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Aldosterone antagonists for people with chronic kidney disease requiring dialysis (Review)

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[Intervention Review]

Aldosterone antagonists for people with chronic kidney disease requiring dialysis

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ABSTRACT

Background

People with chronic kidney disease (CKD) requiring dialysis are at a particularly high risk of cardiovascular death and morbidity. Several clinical studies suggested that aldosterone antagonists would be a promising treatment option for people undergoing dialysis. However, the clinical efficacy and potential harm of aldosterone antagonists for people with CKD on dialysis has yet to be determined.

Objectives

This review aimed to evaluate the benefits and harms of aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), in comparison to control (placebo or standard care) in people with CKD requiring haemodialysis (HD) or peritoneal dialysis (PD).

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 5 August 2020 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 parallel randomised controlled trials (RCTs), cross-over RCTs, and quasi-RCTs (where group allocation is by a method that is not truly random, such as alternation, assignment based on alternate medical records, date of birth, case record number, or other predictable methods) that compared aldosterone antagonists with placebo or standard care in people with CKD requiring dialysis.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias for included studies. We used a random-effects model meta-analysis to perform a quantitative synthesis of the data. We used the I^2 statistic to measure heterogeneity among the studies in each analysis. We indicated summary estimates as a risk ratio (RR) for dichotomous outcomes, mean difference (MD) for continuous outcomes, or standardised mean differences (SMD) if different scales were used, with their 95% confidence interval (CI). We assessed the certainty of the evidence for each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach.

Main results

We included 16 studies (14 parallel RCTs and two cross-over RCTs) involving a total of 1446 participants. Thirteen studies compared spironolactone to placebo or standard care and one study compared eplerenone to a placebo. Most included studies had an unclear or high risk of bias. Compared to control, aldosterone antagonists probably reduced the risk of death (any cause) for people with CKD requiring dialysis (9 studies, 1119 participants: RR 0.45, 95% CI 0.30 to 0.67; I^2 = 0%; moderate certainty of evidence). Aldosterone antagonist probably decreased the risk of death due to cardiovascular disease (6 studies, 908 participants: RR 0.37, 95% CI 0.22 to 0.64; I^2 = 0%; moderate certainty of evidence) and cardiovascular and cerebrovascular morbidity (3 studies, 328 participants: RR 0.38, 95% CI 0.18 to 0.76; I^2 = 0%; moderate certainty of evidence). While aldosterone antagonists probably increased risk of gynaecomastia compared with control (4 studies, 768 participants: RR 5.95, 95% CI 1.93 to 18.3; I^2 = 0%; moderate certainty of evidence), aldosterone antagonists may make little or no difference to the risk of hyperkalaemia (9 studies, 981 participants: RR 1.41, 95% CI 0.72 to 2.78; I^2 = 47%; low certainty of evidence). Aldosterone antagonists had a marginal effect on left ventricular mass among participants undergoing dialysis (8 studies, 633 participants: SMD -0.42, 95% CI -0.78 to 0.05; I^2 = 77%).

In people with CKD requiring dialysis received aldosterone antagonists compared to control, there were 72 fewer deaths from all causes per 1000 participants (95% CI 47 to 98) with a number needed to treat for an additional beneficial outcome (NNTB) of 14 (95% CI 10 to 21) and for gynaecomastia were 26 events per 1000 participants (95% CI 15 to 39) with a number need to treat for an additional harmful outcome (NNTH) of 38 (95% CI 26 to 68).

Authors' conclusions

Based on moderate certainty of the evidence, aldosterone antagonists probably reduces the risk of all-cause and cardiovascular death and probably reduces morbidity due to cardiovascular and cerebrovascular disease in people with CKD requiring dialysis. For the adverse effect of gynaecomastia, the risk was increased compared to control. For this outcome, the absolute risk was lower than the absolute risk of death. It is hoped the three large ongoing studies will provide better certainty of evidence.

PLAIN LANGUAGE SUMMARY

Aldosterone antagonists for people with chronic kidney disease requiring dialysis

What is the issue?

People with chronic kidney disease (CKD) requiring dialysis are at an increased risk of death and other illnesses. One particular cause of this is an increased risk of heart disease. Aldosterone antagonists (e.g. spironolactone or eplerenone) are one kind of drug for treating high blood pressure that may be a promising treatment option for these people, but which can be associated with adverse effects such as high potassium concentration in the blood (also called hyperkalaemia). This high potassium concentration in the blood may be potentially harmful in people undergoing dialysis.

What did we do?

We searched the literature up until 5 August 2020 and identified 16 studies enrolling 1446 patients with kidney failure undergoing dialysis. These studies compared aldosterone antagonists to placebo (inactive treatment) or usual care.

What did we find?

Based on moderate certainty of the evidence, this review showed that people with CKD taking aldosterone antagonists probably had a reduced risk of death from any cause and a reduced risk of death specifically arising from heart disease. Aldosterone antagonists did not appear to increase potassium concentrations in the blood. However, there is moderate evidence that some men with CKD undergoing dialysis may have an increase development of breast tissue (also called gynaecomastia) as a result of taking aldosterone antagonists.

Conclusions

We concluded that aldosterone antagonists probably reduce the risk of death and heart disease but could increase the risk of gynaecomastia for people on dialysis. More studies are needed to clarify how effective and safe aldosterone antagonists are in people with CKD requiring dialysis.

SUMMARY OF FINDINGS

Summary of findings 1. Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or standard care) for people with chronic kidney disease requiring dialysis

Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or standard care) for people with chronic kidney disease requiring dialysis

Patient or population: people with chronic kidney disease requiring dialysis
Setting: haemodialysis and peritoneal dialysis
Intervention: aldosterone antagonists (spironolactone or eplerenone)
Comparison: control (placebo or standard care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)
	Risk with control (placebo or standard care)	Risk with aldosterone antagonists (spironolactone or eplerenone)			
Death (any cause)	131 per 1,000	59 per 1,000 (39 to 88)	RR 0.45 (0.30 to 0.67)	1119 (9)	⊕⊕⊕⊖ MODERATE [1]
Death (cardiovascular)	101 per 1,000	37 per 1,000 (22 to 65)	RR 0.37 (0.22 to 0.64)	908 (6)	⊕⊕⊕⊖ MODERATE [1]
Cardiovascular and cerebrovascular morbidity	133 per 1,000	51 per 1,000 (24 to 101)	RR 0.38 (0.18 to 0.76)	328 (3)	⊕⊕⊕⊖ MODERATE [1]
Hyperkalaemia	91 per 1,000	128 per 1,000 (66 to 253)	RR 1.41 (0.72 to 2.78)	981 (9)	⊕⊕⊖⊖ LOW [1 2]
Gynaecomastia	5 per 1,000	31 per 1,000 (10 to 95)	RR 5.95 (1.93 to 18.28)	768 (4)	⊕⊕⊕⊖ MODERATE [1]
Left ventricular mass Measured with different units in the different studies. Lower number mean less hypertrophy	Left ventricular mass in the aldosterone antagonist group was 0.42 **standard deviations** lower (0.05 to 0.78 lower) compared to placebo or standard care*		--	562 (7)	⊕⊖⊖⊖ LOW [1 3]

*__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).

CI: Confidence interval; **RCT:** randomised controlled trial; **RR:** Risk ratio; **SMD:** standardised mean difference

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

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[1] The total size of the included in the analysis for this outcome were less than optimal information size.
[2] There is inconsistency in the definition of hyperkalaemia between the included studies.
[3] There is inconsistency in the measurement and calculation methods of left ventricular mass between the included studies.
* Rule of thumb according to Cohen's interpretation of effect size

- < 0.41 represents a small effect
- 0.40 to 0.70 represents and moderate effect
- > 0.70 represents a large effect

BACKGROUND

Description of the condition

Over 2.6 million people were estimated to have end-stage kidney disease (ESKD) requiring dialysis worldwide in 2010, with this number expected to more than double by 2030 (Liyanage 2015). Accordingly, the global health burden arising from people with ESKD needing kidney replacement therapy (KRT) has been rapidly increasing in recent years.

People with ESKD requiring dialysis have especially high risk of cardiovascular death and morbidity (Foley 1998; USRDS 2017a). Hypertension, heart failure, and left ventricular hypertrophy are particularly common among people with chronic kidney disease (CKD) undergoing dialysis. The recent epidemiological data based on the US Renal Data System (USRDS) (USRDS 2017a) revealed that the prevalence of any cardiovascular disease was more common in people receiving haemodialysis (HD) (69.8%) than those receiving peritoneal dialysis (PD) (56.6%). The USRDS also showed that 48% of deaths in this population were due to cardiovascular events including arrhythmia/cardiac arrest, acute myocardial infarction and atherosclerotic heart disease, and congestive heart failure (USRDS 2017b). These features greatly contribute to their death and morbidity (Foley 1995; Harnett 1995; Salem 1995; USRDS 2017a; USRDS 2017b).

In healthy people, aldosterone is a mineral corticosteroid hormone produced by the adrenal gland, which regulates water and salt balance in the body by stimulating absorption of sodium and excretion of potassium by the kidneys. However, excess aldosterone induces cardiac fibrosis and vascular damage, and consequently can result in heart failure and kidney injury. In people requiring dialysis, serum aldosterone concentration can be elevated and independently associated with left ventricular hypertrophy (Sato 1999; Steigerwalt 2007). Therefore, it has been postulated that aldosterone antagonists would be a promising therapeutic option for people on dialysis with cardiovascular disease. Moreover, the decreased residual kidney function could result in possible harm because potassium excretion by the kidneys needs tubular flow of urine.

Description of the intervention

Aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), are oral antihypertensive pharmaceutical agents that block the effect of aldosterone at the mineralocorticoid receptors in myocardium, endothelium, and vascular smooth muscles. Administration of aldosterone antagonists may raise serum potassium especially in people without residual kidney function, and the major concern of its use in people requiring dialysis is life-threatening hyperkalaemia. However, several investigations have suggested that aldosterone antagonists can be safely given to people with ESKD on dialysis (Gross 2005; PHASE 2015; Saudan 2003).

How the intervention might work

Previous studies have shown protective effects of aldosterone antagonists on death and morbidity in people with cardiovascular disease (Pitt 1999; Pitt 2003). Addition of aldosterone antagonists to renin-angiotensin system (RAS) inhibitors may address problems with the 'aldosterone escape phenomenon' (Staessen 1981) - a phenomenon which describes the incomplete suppression of serum aldosterone levels with RAS inhibitors alone - and could further improve clinical outcomes of people with heart failure (Yancy 2013).

Recent randomised controlled trials (RCTs) involving people with ESKD who are on dialysis have evaluated the role of both spironolactone and eplerenone in death, morbidity, blood pressure, serum potassium, and on echocardiographic findings including left ventricular mass and ejection fraction (Feniman-De-Stefano 2015; Gross 2005; Saudan 2003; Taheri CAPD 2012; Taheri HD 2009). It has been reported that spironolactone may lower blood pressure without also resulting in hyperkalaemia in people receiving HD (Gross 2005; Ni 2014). On the other, one RCT found that eplerenone increased serum potassium levels slightly with no effect on blood pressure (PHASE 2015). Other RCTs have found that spironolactone prevented progression of left ventricular hypertrophy irrespective of blood pressure control in people on PD (Ito 2014) and HD (Feniman-De-Stefano 2015). Furthermore, Matsumoto 2014 indicated the effects of spironolactone on cardiovascular and cerebrovascular morbidity and death in people receiving HD in an RCT with a three-year follow-up. A more recent RCT has also shown that spironolactone reduced the risk of cardiovascular death and morbidity and improved cardiovascular-related indexes in people requiring dialysis without heart failure (Lin 2016a).

