/1.73 m^2]

	Aldosterone+ACEi+ARB			ACEi			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Bianchi 2010	62.9	2.9	64	55.8	1.9	64	7.10 [6.25 , 7.95]	



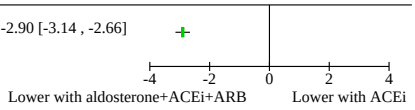
Analysis 9.4. Comparison 9: Spironolactone plus ACEi and ARB versus ACEi, Outcome 4: Systolic BP

Study or Subgroup	Aldosterone+ACEi+ARB Mean [mmHg]	SD [mmHg]	Total	ACEi Mean [mmHg]	SD [mmHg]	Total	Mean Difference IV, Random, 95% CI [mmHg]
Bianchi 2010	113.5	1.4	64	122.7	1.2	64	-9.20 [-9.65 , -8.75]



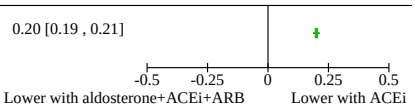
Analysis 9.5. Comparison 9: Spironolactone plus ACEi and ARB versus ACEi, Outcome 5: Diastolic BP

Study or Subgroup	Aldosterone+ACEi+ARB Mean [mmHg]	SD [mmHg]	Total	ACEi Mean [mmHg]	SD [mmHg]	Total	Mean Difference IV, Random, 95% CI [mmHg]
Bianchi 2010	72.3	0.7	64	75.2	0.7	64	-2.90 [-3.14 , -2.66]



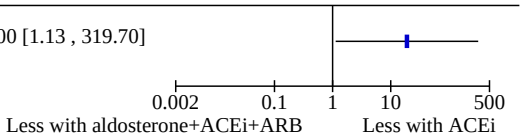
Analysis 9.6. Comparison 9: Spironolactone plus ACEi and ARB versus ACEi, Outcome 6: Serum potassium

Study or Subgroup	Aldosterone+ACEi+ARB Mean [mEq/L]	SD [mEq/L]	Total	ACEi Mean [mEq/L]	SD [mEq/L]	Total	Mean Difference IV, Random, 95% CI [mEq/L]
Bianchi 2010	5	0.04	64	4.8	0.04	64	0.20 [0.19 , 0.21]



Analysis 9.7. Comparison 9: Spironolactone plus ACEi and ARB versus ACEi, Outcome 7: Gynaecomastia

Study or Subgroup	Aldosterone+ACEi+ARB Events	Total	ACEi Events	Total	Risk Ratio M-H, Random, 95% CI
Bianchi 2010	9	64	0	64	19.00 [1.13 , 319.70]



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Aldosterone Antagonists explode all trees 2. (Canrenoate Potassium*):ti,ab,kw in Clinical Trials 3. (Canrenone*):ti,ab,kw in Clinical Trials 4. (spironolactone*):ti,ab,kw in Clinical Trials 5. (aldosterone antagonist*):ti,ab,kw in Clinical Trials 6. (aldactone*):ti,ab,kw in Clinical Trials 7. (practon*):ti,ab,kw in Clinical Trials 8. (sc-9420*):ti,ab,kw in Clinical Trials

(Continued)