Why it is important to do this review

Previous systematic reviews have shown that aldosterone antagonists reduces proteinuria and blood pressure but increases hyperkalaemia in people with CKD who are not receiving dialysis, and that it improves survival of patients with chronic heart failure in combination with CKD (Bolignano 2014). Recently, Quach 2016 published a non-Cochrane systematic review that involved a meta-analysis of nine studies (829 patients) testing the safety and efficacy of aldosterone antagonists in people receiving dialysis. This investigation reported that patients undergoing dialysis who were treated with aldosterone antagonists had a reduced relative risk (RR) for cardiovascular and death (any cause) compared with control patients (RR 0.34, 95% CI 0.15 to 0.75 and RR 0.40, 95% CI 0.23 to 0.69, respectively). The authors also indicated that aldosterone antagonists tended to cause hyperkalaemia (RR 3.05, 95% CI 1.21 to 7.70). However, there is still some uncertainty about both the benefits and harms of aldosterone antagonists for people with CKD requiring dialysis. Indeed, since completion of the review by Quach 2016, a new, large RCT (n = 258) has been published, which assesses the long-term (two years) effects and adverse events in this population (Lin 2016a). Furthermore, the meta-analysis by Quach 2016 only evaluated cardiovascular and death (any cause), hyperkalaemia, blood pressure including hypotension events, and gynaecomastia. The other important surrogate outcomes such as cardiovascular-related indexes, including left ventricular mass based on echocardiographic findings (which would consequently affect the prognosis of the people requiring dialysis) have never been systematically evaluated. There are also several ongoing trials including ACHIEVE 2017 and ALCHEMIST 2014 which will provide addition data on this important issue. Finally, the financial burden of cardiovascular death and morbidity among dialysis population is huge. Aldosterone antagonists may provide an important low-cost treatment option if they are found to be clinically effective.

OBJECTIVES

This review aimed to assess the benefits and harms of aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), in comparison to placebo or no intervention or standard care in people with ESKD requiring HD or PD.

METHODS

Criteria for considering studies for this review

Types of studies

All parallel-group RCTs, cross-over trials, and quasi-RCTs (where group allocation is by a method that is not truly random, such as alternation, assignment based on alternate medical records, date of birth, case record number, or other predictable methods) looking at aldosterone antagonists use, both non-selective (spironolactone) and selective (eplerenone), in comparison to placebo or no intervention or standard care in people with ESKD requiring HD or PD.

Types of participants

Inclusion criteria

People with ESKD (CKD stage 5D) defined by Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines (Levey 2011), who are being treated with KRT including HD or PD.

Exclusion criteria

We excluded studies involving people with ESKD who have received a kidney transplant.

Types of interventions

We included studies comparing aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), to placebo, no intervention, standard care, or head-to head studies.

Types of outcome measures

The outcomes selected included the relevant SONG core outcome sets as specified by the Standardised Outcomes in Nephrology initiative (SONG 2017). The outcome measures in studies did not form part of the inclusion/exclusion criteria.

Primary outcomes

1. Death (any cause)*
2. Death (cardiovascular)*
3. Cardiovascular* and cerebrovascular morbidity including but not limited to myocardial infarction, stroke, congestive heart failure
4. Hyperkalaemia

Secondary outcomes

1. Left ventricular mass based on echocardiographic findings
2. Ejection fraction based on echocardiographic findings
3. Residual kidney function
4. Serum potassium
5. Vascular access failure*
6. Fatigue score*
7. Gynaecomastia
8. Peritoneal function (only in people undergoing PD)

*SONG core outcomes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 5 August 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. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

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

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

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

Data collection and analysis

Selection of studies

We used the search strategy described above to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable. Studies and reviews that might have included relevant data or information on trials were retained. Two authors independently assessed retrieved abstracts and, if necessary, the full text, of these studies to determine which studies satisfy the inclusion criteria. Any disagreements were resolved through consensus with two authors or by a third author if consensus was not reached.

Data extraction and management

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

data were used. Any discrepancy between published versions was 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)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

We expressed dichotomous outcomes (e.g. death, cardiovascular and cerebrovascular morbidity, hyperkalaemia) as RR. We reported continuous outcome data (e.g. left ventricular mass and ejection fraction based on echocardiographic findings, residual kidney function, serum potassium) as mean differences (MD) if the same measurement scales were used, or as standardised mean differences (SMD) if different scales were used. We reported 95% confidence intervals (CI) for all outcomes.

Unit of analysis issues

We did not consider unit of analysis issues because we used data from parallel RCTs only.

Dealing with missing data

We requested further information from the original authors of included studies if this was required (e.g. emailing corresponding author) and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population were carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We 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). We interpreted the I^2 values 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

Where possible, we used funnel plots to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

We pooled data using the random-effects model but examined the influence of the fixed-effect model to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analysis to explore possible sources of heterogeneity (e.g. participants, interventions, and study quality). We tested the following subgroups.

- Dialysis modality: HD or PD.

Adverse effects were tabulated and assessed with descriptive techniques as they were likely to be different for the various agents used. Where possible, the risk difference with 95% CI was calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

We performed sensitivity analyses in order to explore the influence of the following factors on effect size: repeating the analysis excluding unpublished studies and excluding the studies at high risk of bias for allocation concealment and incomplete outcome data.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables for comparing aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), to placebo, no intervention, or standard care. These tables presented 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 included 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.

1. Death (any cause)*
2. Death(cardiovascular)*
3. Cardiovascular and cerebrovascular morbidity including but not limited to myocardial infarction, stroke, and congestive heart failure.

4. Hyperkalaemia
5. Gynaecomastia
6. Left ventricular mass based on echocardiographic finding

RESULTS

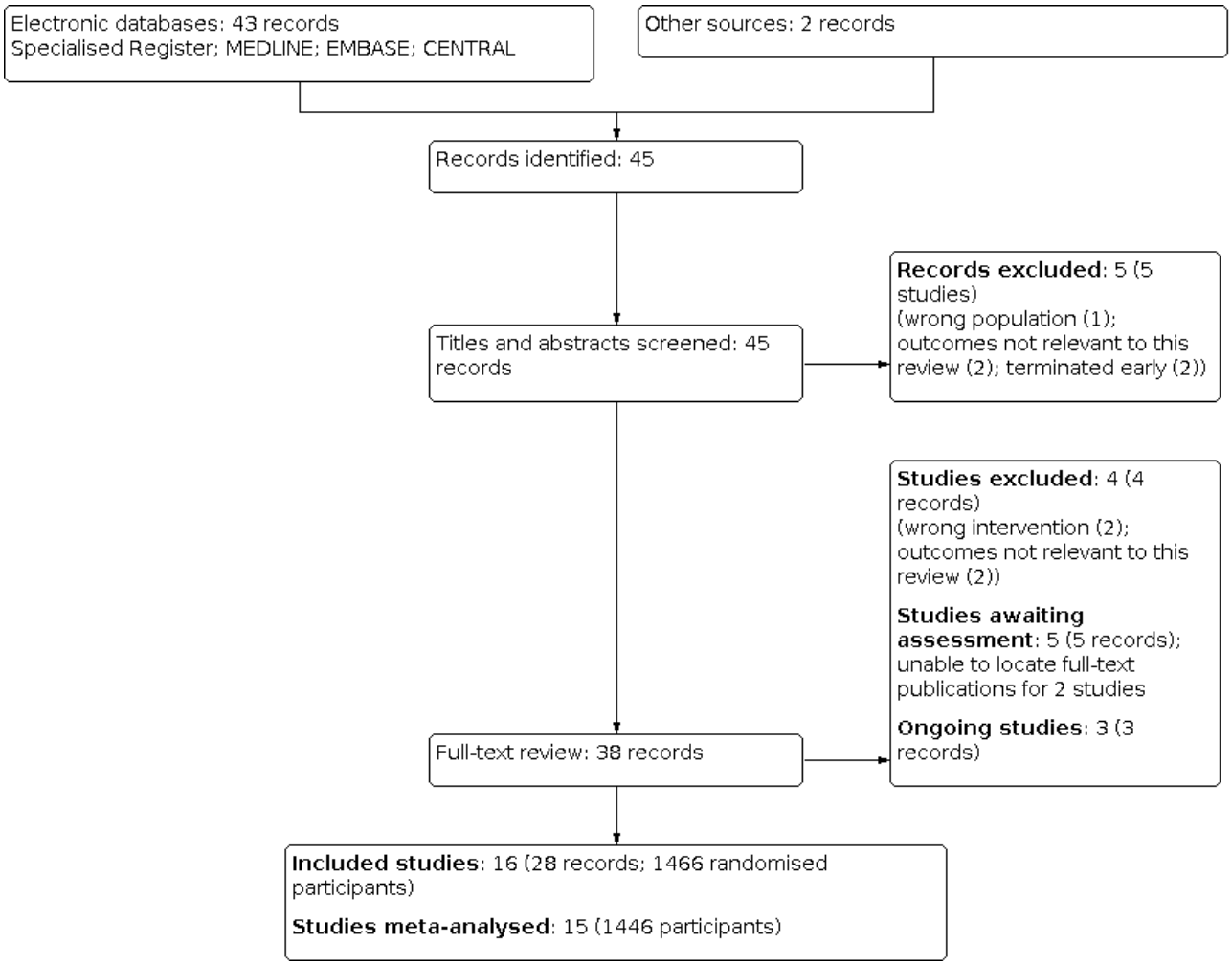
Description of studies

Results of the search

We identified 43 publications (31 studies) from the Cochrane Kidney and Transplant Register of Studies. After screening, nine studies were excluded (Eklund 2016; EPURE 2018; Essaian 2007; Host 2000; Koh 2010; LAST-D 2013; Nakao 2007; NCT00328809; Witoon 2019), two studies are awaiting classification (Gueiros 2019; NCT02190318), and three studies are ongoing (ACHIEVE 2017; ALCHEMIST 2014: NCT00277693). We identified two additional studies (Song 2017; Wang 2018) from a recent non-Cochrane systematic review (Li 2019). These studies are awaiting assessment while we attempt to access the full text publications.

A total of 16 studies (28 records, 1466 participants) were included, 9 excluded, 5 studies are awaiting assessment, and there are 3 ongoing studies (Figure 1).

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies.

Fourteen studies were parallel RCTs (Feniman De Stefano 2015; MiREnDa 2014; Ito 2014; Lin 2016a; Matsumoto 2014; Ni 2014; PHASE 2015; SPIN-D 2019; Taheri CAPD 2012; Taheri HD 2009; Vazquez-Rangel 2014; Vukusich 2010; Zaripova 2012; Ziaee 2019), and two were cross-over studies (Gross 2005; Yongsiri 2015). The results of Vazquez-Rangel 2014 could not be meta-analysed because outcomes of interest for this review were not available.

Eleven studies only included HD patients (Feniman De Stefano 2015; Gross 2005; Matsumoto 2014; MiREnDa 2014; Ni 2014; PHASE 2015; SPIN-D 2019; Taheri HD 2009; Vukusich 2010; Zaripova 2012; Ziaee 2019), four studies only included PD patients (Ito 2014; Taheri CAPD 2012; Vazquez-Rangel 2014; Yongsiri 2015), and one study included both HD and PD patients (Lin 2016a).

Sample size ranged from 8 to 309 participants. Seven studies were multicentre (Ito 2014; Lin 2016a; Matsumoto 2014; MiREnDa 2014; Ni 2014; PHASE 2015; SPIN-D 2019) and eight were single-centre studies (Feniman De Stefano 2015; Gross 2005; Taheri CAPD

2012; Taheri HD 2009; Vukusich 2010; Yongsiri 2015; Zaripova 2012; Ziaee 2019). There were 1147 participants undergoing HD and 299 undergoing PD.

Fourteen studies compared non-selective aldosterone antagonist (spironolactone) to either placebo (Feniman De Stefano 2015; Gross 2005; MiREnDa 2014; Ni 2014; SPIN-D 2019; Taheri CAPD 2012; Taheri HD 2009; Vukusich 2010; Yongsiri 2015) or standard care (Ito 2014; Lin 2016a; Matsumoto 2014; Zaripova 2012; Ziaee 2019). One study (PHASE 2015) compared selective aldosterone antagonist (eplerenone) to placebo. The doses were as follows:

- Spironolactone
  - 25 mg/day: 10 studies (Feniman De Stefano 2015; Ito 2014; Lin 2016a; Matsumoto 2014; Ni 2014; Taheri CAPD 2012; Taheri HD 2009; Vazquez-Rangel 2014; Yongsiri 2015; Zaripova 2012)
  - 12.5 mg, 25 mg or 50 mg/day: 1 study (SPIN-D 2019)
  - 50 mg/day: 1 study (MiREnDa 2014)
  - 100 mg/day: 1 study (Gross 2005)
  - 50 mg/HD: 1 study (Vukusich 2010)
  - 25 mg/HD: 1 study (Ziaee 2019).
- Eplerenone
  - 50 mg/day: 1 study (PHASE 2015).

The following reported outcomes were included in quantitative syntheses for this review:

- Death (any cause): nine studies (Ito 2014; Lin 2016a; Matsumoto 2014; MiREnDa 2014; PHASE 2015; Taheri CAPD 2012 Taheri HD 2009; Vukusich 2010; Ziaee 2019) (1119 participants)
- Death (cardiovascular): six studies (Ito 2014; Lin 2016a; Matsumoto 2014; PHASE 2015; Taheri CAPD 2012 Taheri HD 2009) (908 participants)
- Cardiovascular and cerebrovascular morbidity: three studies (Ito 2014; PHASE 2015; Taheri HD 2009) (328 participants)
  - Ito 2014 only reported acute myocardial infarction events
  - Taheri HD 2009 reported hospitalisation due to cardiovascular events
  - PHASE 2015 reported fatal or nonfatal cardiovascular events.
- Hyperkalaemia: nine studies (SPIN-D 2019; MiREnDa 2014; Ito 2014; Matsumoto 2014; Ni 2014; Taheri HD 2009; Taheri CAPD 2012; PHASE 2015; Yongsiri 2015) (981 participants)
  - Hyperkalaemia was defined as serum potassium level > 5.0 mEq/L (Ni 2014); > 5.5 mEq/L (Taheri CAPD 2012; Taheri HD 2009; Yongsiri 2015); > 6.0 mEq/L (MiREnDa 2014; Ito 2014); > 6.5 mEq/L (Matsumoto 2014; SPIN-D 2019); and > 6.8 mEq/L (Matsumoto 2014).
- Gynaecomastia: four studies (Ito 2014; Lin 2016a; Matsumoto 2014; Ziaee 2019) (768 participants)
- Left ventricular mass: eight studies (Feniman De Stefano 2015; Ito 2014; Lin 2016a; MiREnDa 2014; SPIN-D 2019; Taheri HD 2009; Zaripova 2012; Ziaee 2019) (633 participants)
- Ejection fraction: seven studies (Feniman De Stefano 2015; MiREnDa 2014; Ito 2014; Lin 2016a; Taheri HD 2009; Taheri CAPD 2012; Ziaee 2019) (458 participants)
- Serum potassium: seven studies (SPIN-D 2019; Feniman De Stefano 2015; Gross 2005; Lin 2016a; Ni 2014; ; Yongsiri 2015; Ziaee 2019) (519 participants)
- Residual kidney function (urine volume/day): three studies (Gross 2005; Ni 2014; Yongsiri 2015) (132 participants)
- Vascular access failure, fatigue score, and peritoneal function: the data for these outcomes were either not reported in an extractable format, or not reported in any of the included studies.

Excluded studies

See Characteristics of excluded studies.

We excluded nine studies for the following reasons.

- Wrong population (EPURE 2018)
- Wrong interventions (Nakao 2007; Witoon 2019)
- Not designed to measure the outcomes of interest (Eklund 2016; Essaian 2007; Host 2000; Koh 2010)
- Withdrawn without being completed (LAST-D 2013; NCT00328809).

Risk of bias in included studies

The assessment of risk of bias in the included studies are shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

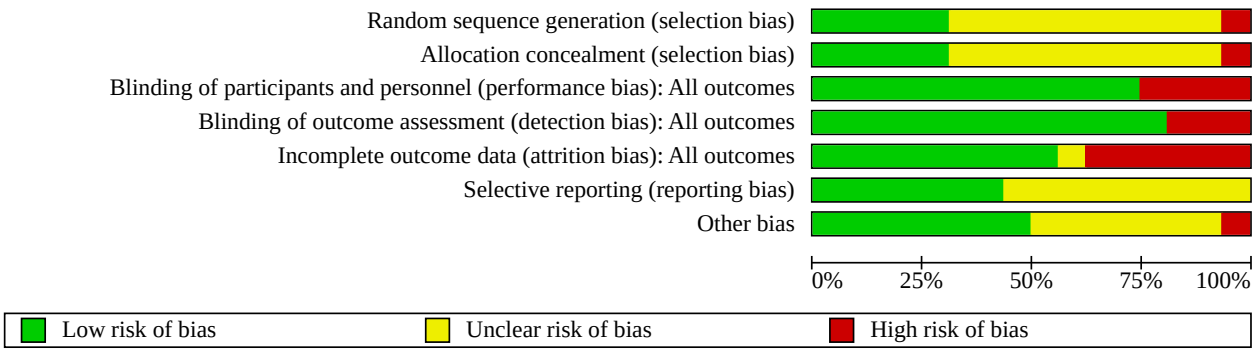
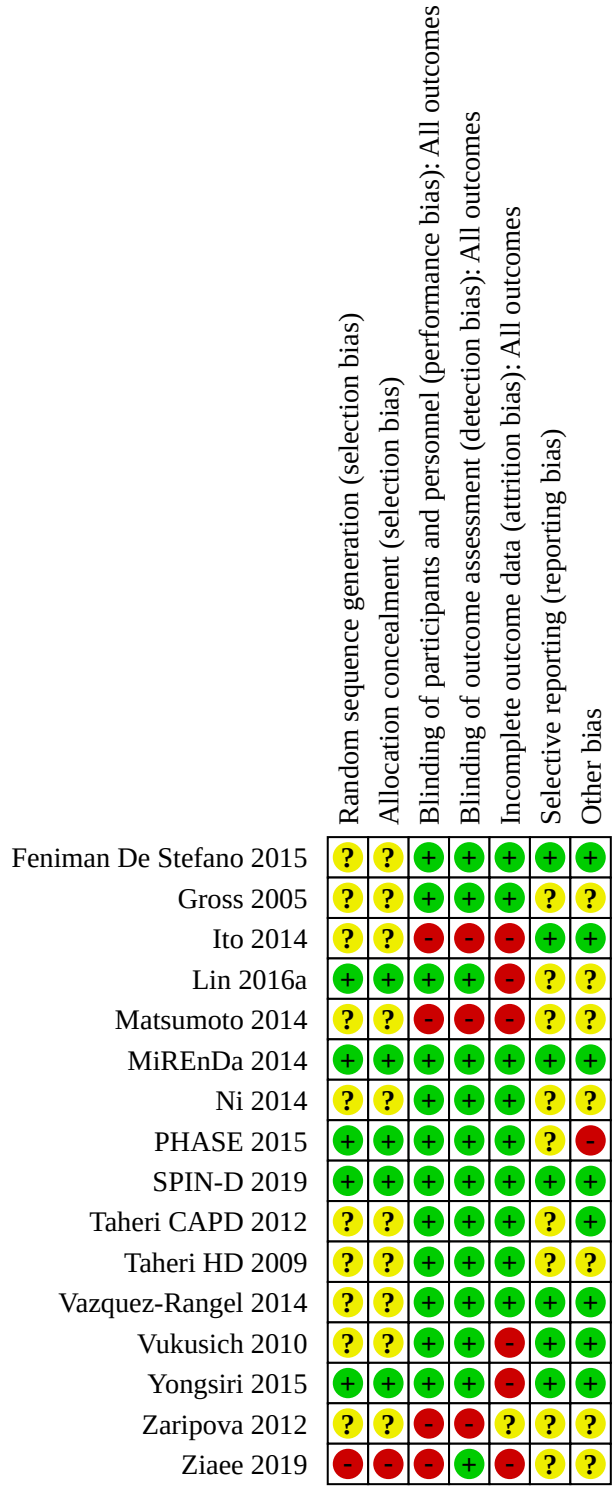


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Random sequence generation was judged to be at low risk of bias in five studies (Lin 2016a; MiREnDa 2014; PHASE 2015; SPIN-D 2019; Yongsiri 2015) and at high risk of bias in one quasi-RCT (odd or even days) (Ziaee 2019). The risk of bias was unclear in 10 studies (Feniman De Stefano 2015; Gross 2005; Ito 2014; Matsumoto 2014; Ni 2014; Taheri CAPD 2012; Taheri HD 2009; Vazquez-Rangel 2014; Vukusich 2010; Zaripova 2012).

Allocation concealment

Allocation concealment was judged to be at low risk of bias in five studies (Lin 2016a; MiREnDa 2014; PHASE 2015; SPIN-D 2019; Yongsiri 2015) and at high risk of bias in one quasi-randomised study (odd or even days) (Ziaee 2019). The risk of bias was unclear in 10 studies (Feniman De Stefano 2015; Gross 2005; Ito 2014; Matsumoto 2014; Ni 2014; Taheri CAPD 2012; Taheri HD 2009; Vazquez-Rangel 2014; Vukusich 2010; Zaripova 2012).

Blinding

Performance bias

Performance bias (blinding of participants and research personnel) was judged to be at low risk of bias in 12 studies (Feniman De Stefano 2015; Gross 2005; Lin 2016a; MiREnDa 2014; Ni 2014; PHASE 2015; SPIN-D 2019; Taheri CAPD 2012; Taheri HD 2009; Vazquez-Rangel 2014; Vukusich 2010; Yongsiri 2015). Three studies were open-label and judged to be high risk of bias (Ito 2014; Matsumoto 2014; Zaripova 2012), and in Ziaee 2019 the intervention group were given spironolactone (aldactone) acquired on the market after each HD session and was also judged to be at high risk of bias.

Detection bias

Detection bias (blinding of outcome assessors) was judged to be at low risk of bias in 13 studies (Feniman De Stefano 2015; Gross 2005; Lin 2016a; MiREnDa 2014; Ni 2014; PHASE 2015; SPIN-D 2019; Taheri CAPD 2012; Taheri HD 2009; Vazquez-Rangel 2014; Vukusich 2010; Yongsiri 2015; Ziaee 2019). Three studies were open-label and judged to be high risk of bias (Ito 2014; Matsumoto 2014; Zaripova 2012).