	9. (spiractin*):ti,ab,kw in Clinical Trials 10.(sc-14266*):ti,ab,kw in Clinical Trials 11.(soldactone*):ti,ab,kw in Clinical Trials 12.(soludactone*):ti,ab,kw in Clinical Trials 13.(aldadiene*):ti,ab,kw in Clinical Trials 14.(phanurane*):ti,ab,kw in Clinical Trials 15.(sc-9376*):ti,ab,kw in Clinical Trials 16.(eplerenone*):ti,ab,kw in Clinical Trials 17.(finerenone*):ti,ab,kw in Clinical Trials 18.{and #1-#17} 19.MeSH descriptor Renal Insufficiency, Chronic explode all trees 20.(chronic kidney disease* or chronic renal disease*):ti,ab,kw in Clinical Trials 21.(chronic kidney failure* or chronic renal failure*):ti,ab,kw in Clinical Trials 22.(chronic kidney insufficiency or chronic renal insufficiency):ti,ab,kw in Clinical Trials 23.MeSH descriptor Renal Insufficiency, this term only 24.MeSH descriptor Kidney Diseases, this term only 25.(CKF or CKD or CRF or CRD):ti,ab,kw in Trials 26.(predialysis or pre-dialysis):ti,ab,kw in Trials 27.MeSH descriptor Uremia, this term only 28.uremia or uraemia or uremic or uraemic:ti,ab,kw in Trials 29.MeSH descriptor Diabetic Nephropathies, this term only 30.(diabetic nephropath*):ti,ab,kw in Trials 31."diabetic kidney disease":ti,ab,kw in Trials 32.{and #19-#31} 33.(#18 AND #32)
MEDLINE	1. exp Aldosterone Antagonists/ 2. Canrenoate Potassium.tw. 3. Canrenone$.tw. 4. spironolactone$.tw. 5. aldosterone antagonist$.tw. 6. aldactone$.tw. 7. practon$.tw. 8. sc-9420$.tw. 9. spiractin$.tw. 10.sc-14266$.tw. 11.soldactone$.tw. 12.soludactone$.tw. 13.aldadiene$.tw. 14.phanurane$.tw. 15.sc-9376.tw. 16.eplerenone$.tw. 17.Finerenone.tw 18.or/1-17 19.Renal Insufficiency/ 20.exp Renal Insufficiency, Chronic/ 21.Kidney Diseases/ 22.(chronic kidney or chronic renal).tw. 23.(CKF or CKD or CRF or CRD).tw. 24.(predialysis or pre-dialysis).tw. 25.exp Uremia/ 26.uremi.tw.

(Continued)

	27.(pre-dialy$ or predialy$).tw. 28.Diabetic Nephropathies/ 29.diabetic nephropath$.tw. 30."diabetic kidney disease".tw. 31.or/18-29 32.and/18,31
EMBASE	1. exp Aldosterone Antagonist/ 2. aldosterone antagonist$.tw. 3. spironolactone$.tw. 4. eplerenone$.tw. 5. soludactone$.tw. 6. canrenoate potassium.tw. 7. canrenone$.tw. 8. Finerenone 9. or/1-8 10.Kidney Disease/ 11.Chronic Kidney Disease/ 12.Kidney Failure/ 13.Chronic Kidney Failure/ 14.Kidney dysfunction/ 15.(chronic kidney or chronic renal).tw. 16.(CKF or CKD or CRF or CRD).tw. 17.(pre-dialy$ or predialy$).tw. 18.diabetic nephropathy/ 19."diabetic kidney disease".tw. 20.or/9-18 21.and/9,20

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	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: 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.
	Unclear: 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	*Low risk of bias:* 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).

(Continued)

	High risk of bias: 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.
	Unclear: 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	*Low risk of bias*: 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.
	High risk of bias: 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.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* 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.
	High risk of bias: 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.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* 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 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 standardized 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. subscales) 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 can-

(Continued)

	not 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.

WHAT'S NEW

Date	Event	Description
15 September 2020	New citation required but conclusions have not changed	New studies added; no change to conclusions
13 January 2020	New search has been performed	New search update

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 3, 2009

Date	Event	Description
28 April 2014	New citation required and conclusions have changed	10 new studies added, new comparisons added
30 January 2013	New search has been performed	New update search completed, new studies identified
22 February 2012	Amended	Update search completed
20 February 2012	Amended	Search methods & search strategies updated
2 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review: EC, SP, GS
- Screening of titles and abstracts: EC, MR, PN, SP
- Assessment for inclusion: EC, MR, PN, SP
- Quality assessment: EC, MR, PN, SP
- Data extraction: EC, MR, PN, SP
- Data entry into RevMan: EC, MR, PN, SP
- Data analysis and interpretation: All authors

- Disagreement resolution: GS

DECLARATIONS OF INTEREST

- Edmund YM Chung: none known
- Marinella Ruospo: none known
- Patrizia Natale: none known
- Davide Bolignano: none known
- Sankar D Navaneethan: none known
- Suetonia C Palmer: none known
- Giovanni FM Strippoli: none known

INDEX TERMS

Medical Subject Headings (MeSH)

Angiotensin Receptor Antagonists [*therapeutic use]; Angiotensin-Converting Enzyme Inhibitors [*therapeutic use]; Disease Progression; Eplerenone; Hyperkalemia [chemically induced] [prevention & control]; Kidney Failure, Chronic [*drug therapy]; Mineralocorticoid Receptor Antagonists [adverse effects] [*therapeutic use]; Proteinuria [*drug therapy]; Randomized Controlled Trials as Topic; Spironolactone [adverse effects] [analogs & derivatives] [therapeutic use]

MeSH check words

Humans