Incomplete outcome data

Eight studies were judged to be at as low risk for attrition bias because almost all of the participants were followed up and missing outcome data balanced across the intervention and control groups (Feniman De Stefano 2015; Gross 2005; MiREnDa 2014; Ni 2014; PHASE 2015; SPIN-D 2019; Taheri CAPD 2012; Taheri HD 2009). Six studies were judged to be at high risk for attrition bias as more than 10% of participants were not followed up and there was imbalance in numbers for missing data across the intervention and control groups (Ito 2014; Lin 2016a; Matsumoto 2014; Vukusich 2010; Yongsiri 2015; Ziaee 2019). One study with incomplete outcome data was judged unclear (Zaripova 2012).

Selective reporting

All the prespecified outcomes were reported in seven studies (SPIN-D 2019; Feniman De Stefano 2015; MiREnDa 2014; Ito 2014; Vazquez-Rangel 2014; Vukusich 2010; Yongsiri 2015). The remaining nine studies were classified as unclear for reporting bias because their study protocol was not available (Gross 2005; Lin 2016a; Matsumoto 2014; Ni 2014; Taheri CAPD 2012 Taheri HD 2009; PHASE 2015; Ziaee 2019; Zaripova 2012).

Other potential sources of bias

We judged eight studies to be at low risk of bias due to funding (Feniman De Stefano 2015; MiREnDa 2014; Ito 2014; SPIN-D 2019; Taheri HD 2009; Vazquez-Rangel 2014; Vukusich 2010; Yongsiri 2015). One study was judged to be at high risk of bias because it was partly funded by a pharmaceutical company (PHASE 2015). The risk of bias were judged to be unclear in the remaining seven studies as there was no reported information on funding (Gross 2005; Lin 2016a; Matsumoto 2014; Ni 2014; Taheri HD 2009; Ziaee 2019; Zaripova 2012).

Effects of interventions

See: **Summary of findings 1** Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or standard care) for people with chronic kidney disease requiring dialysis

See Summary of findings 1 (Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or standard care) for people with chronic kidney disease requiring dialysis)

Death (*any* cause)

Aldosterone antagonists probably reduces the risk of death (any cause) compared to control interventions (Analysis 1.1 (9 studies, 1119 participants): RR 0.45, 95% CI 0.30 to 0.67; I^2 = 0%; moderate certainty of evidence).

In people with CKD requiring dialysis received aldosterone antagonists compared to control, there were 72 fewer deaths from all causes per 1000 participants (95% CI 47 to 98) with a number needed to treat for an additional beneficial outcome (NNTB) of 14 (95% CI 10 to 21).

Death (cardiovascular)

Aldosterone antagonists probably reduces the risk of death due to cardiovascular events compared to control interventions (Analysis 1.2 (6 studies, 908 participants): RR 0.37, 95% CI 0.22 to 0.64; I^2 = 0%; moderate certainty of evidence).

In people receiving aldosterone antagonists compared to control, there were 64 fewer deaths from cardiovascular events per 1000 participants (95% CI 42 to 87) with a NNTB of 16 (95% CI 12 to 24).

Cardiovascular and cerebrovascular morbidity

Aldosterone antagonists probably reduces the risk of cardiovascular and cerebrovascular morbidity compared to control interventions (Analysis 1.3 (3 studies, 328 participants): RR 0.38, 95% CI 0.18 to 0.76; I^2 = 0%; moderate certainty of evidence).

In people receiving aldosterone antagonists compared to control, there were 82 fewer cardiovascular and cerebrovascular events per 1000 participants (95% CI 57 to 108) with a NNTB of 12 (95% CI 9 to 18).

Hyperkalaemia

Aldosterone antagonists may make little or no difference to the risk of hyperkalaemia compared to control interventions (Analysis 1.4 (9 studies, 981 participants): RR 1.41, 95% CI 0.72 to 2.78; I^2 = 47%; low certainty of evidence).

In people receiving aldosterone antagonists compared to control, there were 37 more hyperkalaemia per 1000 participants (95% CI 10 to 65) with a number needed to treat for an additional harmful outcome (NNTH) of 27 (95% CI 16 to 104).

Gynaecomastia

Aldosterone antagonists probably increases the risk of gynaecomastia compared to control interventions (Analysis 1.5 (4 studies, 768 participants): RR 5.95, 95% CI 1.93 to 18.28; I^2 = 0%; moderate certainty of evidence).

In people receiving aldosterone antagonists compared to control, there were 26 more gynaecomastia per 1000 participants (95% CI 15 to 39) with a NNTH of 38 (95% CI 26 to 68).

Left ventricular mass

Aldosterone antagonists may prevent left ventricular mass hypertrophy compared to control interventions (Analysis 1.6 (8 studies, 633 participants): SMD -0.42, 95% CI -0.78 to -0.05; I^2 = 77%; low certainty evidence).

Because of the significant heterogeneity among the included studies for left ventricular mass, we carried out the subgroup analyses by dialysis modality (HD or PD). In this analysis Lin 2016a was excluded as it included both HD and PD patients. There were no differences in left ventricular mass found between the aldosterone antagonists and control interventions for either HD participants (Analysis 1.7.1 (6 studies, 342 participants): SMD -0.40, 95% CI -0.92 to 0.12; I^2 = 79%) or in Ito 2014 which only included PD participants (Analysis 1.7.2 (1 study, 93 participants): SMD -0.37, 95% CI -0.78 to 0.04). Heterogeneity was still high.

Ejection fraction

Aldosterone antagonists may make little or no difference to preserving ejection fraction compared to control interventions (Analysis 1.8 (7 studies, 458 participants): MD 3.15, 95% CI -0.74 to 7.04; I^2 = 84%).

Subgroup analyses (HD or PD) were also performed because of the significant heterogeneity among the included studies for left ejection fraction. There was no evidence that aldosterone antagonists altered ejection fraction in comparison to control interventions for either HD participants (Analysis 1.9.1 (4 studies, 156 participants): MD 3.13, 95% CI -4.25 to 10.51; I^2 = 84%) or PD participants (Analysis 1.9.2 (2 studies, 104 participants): MD 2.31, 95% CI -1.99 to 6.61; I^2 = 0%).

Serum potassium

Aldosterone antagonists may make little or no difference to serum potassium concentration compared to control interventions (Analysis 1.10 (7 studies, 519 participants): MD 0.21, 95% CI -0.06 to 0.47; I^2 = 84%).

Subgroup analyses (HD or PD) were also performed because there was significant heterogeneity among the included studies for serum potassium due to Lin 2016a which included both HD and PD patients. There was no evidence of differences in serum potassium concentration between the intervention and control groups for HD participants (Analysis 1.11.1 (5 studies, 281 participants): MD 0.07 mmol/L, 95% CI -0.05 to 0.20; I^2 = 0%) or in Ito 2014 which only included PD participants (Analysis 1.11.2 (1 study, 40 participants): MD -0.01 mmol/L, 95% CI -0.35 to 0.33).

Residual kidney function

Aldosterone antagonists may make little or no difference to residual kidney function compared to control interventions (Analysis 1.12 (3 studies, 132 participants): MD -36.23 urine volume/day, 95% CI -114.61 to 42.15; I^2 = 0%).

DISCUSSION

Summary of main results

Based on the results from our systematic reviews and meta-analysis, we found that aldosterone antagonists (spironolactone or eplerenone) probably reduced all-cause and cardiovascular death and probably reduced cardiovascular and cerebrovascular morbidity compared to control interventions (placebo or standard care) for people with CKD requiring dialysis.

Aldosterone antagonists made little or no difference to the risk of hyperkalaemia and increased serum potassium. However, aldosterone antagonists probably increased the risk of gynaecomastia compared with control interventions. Although the relative risk of gynaecomastia with aldosterone antagonists was increased compared with controls, in people receiving aldosterone antagonists there were 64 fewer deaths from cardiovascular events per 1000 participants (95% CI 42 to 87) with a NNTB of 16 (95% CI 12 to 24) and for gynaecomastia there were 26 more reports of gynaecomastia per 1000 participants (95% CI 15 to 39) with a NNTH of 38 (95% CI 26 to 68).

Aldosterone antagonists may prevent left ventricular mass hypertrophy. Aldosterone antagonists may make little or no difference to ejection fraction or residual kidney function among participants undergoing dialysis.

Overall completeness and applicability of evidence

In terms of completeness, we performed a comprehensive systematic search strategy of the Cochrane Kidney and Transplantation's Register. As shown in Characteristics of included studies, the analyses included studies with participants receiving HD (Feniman De Stefano 2015; Gross 2005; Matsumoto 2014; MiREnDa 2014; Ni 2014; PHASE 2015; SPIN-D 2019; Taheri HD 2009; Vukusich 2010; Zaripova 2012; Ziaee 2019), PD (Ito 2014; Taheri CAPD 2012; Yongsiri 2015) or both (Lin 2016a), and most studies reported the inclusion and exclusion criteria. These included studies were conducted from the late 2000s through to the late 2010s. During this period, only spironolactone was available for people with CKD requiring dialysis. Therefore, we judged that our review had high external validity. However, there was little evidence for selective aldosterone antagonists (eplerenone) (PHASE 2015).

Quality of the evidence

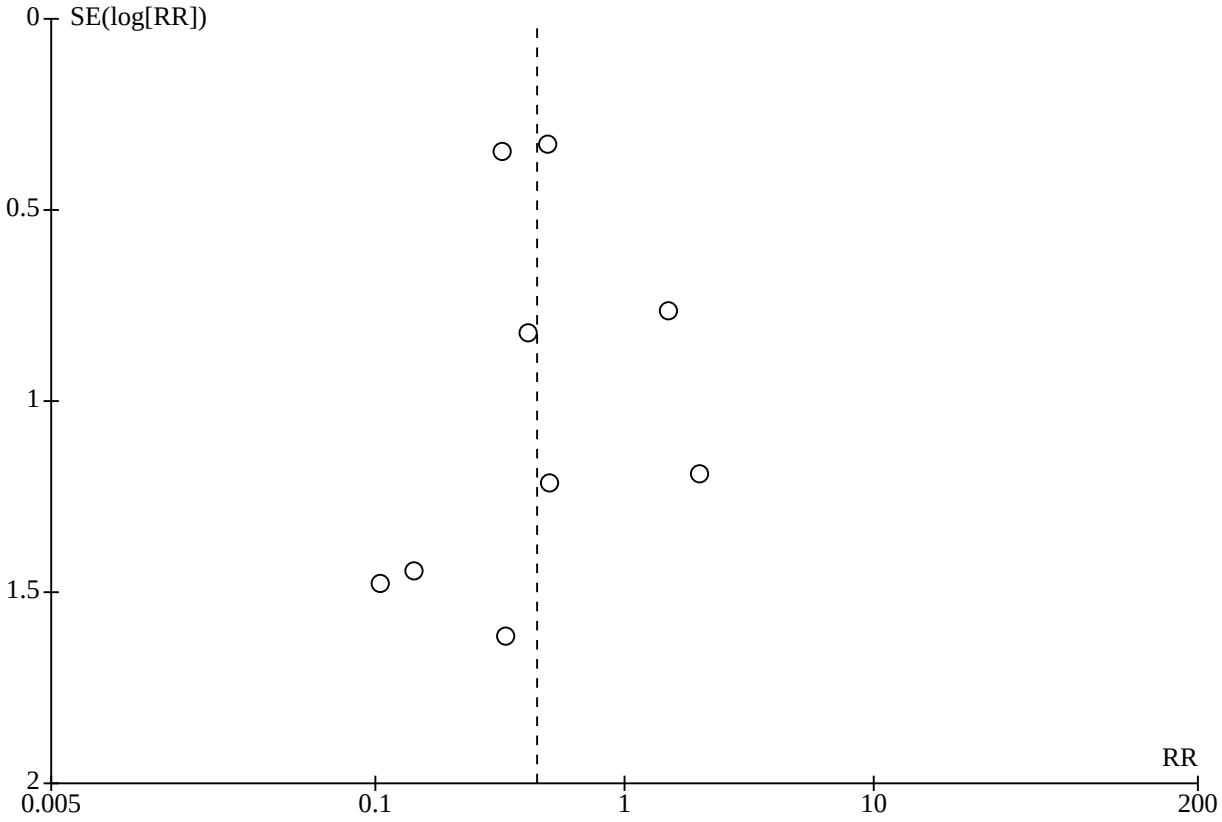
We assessed the certainty of the evidence using the grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADE 2008; GRADE 2011). As shown in the Summary of findings 1, we graded the overall certainty of the body of the evidence in this review. We rated the certainty of the evidence for the patient-focused outcomes including death (any cause), death (cardiovascular), cardiovascular and cerebrovascular morbidity, and adverse events (gynaecomastia) as moderate

because the total size of the included in the analysis for these outcomes were less than the optimal information size (OIS) of 400 (Guyatt 2011) and because three of the 14 included studies did not used a placebo intervention for the control group. The certainty of the evidence for the adverse events (hyperkalaemia) was also rated as low because the number of the included participants did not meet the OIS and because there was inconsistency in the definition of hyperkalaemia between the included studies. The certainty of the evidence for surrogate endpoint (left ventricular mass) was assessed as very low because of the risk of bias issue regarding the lack of blinding of outcomes, inconsistency in the definition of left ventricular mass between the included studies, and the number of the included participants did not meet the OIS. As shown in Figure 2 and Figure 3, some of the included articles did not adequately reported on key aspects of the study methods which could result in an increased risk of selection, reporting, and other (especially due to funding) bias. Moreover, attrition bias due to incomplete outcome data should be considered in this review.

Potential biases in the review process

We conducted this review on the basis of the peer-reviewed protocol and a comprehensive systematic search strategy using the Cochrane Kidney and Transplant's Specialised Register. Two independent authors evaluated the quality of the studies, extracted, and analysed the data. However, this review has several limitations. First, long-term data on the effects of aldosterone antagonists was limited for patient-focused outcomes including mortality (all-cause or cardiovascular), and cardiovascular and cerebrovascular morbidity. Further, some of the analysed data for primary outcomes of death (all-cause) from the included studies were considered at high risk of selection bias due to obscure or inadequate random sequence allocation and allocation concealment (Ito 2014; Matsumoto 2014; Taheri CAPD 2012; Taheri HD 2009; Vukusich 2010; Ziaee 2019). Some studies were also at risk of performance and detection bias due to lack of blinding ((Ito 2014; Matsumoto 2014; Ziaee 2019), and attrition bias due to incomplete outcome data (Ito 2014; Lin 2016a; Matsumoto 2014; Vukusich 2010; PHASE 2015; Ziaee 2019). Therefore, although the point estimates of risk reduction were substantial, we recognised that the data of this review are insufficient to reliably determine whether aldosterone antagonists are truly beneficial for the participants with CKD requiring dialysis. We also consider the integration of the results of hyperkalaemia incidence, defined at different thresholds in each study, as one of the limitations in the interpretation of this systematic review. Finally, despite a comprehensive systematic search strategy of Cochrane Kidney and Transplant's Specialised Register, publication bias may exist in this review (Figure 4).

Figure 4. Funnel plot of comparison: 1 Aldosterone antagonists (Spironolactone or eplerenone) versus control (placebo or standard care), outcome: 1.1 Death (any cause).



Agreements and disagreements with other studies or reviews

Findings from our review were similar to those reported in a previous systematic review (Quach 2016). Compared to control, aldosterone antagonists reduced the risk of all-cause and cardiovascular death among participants with CKD undergoing dialysis with a similar effect size reported in both this and the prior review. Although these findings suggested that aldosterone antagonists could provide clinical benefit to people with CKD requiring dialysis, the potential adverse events such as hyperkalaemia should also be considered. The previous meta-analysis by Quach 2016 showed that aldosterone antagonists could increase the risk of severe hyperkalaemia among participants with CKD undergoing dialysis. However, the association between increased risk of hyperkalaemia with aldosterone antagonists was uncertain in this review. Quach 2016 only reported the greater overall incidence of gynaecomastia in the aldosterone antagonist arms compared to controls.

Gynaecomastia, a known side effect of aldosterone antagonists, was increased compared to controls in one study reported in Quach 2016. Our analysis included three additional studies for this outcome with a similar finding. Of note, all of the studies included in the gynaecomastia analysis used spironolactone and this outcome was not reported in the one study using eplerenone (PHASE 2015).

A non-Cochrane systematic review was recently published that examined the clinical effects of aldosterone antagonists on the following outcomes: death (any cause), cardiovascular death, adverse effects, and cardiac function (left ventricular mass, ejection fraction) in patients on dialysis (Li 2019). There were some differences between the results of our systematic review and that of Li 2019. One key reason for these differences arises from the variation in the studies included in the review. In particular, we included three studies published in 2019 (SPIN-D 2019; MiREnDa 2014; Ziaee 2019) that were not included in Li 2019. Our search strategy (based on the Cochrane Kidney and Transplant Register) differed from Li 2019, and did not identify two studies written in Chinese (Song 2017; Wang 2018). Li 2019 identified these studies through the Chinese Biomedical Literature Database and the China National Knowledge Infrastructure, which are not searched as part of the methods used for the Cochrane Kidney and Transplant Register. We were not able to access the full text reports on these additional two studies identified by Li 2019 at the time of our Cochrane review, however, so have categorised these studies as awaiting classification and will be assessed in a future update of this review. In summary, our systematic review includes all the studies included in Li 2019 (with the exception of Song 2017 and Wang 2018), plus an additional six studies (Table 1).

In this review we dichotomized the onset of hyperkalaemia according to the definition used in each study and meta-analysed the results whereas Li 2019 use a threshold of K > 6 mEq/L to define hyperkalaemia. In PHASE 2015, significant hyperkalaemia was defined as K > 6.5 mEq/L, above the threshold of adopted by Li 2019 for their sensitivity analysis. We therefore used the threshold of hyperkalaemia of K > 6.5 mEq/L in the PHASE study (PHASE 2015), which is consistent with the prior non-Cochrane systematic review (Quach 2016). In addition, Li 2019 used per-protocol analysis to estimate the RR of each study in a meta-analysis of gynaecomastia. This method differs from those adopted by us and Quach 2016 which used the principles of intention-to-treat analysis.

We found a small effect of aldosterone antagonists on preventing left ventricular mass hypertrophy based on echocardiographic findings, which is similar to that of the systematic review by Li 2019. We observed a more conservative effect of aldosterone antagonists on ejection fraction based on echocardiographic findings in our systematic review compared to Li 2019. We consider this difference attributable to Li 2019 not including the two most recent studies (MiREnDa 2014; Ziaee 2019). We consider that the differences in analysis methods described above led to small differences in point estimates and 95% CI in Li 2019 and our systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

In people with CKD requiring dialysis, aldosterone antagonists probably reduces the risk of death (any cause and cardiovascular) and morbidity due to cardiovascular and cerebrovascular disease. Although non-selective aldosterone antagonists (spironolactone) may increase the risk of gynaecomastia in people with CKD requiring dialysis, its incidence and clinical significance are not comparable to those of aldosterone antagonists in reducing the risk of death or cardiovascular disease. However, there was no clear association between hyperkalaemia and/or serum potassium elevation with aldosterone antagonists in this review. There is currently insufficient data to draw conclusions about the effect of aldosterone antagonists on echocardiographic findings such as left ventricular mass and ejection fraction. We should recognise that these findings were based on very low to moderate certainty of the evidence. There are three ongoing studies investigating this issue and these will strengthen the evidence.

Implications for research

Some of the included studies in this review were affected by certain selection bias due to inappropriate random sequence generation or/and allocation concealment. Lack of blinding of participants and outcome assessors also biased the findings from some studies. There was more concern that the potential outcomes of participants in the included studies could largely affect the results of the meta-analysis in this review. Moreover, the low sample size in studies included in this review might mean some clinically significant findings may have been missed. Therefore, it is important to plan the methods carefully in future studies to avoid these selection and information biases.

Following spironolactone and eplerenone, the third-generation of aldosterone antagonists has recently become available for clinical use. It is expected that the third-generation aldosterone antagonists would be better tolerated in individuals with kidney dysfunction compared to spironolactone and eplerenone. Future systematic reviews should incorporate the findings from clinical studies of the third-generation aldosterone antagonists not yet published.

Due to the small number of included studies eligible for subgroup analysis and the lack of information on each study, we were not able to perform the following subgroup analyses (residual kidney function, diabetic kidney disease, and concomitant use of RAS inhibitors) as planned in the protocol. It would also be important to investigate the difference in the clinical efficacy of aldosterone antagonists in subgroups of patients with or without pre-existing comorbidities such as cardiovascular disease and heart failure.

We believe that patient-oriented outcome measures as listed in the SONG core outcomes (SONG 2017) such as fatigue score are also required to be examined in the future.

Additionally, there has been no cost-effective analyses of aldosterone antagonists among people undergoing dialysis. These gaps in the evidence base indicate that larger and well-designed clinical RCTs are required to clarify the efficacy of aldosterone antagonists in people with CKD requiring dialysis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Feniman De Stefano 2015

Study characteristics

Methods	• Study design: parallel RCT • Study duration: March 2011 to December 2012 • Follow-up period: 24 weeks
Participants	• Setting: single centre • Country: Brazil • Relevant health status: CKD-5D on HD; stable antihypertensive treatment in the last 6 months • Number (randomised/analysed): treatment group (10/8); control group (9/9) • Mean age ± SD (years): treatment group (52.0 ± 19.2); control group (56.0 ± 10.9) • Sex (M/F): treatment group (4/4); control group (5/4) • Exclusion criteria: dialysis dose measured by Kt/V < 1.2; history or evidence of angina or MI, heart failure, peripheral vascular disease, previous hyperkalaemia, valvular heart disease, atrial fibrillation; Hb < 10 g/dL; patients under treatment with spironolactone
Interventions	Treatment group • Spironolactone: 25 mg/day for 24 weeks Control group • Placebo for 24 weeks
Outcomes	• LVM • EF • Serum potassium
Identification	• Authors name: Greicy Mara Mengue Feniman-De-Stefano • Institution: Dpto de Clínica Médica da Faculdad • Email: gmmfds@yahoo.com.br • Address: UNESP, 440 Rua João Miguel Rafael, Botucatu, CEP 18602-220, São Paulo, Brazil
Notes	• Funding source: Funded by FUNDUNESP (Foundation for the Development of UNESP, Process 0090910) and FAPESP (Foundation for Research Support of São Paulo, Process 2010/10439-1) • Complete follow-up: treatment group (8/10, 80%); control group (9/9, 100%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how allocation concealment was done

Feniman De Stefano 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind", "placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind", "placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been reported in ClinicalTrials.gov identifier NCT01128101
Other bias	Low risk	Funded by FUNDUNESP (Foundation for the Development of UNESP, Process 0090910) and FAPESP (Foundation for Research Support of São Paulo, Process 2010/10439-1)

Gross 2005

Study characteristics	
Methods	• Study design: cross-over RCT (3-week washout period) • Study duration: not reported • Follow-up period: 7 weeks (total study time)
Participants	• Setting: single centre • Country: USA • Relevant health status: CKD-5D on HD; nil or minimal urine output (< 500 mL/24 hours) • Number: 8 • Mean age ± SD: 53.0 ± 10.0 years • Sex (M/F): 3/5 • Exclusion criteria: women of childbearing age had a negative pregnancy test result before entering into the study; known allergy to spironolactone; any acute illness; hypotension, defined as a predialysis SBP < 100 mm Hg; severe hypertension (predialysis SBP > 180 mm Hg and/or DBP > 100 mm Hg); decompensated heart failure; inability to give informed consent; noncompliance
Interventions	Treatment group • Spironolactone: 50 mg twice/day for 2 weeks Control group • Placebo for 2 weeks
Outcomes	• Serum potassium • Residual kidney function: 24 hour urine volume
Identification	• Authors name: Henrikas Irmantas Juknis, MD • Institution: Department of Internal Medicine, Renal Division, Washington University School of Medicine, St Louis, MO • Email: ijuknevi@im.wustl.edu

Gross 2005 *(Continued)*

	• Address: 4205 Forest Park Ave, St Louis, MO 63108.
Notes	• Funding source: not reported • Complete follow-up: (8/8, 100%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind", "placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind", "placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Funding: not reported

Ito 2014

Study characteristics

Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up period: 24 months
Participants	• Setting: multicentre (12 sites) • Country: Japan • Relevant health status: CKD-5D on PD; NYHA-FC I and II • Number: treatment group (78); control group (80) • Mean age ± SD (years): treatment group (57.4 ± 12.3); control group (55.6 ± 14.4) • Sex (M/F); treatment group (55/23); control group (58/22) • Exclusion criteria: severe anaemia (Hb < 9.0 g/dL); NYHA-FC III and IV heart failure; treatment with acid-pH fluid dialysate; previous treatment with HD or transplantation within the preceding 3 years; pregnancy or suspected pregnancy
Interventions	Treatment group • Spironolactone: 25 mg/day for 104 weeks

Ito 2014 *(Continued)*

	Control group • Standard care for 104 weeks
Outcomes	• Death (any cause) • Death (cardiovascular) • Cardiovascular and cerebrovascular morbidity: acute MI • Hyperkalaemia: K > 6.0 mEq/L • Gynaecomastia • LVM • EF
Identification	• Authors name: Yasuhiko Ito • Institution: Nephrology and Renal Replacement Therapy, Nagoya University, Nagoya, Japan • Email: yasuito@med.nagoya-u.ac.jp • Address: 65 Tsurumai-cho, Showaku, Nagoya 466-8550, Japan
Notes	• Funding source: This study was supported in part by a Grant-in-Aid for Progressive Renal Disease Research, Research on Rare and Intractable Diseases, from the Ministry of Health, Labor and Welfare of Japan • Complete follow-up: treatment group (50/78, 64.1%); control group (58/80, 72.5%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been reported in The University Hospital Medical Information Network Clinical Trials Registry as UMIN000492
Other bias	Low risk	This study was supported in part by a Grant-in-Aid for Progressive Renal Disease Research, Research on Rare and Intractable Diseases, from the Ministry of Health, Labor and Welfare of Japan

Lin 2016a

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up period: 2 years
Participants	• Setting: multicentre (3 sites) • Country: China • Relevant health status: CKD-5D on HD/PD • Number: treatment group (125); control group (128) • Mean age ± SD (years): treatment group (70.3 ± 10.9); control group (70.6 ± 8.4) • Sex (M): treatment group (58.4%); control group (62.5%) • Exclusion criteria: hypotension, hepatic failure, and any life-threatening disease other than ESKD; congestive heart failure (EF ≤ 50%) in recent 6 months; occurrence of an acute MI or stroke within 6 months after the study initiation; prior use of spironolactone or potassium level > 6.0 mmol/L
Interventions	Treatment group • Spironolactone: 25 mg/day for 2 years Control group • Standard care for 2 years
Outcomes	• Death (any cause) • Death (cardiovascular) • LVM index: men, women • EF • Serum potassium • Gynaecomastia
Identification	• Authors name: Chong Ting Lin, MD • Institution: Department of Hemodialysis Room, Yantaishan Hospital Taishan Medical College • Email: lingchongting0535@126.com
Notes	• Funding source: not reported • Complete follow-up: treatment group (100/125, 80.0); control group (98/128, 76.6)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The allocation sequence was generated independently by a nurse and concealed in opaque envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "Both investigators and participants were not aware of the allocations."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo-controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "placebo-controlled"

Lin 2016a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	Protocol: not reported
Other bias	Unclear risk	Funding: not reported

Matsumoto 2014

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up period: 3 years
Participants	• Setting: multicentre (5 sites) • Country: Japan • Relevant health status: CKD-5D on HD; 24-hour urinary output of < 500 mL • Number: treatment group (157); control group (152) • Mean age ± SD (years): treatment group (67.4 ± 12.3); control group (66.7 ± 11.2) • Sex (M/F); treatment group (113/157); control group (90/152) • Other relevant information: • Exclusion criteria: history of non-compliance (including noncompliance with HD); unstable vascular access, hypotension, hepatic failure, active malignancy, or any life-threatening disease other than ESKD
Interventions	Treatment group • Spironolactone: 25 mg/day for 156 weeks Control group • Standard care for 156 weeks
Outcomes	• Death (any cause) • Death (cardiovascular) • Hyperkalaemia: life-threatening hyperkalaemia (serum potassium level > 6.8 mEq/L) • Gynaecomastia
Identification	• Authors name: Matsumoto Y, MD • Institution: Department of Nephrology and Dialysis, Shizuoka City Hospital, Shizuoka, Japan • Email: matsumoto16@aol.com • Address: 10-93 Ohtemachi, Aoi-ku, Shizuoka 420-8630, Japan
Notes	• Funding source: not reported • Complete follow-up: treatment group (112/157, 71.3%); control group (128/152, 84.2%)
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Matsumoto 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label" study
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label" study
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	Protocol: not reported
Other bias	Unclear risk	Funding: not reported

MiREnDa 2014

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: December 2012 to March 2018 • Follow-up period: 44 weeks
Participants	• Setting: multicentre (3 sites) • Country: Germany • Relevant health status: CKD5D on HD • Number: treatment group (50); control group (47) • Mean age ± SD (years): treatment group (60.6 ± 11.3); control group (59.9 ± 13.4) • Sex (M/F); treatment group (40/10); control group (35/12) • Exclusion criteria: previous aldosterone antagonist treatment; history of hyperkalaemia and hypotension; pregnancy/lactation
Interventions	Treatment group • Spironolactone 50 mg/day for 40 weeks Control group • Placebo for 40 weeks
Outcomes	• Death (any cause) • Hyperkalaemia: moderate hyperkalaemia (pre-dialysis potassium levels of 6.0 to 6.5 mmol/L); severe hyperkalaemia (≥ 6.5 mmol/L) • LVM • EF

MiREnDa 2014 *(Continued)*

	• Residual kidney function: urine volume, mGFR
Identification	• Authors name: Fabian Hammer • Institution: Department of Medicine I, Division of Cardiology, University Hospital Würzburg, Würzburg, Germany • Email: fabian.hammer@uni-greifswald.de • Address: Department of Internal Medicine B, University Hospital Greifswald, Ferdinand-Sauerbruch-Street, 17475 Greifswald, Germany
Notes	• Funding source: The MiREnDa trial was funded by the German Federal Ministry of Education and Research (01KG1202) and conducted under the auspices of the German Society of Nephrology. Additional funding was obtained from E.N.D.I.—the European Nephrology and Dialysis Institute • Complete follow-up: treatment group (44/50, 88.0%); control group (41/47, 87.2%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated 1:1 to either 50 mg spironolactone once daily or matching placebo using an algorithm for balanced randomised assignment for stratified randomizations."
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly allocated 1:1 to either 50 mg spironolactone once daily or matching placebo using an algorithm for balanced randomised assignment for stratified randomizations."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "MiREnDa was an investigator-initiated, randomised, double-blind, placebo- controlled trial to study the efficacy and safety of spironolactone in HD patients."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "MiREnDa was an investigator-initiated, randomised, double-blind, placebo- controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been reported in ClinicalTrials.gov identifier NCT01691053
Other bias	Low risk	The MiREnDa trial was funded by the German Federal Ministry of Education and Research (01KG1202) and conducted under the auspices of the German Society of Nephrology. Additional funding was obtained from E.N.D.I.—the European Nephrology and Dialysis Institute

Ni 2014

Study characteristics

Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up period: 12 weeks

Ni 2014 *(Continued)*

Participants	• Setting: multicentre (2 sites) • Country: China • Relevant health status: CKD-5D on HD or PD; refractory hypertension • Number: treatment group (40); control group (36) • Mean age ± SD (years): treatment group (55.7 ± 12.3); control group (54.9 ± 14.2) • Sex (M): treatment group (60.0%); control group (58.3%) • Exclusion criteria: prior use of spironolactone; potassium level > 5 mmol/L
Interventions	Treatment group • Spironolactone: 25 mg/day for 12 weeks Control group • Placebo for 12 weeks
Outcomes	• Serum potassium • Residual kidney function: urine volume
Identification	• Authors name: Xiaoying Ni • Institution: Department of Nephrology, People's Hospital of Yinzhou, College of Medicine, Ningbo University • Email: jishengz2013@163.com • Address: Ningbo, Zhejiang, PR China
Notes	• Funding source: not reported • Complete follow-up: treatment group (36/40, 90.0%); control group (34/36, 94.4%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind" study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups.
Selective reporting (reporting bias)	Unclear risk	Protocol unclear
Other bias	Unclear risk	Funding: not reported

PHASE 2015

Study characteristics

Methods	• Study design: parallel RCT • Study duration: April 2013 to October 2013 • Follow-up period: 12 weeks
Participants	• Setting: multicentre (5 sites) • Country: Canada • Relevant health status: CKD5D on HD • Number: treatment group (77); control group (77) • Mean age ± SD (years): treatment group (62.1 ± 14.6); control group (63.1 ± 13.7) • Sex (M/F); treatment group (47/30); control group (49/28) • Exclusion criteria: documented hyperkalaemia (potassium level.> 6.0 mEq/L) within the prior 4 weeks; hypotension (SBP< 90 mmHg that required treatment), change in antihypertensive medications in the preceding 4 weeks; a previously documented sensitivity to eplerenone; ongoing use of spironolactone or eplerenone; pregnancy; or living-related transplant scheduled within the next 6 months
Interventions	Treatment group • Eplerenone: 50 mg/day for 12 weeks Control group • Placebo for 12 weeks
Outcomes	• Death (any cause) • Death (cardiovascular) • Cardiovascular and cerebrovascular morbidity: cardiovascular events (fatal or nonfatal) • Hypokalaemia: > 6 mEq/L, > 6.5 mEq/L, > 7 mEq/L
Identification	• Authors name: Michael Walsh • Institution: Division of Nephrology, St. Joseph's Hospital • Email: lastwalsh1975@gmail.com • Address: 50 Charlton Avenue E, Hamilton, ON, Canada L8N 4A6
Notes	• Funding source: This trial was funded by the Canadian Institutes of Health Research, the Canadian Network and Centre for Trials Internationally, the Canadian Kidney Knowledge Translation and Generation Network, and the Pfizer Investigator Initiated Research program • Complete follow-up: treatment group (77/77, 100%); control group (77/77, 100%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants were randomly allocated to eplerenone or placebo using a computerized web-based randomisation system maintained by the coordinating canter (the Population Health Research Institute)."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible participants were randomly allocated to eplerenone or placebo using a computerized web-based randomisation system maintained by the coordinating centre (the Population Health Research Institute)."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Participants, health care providers, study personnel, and outcome assessors were all blind to treatment allocation."

PHASE 2015 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, health care providers, study personnel, and outcome assessors were all blind to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Unclear risk	Pre-specified protocol unclear
Other bias	High risk	Funding: this trial was partly funded by pharmaceutical company

SPIN-D 2019

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: November 2014 to July 2017 • Follow-up period: 40 weeks
Participants	• Setting: multicentre (number of sites not reported) • Country: USA • Relevant health status: CKD-5D on HD • Number: treatment group (78); control group (51) • Mean age ± SD: 55.5 ± 12.0 years • Sex (M/F); 85/44 • Exclusion criteria: serum potassium ≥ 6.5 mEq/L or unscheduled dialysis for hyperkalaemia within 3 months; potassium ≥ 6.0 mEq/L within 2 weeks prior to baseline; pre-dialysis SBP < 100 mm Hg within 2 weeks prior to screening or at baseline; ≥ 2 dialysis sessions within the month prior to screening with BP < 80 mm Hg; treatment for cramping, light-headedness, nausea, or hypotension; use of digoxin, spironolactone, eplerenone, or dual use of ACEI and ARB; allergy to spironolactone; inability to maintain dialysis machine blood flow ≥ 300 mL/min during the 3 sessions before screening; anticipated pregnancy, transplantation, modality transfer, or transfer to a nonparticipating dialysis unit within 9 months; history of mitral valve surgery or severe mitral valve disease were excluded because of anticipated inability to determine mitral annular E` velocity
Interventions	Treatment group • Spironolactone: 12.5 mg/day (27) for 36 weeks • Spironolactone 25 mg/day (26) for 26 weeks • Spironolactone 50 mg/day (25) for 36 weeks Control group • Placebo for 36 weeks
Outcomes	• Incidence of serum potassium > 6.5 mEq/L • Mean potassium during follow-up • Change in LVM index
Identification	• Authors name: David Charytan • Institution: Brigham & Women's Hospital

SPIN-D 2019 *(Continued)*

	• Email: dcharytan@bwh.harvard.edu • Address: 1620 Tremont Street, 3-012L, Boston, Massachusetts, USA
Notes	• Funding source: This trial was funded by the following cooperative agreements from the National Institute of Diabetes and Digestive and Kidney Diseases: U01 DK096189, U01 DK099923, U01 DK099914, and U01DK099919. Additional support was provided by the Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL1TR001102) and financial contributions from Harvard University and its affiliated academic health care centres. AMH was supported byI01CX000982 CSR&D. The SEEQ Mobile Cardiac Telemetry (MCl) Systems used for heart rate and rhythm monitoring were donated by Medtronic Inc • Complete follow-up: treatment group (67/78, 85.9%); control group (48/51, 94.1%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a random number generator, the data coordinating centre prepared permuted blocks of random sizes with stratification by centre"
Allocation concealment (selection bias)	Low risk	Quote: "Web-based randomisation was performed with participants and all research personnel masked to the treatment assignment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Web-based randomisation was performed with participants and all research personnel masked to the treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Web-based randomisation was performed with participants and all research personnel masked to the treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Quote: "The complete list of primary and secondary outcomes with definitions is provided in Supplementary Table S1."
Other bias	Low risk	Quote: "This trial was funded by the following cooperative agreements from the National Institute of Diabetes and Digestive and Kidney Diseases: U01DK096189, U01DK099923, U01DK099914, and U01DK099919."

Taheri CAPD 2012

Study characteristics

Methods	• Study design: parallel RCT • Study duration: February 2008 to September 2008 • Follow-up period: 6 months
Participants	• Setting: single centre • Country: Iran • Relevant health status: CKD-5D on PD; NYHA classification III or IV • Number: treatment group (9); control group (9) • Mean age ± SD (years): treatment group (50.7 ± 17.4); control group (57.2 ± 13.1)

Taheri CAPD 2012 *(Continued)*

	• Sex (M): treatment group (55.6%); control group (55.6%) • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 25 mg/day for 24 weeks Control group • Placebo for 24 weeks
Outcomes	• Death (any cause) • Death (cardiovascular) • Hyperkalaemia • Mean EF
Identification	• Authors name: Shahram Taheri • Institution: Isfahan Kidney Diseases Research Center/Nephrology Division, Department of Internal Medicine, Isfahan School of Medicine, Isfahan University of Medical Sciences • Email: shah63tah@yahoo.com • Address: Soffeh Ave., Isfahan, Iran
Notes	• Funding source: granted (research project No. 386273) by the research committee of Isfahan Kidney Research Center, Isfahan University of Medical Science • Complete follow-up: treatment group (7/9, 77.8%); control group (9/9, 100%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind placebo-controlled" clinical study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind placebo-controlled" clinical study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Unclear risk	Protocol unclear
Other bias	Low risk	Funding: internally funded

Taheri HD 2009

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up period: 6 months
Participants	• Setting: single centre • Country: Iran • Relevant health status: CKD5D on HD; NYHA classification III or IV • Number: treatment group (8); control group (8) • Mean age ± SD (years): treatment group (59.5 ± 6.5); control group (56.8 ± 9.3) • Sex (M/): treatment group (62.5%); control group (75.0%) • Exclusion criteria: not reported
Interventions	Treatment group • Spironolactone: 25 mg/day for 24 weeks Control group • Placebo for 24 weeks
Outcomes	• Death (any cause) • Death (cardiovascular) • Cardiovascular and cerebrovascular morbidity: hospitalisation (cardiovascular) • Hyperkalaemia • LVM • EF
Identification	• Authors name: Dr Shahram Taheri • Institution: Divisions of Nephrology and Cardiology, Department of Internal Medicine, Isfahan School of Medicine • Email: shah63tah@yahoo.com • Address: Soffeh Ave., Isfahan, Iran
Notes	• Funding source: not reported. • Complete follow-up: treatment group (8/8, 100%); control group (8/8, 100%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias)	Low risk	"double-blind placebo-controlled" study

Taheri HD 2009 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Unclear risk	Protocol unclear
Other bias	Unclear risk	Funding: not reported

Vazquez-Rangel 2014

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: July 2008 to March 2012 • Follow-up duration: 6 months
Participants	• Setting: single centre • Country: Mexico • Relevant health status: CKD-5D on PD; hospitalised for peritoneal catheter placement for PD • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (40.2 ± 18.8); control group (50.0 ± 20.0) • Sex (M/F); treatment group (6/3); control group (5/4) • Exclusion criteria: pregnancy; hyperkalaemia (potassium > 5.5 mEq/L); intolerance to spironolactone
Interventions	Treatment group • Spironolactone: 25 mg/day for 26 weeks Control group • Placebo for 26 weeks
Outcomes	• Peritoneal fibrosis
Identification	• Authors name: Dr Armando Vazquez-Rangel • Institution: National Heart Institute, México City, México • Email: madero.magdalena@gmail.com • Address: not reported
Notes	• Funding source: the Mexican Kidney Foundation and the Miguel Aleman Foundation • Complete follow-up: treatment group (9/10, 90%); control group (9/10, 90%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how allocation concealment was done

Vazquez-Rangel 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been reported in ClinicalTrials.gov identifier NCT00865449
Other bias	Low risk	This research was supported by the Mexican Kidney Foundation and the Miguel Aleman Foundation

Vukusich 2010

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up duration: 2 years
Participants	• Setting: single centre • Country: Chile • Relevant health status: CKD-5D on HD • Number: treatment group (33); control group (33) • Mean age ± SD (years): treatment group (60.1 ± 5.2); control group (55.6 ± 3.6) • Sex (M/F): treatment group (14/9); control group (20/10) • Exclusion criteria: pregnancy or potassium level > 5.5 mEq/L
Interventions	Treatment group • Spironolactone 50 mg/HD for 104 weeks Control group • Placebo for 104 weeks
Outcomes	• Death (any cause) • Serum potassium
Identification	• Authors name: Antonio Vukusich • Institution: Faculty of Medicine, Universidad Los Andes, Santiago • Email: emarusic@uandes.cl • Address: S. Carlos Apoquindo2200, Santiago, Chile
Notes	• Funding source: This research was supported by grants FONDECYT 1040338 and Fondo Ayuda Investigaction Universidad Los Andes MED 002/06. • Complete follow-up: treatment group (30/33, 90.9%); control group (23/33, 69.7%)

Vukusich 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo-controlled randomised clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "placebo-controlled randomised clinical trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes have been reported in study protocol in materials and methods section
Other bias	Low risk	This research was supported by grants FONDECYT 1040338 and Fondo Ayuda Investigacion Universidad Los Andes MED 002/06

Yongsiri 2015

Study characteristics

Methods	• Study design: cross-over RCT (2-week washout period) • Study duration: March 2013 to May 2013 • Follow-up duration: 10 weeks (total study time)
Participants	• Setting: single centre • Country: Thailand • Relevant health status: CKD-5D on PD; history of hypokalaemia (serum potassium < 3.5 mEq/L) or required potassium supplements to maintain a normal serum potassium at any time in the past • Number: 24 • Mean age ± SD (years): 52.4 ± 12.4 • Sex (M/F); 8/12 • Exclusion criteria: history of hyperkalaemia (serum K+ > 5.5 mEq/L) at any time in the past and recent peritonitis within one month
Interventions	Treatment group • Spironolactone: 25 mg/day for 12 weeks Control group • Placebo for 12 weeks

Yongsiri 2015 *(Continued)*

Outcomes	• Serum potassium • Residual kidney function: urine volume • Fatigue
Identification	• Authors name: Somchai Yongsiri • Institution: Faculty of Medicine, Burapha University • Email: syongsiri@yahoo.com • Address: Chonburi 20131, Thailand
Notes	• Funding source: This study was supported by the Office of the Higher Education Commission of Thailand and Faculty of medicine, Burapha University, Thailand. • Complete follow-up: (20/24, 83.3%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomisation was done by a computerized program."
Allocation concealment (selection bias)	Low risk	Quote: "Block randomisation was done by a computerized program."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomised, double-blind, placebo-controlled cross-over study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomised, double-blind, placebo-controlled cross-over study"
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% of participants were not followed up
Selective reporting (reporting bias)	Low risk	Quote: "The study protocol was approved by the institutional review board of Burapha University and registered at http://www.clinicaltrials.in.th, identification number TCTR20130314001."
Other bias	Low risk	Quote: "This study was supported by the Office of the Higher Education Commission of Thailand and Faculty of Medicine"

Zaripova 2012

Study characteristics

Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up duration: 6 months
Participants	• Setting: single centre • Country: Russia • Relevant health status: CKD-5D on HD

Zaripova 2012 *(Continued)*

- Number: treatment group (36); control group (35)
- Mean age ± SD: 50.7 ± 9.4 years
- Sex (M/F); not reported
- Exclusion criteria: not reported

Interventions	Treatment group • Spironolactone: 25 mg/day for 36 weeks • Lisinopril and valsartan for 26 weeks (dose not reported) Control group • Lisinopril and valsartan for 26 weeks (dose not reported)
Outcomes	• LVM index
Identification	• Authors name: Zaripova I • Institution: not reported • Email: not reported • Address: not reported
Notes	• Funding source: not reported • Complete follow-up: not reported • Abstract-only publication • Complete follow-up: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how sequence generation was done
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open-label" study
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label" study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Complete follow-up rate was not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Funding: not reported

Ziaee 2019

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up duration: 9 months
Participants	• Setting: single centre • Country: Iran • Relevant health status: CKD-5D on HD; serum potassium level < 5.5 mEq/L; SBP > 100 mm Hg at the beginning of the study; LVM index > 51 g/m^2 indexed for height; stable antihypertensive treatment in the preceding 6 months • Number: treatment group (24); control group (24) • Mean age ± SD (years): treatment group (69.2 ± 13.5); control group (67.5 ± 10.0) • Sex (M/F): treatment group (12/10); control group (13/8) • Exclusion criteria: high risk of hyperkalaemia (predialysis serum potassium level > 6 mEq/L); kidney transplantation during the study; a dialysis dose of Kt/V < 1.2; history or evidence of angina or MI, heart failure, peripheral vascular disease, previous hyperkalaemia, valvular heart disease, atrial fibrillation; Hb < 9.5 g/dL; receiving treatment with spironolactone
Interventions	Treatment group • Spironolactone: 25 mg/HD for 36 weeks Control group • Standard care for 36 weeks
Outcomes	• Left ventricular volume • EF • Death (any cause) • Gynaecomastia • Serum potassium
Identification	• Authors name: Azamolsadat Roshan • Institution: Taleghani Hospital • Email: shivaroshana@yahoo.com • Address: not reported
Notes	• Funding source: not reported • Complete follow-up: treatment group (20/24, 83.3%); control group (18/24, 75.0%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "In the allocation of the patients to the 2 groups, those who referred on even days were assigned to the control group, and those who referred on odd days were assigned to the case group (receiving spironolactone)."
Allocation concealment (selection bias)	High risk	Quote: "In the allocation of the patients to the 2 groups, those who referred on even days were assigned to the control group, and those who referred on odd days were assigned to the case group (receiving spironolactone)."
Blinding of participants and personnel (performance bias)	High risk	Quote: "The patients in the case group, after each HD session, were given 25 mg of spironolactone by a nurse, who was unaware of the grouping of the pa-

Ziaee 2019 *(Continued)*

All outcomes		tients. Spironolactone used in this protocol was acquired on the market as Aldactone 25 mg. The patients in the second group were given no medication."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In order to follow up the patients and measure the study variables at baseline and after 9 months, echocardiography was conducted by a single examiner, who was unaware of the study procedure and the allocation of the patients."
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Funding: not reported

ACEi - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; CKD - chronic kidney disease; DBP - diastolic blood pressure; EF - ejection fraction; ESKD - end-stage kidney disease; (m)GFR - (measured) glomerular filtration rate; Hb - haemoglobin; HD - haemodialysis; KtV - dialysis adequacy; LVM - left ventricular mass; M/F - male/female; MI - myocardial infarction; NYHA - New York Heart Association; PD - peritoneal dialysis; RCT - randomised control trial; SBP - systolic blood pressure

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

Study	Reason for exclusion
Eklund 2016	Wrong outcomes: vascular stiffness
EPURE 2018	Wrong participants: patients undergoing kidney transplantation
Essaian 2007	Wrong outcomes: plasma level of plasminogen-activator inhibitor type 1
Host 2000	Wrong outcomes: left ventricular cavity
Koh 2010	Wrong outcomes: estimated sodium intake
LAST-D 2013	This study was withdrawn due to funding issue
Nakao 2007	Wrong interventions: combination of carvedilol with spironolactone
NCT00328809	This study has been withdrawn due to personnel shortage
Witoon 2019	Wrong interventions: combination of furosemide, hydrochlorothiazide, and spironolactone

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

Gueiros 2019

Methods	Single-centre parallel RCT (open label)
Participants	PD patients
Interventions	Spironolactone

Gueiros 2019 *(Continued)*

Outcomes	Relative and absolute progression of the coronary calcium score; hyperkalaemia; adverse effects (hypotension, hyperpotassaemia, gynaecomastia); mineral metabolism at 12 months; change in inflammation markers at 12 months; causes of study discontinuation
Notes	Protocol registration only; recruitment completed, current status is unknown

NCT02190318

Methods	Single-centre parallel RCT (open label)
Participants	PD patients
Interventions	Losartan plus spironolactone
Outcomes	Residual kidney function, peritoneal membrane function
Notes	Protocol registration only; current status is unknown

NCT03953950

Methods	Parallel RCT (open label)
Participants	PD patients
Interventions	Losartan plus spironolactone versus losartan alone
Outcomes	Peritoneal dialysate effluent CA-125; PET indices; dialysate adequacy; creatinine clearance; serum albumin; serum potassium; waist circumference; BMI; nutritional status; Malnutrition-Inflammation Score; quality of life score; health utility; disease-specific Thai quality of life score; participant well-being score; disability; blood pressure; PD technique failure; PD-related infections; peritonitis or exit-site and tunnel infection; medicinal products-related adverse events
Notes	Registered May 2019; not yet recruiting (December 2020)

Song 2017

Methods	Not available at this time
Participants	Not available at this time
Interventions	Not available at this time
Outcomes	Not available at this time
Notes	Not available at this time

Wang 2018

Methods	Not available at this time
Participants	Not available at this time
Interventions	Not available at this time
Outcomes	Not available at this time
Notes	Not available at this time

BMI - body mass index; PD - peritoneal dialysis; RCT - randomised controlled trial

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

ACHIEVE 2017

Study name	Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease (ACHIEVE)
Methods	Multi-centre parallel RCT
Participants	Estimated enrolment: 2750 Inclusion criteria 1. Age ≥ 45 or ≥18 years with a history of diabetes 2. On dialysis ≥ 90 days 3. On either HD prescribed at least 2 treatments/week or PD prescribed with at least 1 exchange daily 4. Provides informed consent Exclusion criteria 1. Hyperkalaemia: serum potassium > 5.8 mmol/L in the 6 weeks prior to enrolment or serum potassium > 6.0 mmol/L during active run-in 2. Currently taking and unable to withdraw a mineralocorticoid receptor antagonist (i.e. spironolactone or eplerenone) 3. Known sensitivity or allergy to spironolactone 4. Current or planned pregnancy or breastfeeding 5. Scheduled living-related donor kidney transplant 6. Life expectancy < 6 months in the opinion of a treating nephrologist 7. Enrolled in another interventional trial testing a mineralocorticoid receptor antagonist or drug that has a known or likely interaction with spironolactone 8. Treating physician believes either spironolactone is either absolutely indicated or absolutely contra-indicated
Interventions	Intervention: spironolactone 25 mg/day Control: placebo
Outcomes	Primary outcome • CV death or hospitalisation for heart failure up to 5 years Secondary outcome • Cause specific death to 5 years • Hospitalisation for heart failure to 5 years • Death (any cause) up to 5 years

ACHIEVE 2017 *(Continued)*

	• Hospitalisation (any cause) up to 5 years • Hospitalisation for hyperkalaemia up to 5 years
Starting date	7 July 2017
Contact information	Michael Walsh, MD, PhD Population Health Research Institute, McMaster University, Canada
Notes	

ALCHEMIST 2014

Study name	ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST)
Methods	Multi-centre parallel RCT
Participants	Estimated enrolment: 825 Inclusion criteria • Written informed consent • Adult men and women on HD for at least 45 days for ESKD regardless of the aetiology including diabetes, with at least 3 HD sessions/week • Presenting at least one of the follow co-morbidities, cardiovascular abnormalities, or CV risk factors: • LVH defined by * LVM > 130 g/m^2 in men and 100 g/m^2 in women (ECG), **OR** * Cornell (RaVL + SV3) >28 mm in men, > 20 mm in women (ECG), **OR** * Left ventricular EF < 40%, **OR** * Large QRS > 0.14 sec, **OR** * Left bundle branch block (ECG) measured during the twelve months preceding inclusion; diabetes, **OR** * History of cardiovascular disease: coronary artery disease, symptomatic lower limb peripheral arterial disease, carotid or renal artery stenosis > 50%, stroke, hospitalisation for heart failure, permanent AF, oral anticoagulant treatment for AF, valvular heart prosthesis, **OR** * CRP > 5 mg/L for 3 months without infectious or neoplastic disease documented in progress Exclusion criteria • History of hypersensitivity to spironolactone or galactose intolerance • Lapp lactase deficiency or malabsorption of glucose or galactose • Hyperkalaemia > 5.5 mmol/L during the 2 weeks prior to enrolment • History of unscheduled HD for hyperkalaemia during the last 6 months • Hospitalisations for hyperkalaemia during the last 6 months • Patients with imperative indication of a combination of ACEi and ARB or renin inhibitor (each being authorised separately), NSAIDS, Cox-2 inhibitors • Kidney transplant scheduled within the year • Symptomatic interdialytic hypotension • Acute systemic disease • Uncompensated hypothyroidism • Acute hyperthyroidism • Any prior or concomitant clinical condition compromising the inclusion, in the discretion of the investigator • Cardiac transplant

ALCHEMIST 2014 *(Continued)*

	• Severe uncontrolled arrhythmia • Stroke within 3 months prior to enrolment • Acute coronary syndrome in the previous month inclusion • Recent (1 month) or planned coronary revascularization by angioplasty • Recent (3 months) or planned CV surgery (excluding HD vascular access) • Non-menopausal women or without effective contraceptive methods • Pregnancy, breastfeeding or planning a pregnancy within 2 years • Non-compliance • Protected adult • SBP > 200 mm Hg and/or DBP > 110 mm Hg • Concomitant treatment cannot be stopped by another potassium-sparing diuretic, a potassium supplements, NSAID or Cox 2 inhibitors
Interventions	Intervention • Spironolactone 25 mg/day Control • Placebo
Outcomes	Primary outcome • The time to onset of the first incident:non-fatal MI or acute coronary syndrome or hospitalisation for heart failure or nonfatal stroke or CV death [Time Frame: 25 months] Secondary outcome • The cumulate rate of non-fatal MI or acute coronary syndrome, hospitalisation for heart failure, non-fatal stroke, or CV death [Time Frame: 25 months] • The time to onset of death from i) any cause and ii) from a CV event and iii) from a non CV cause [Time Frame: 25 months] • The time of survival without a major CV event (non fatal MI, acute coronary syndrome, hospitalisation for heart failure, non-fatal stroke, cardiac arrest resuscitation) [Time Frame: 25 months] • Incidence of procedures related to stenosis or vascular access thrombosis for HD [Time Frame: 25 months] • Incidence of coronary or peripheral revascularizations (including lower limb amputations) [Time Frame: 25 months] • BP and its inter-visit variability [Time Frame: 25 months] • The occurrence of atrial fibrillation [Time Frame: 25 months] • Incidence of hyperkalaemia > 6 mmol/L [Time Frame: 25 months] • Estimation of the effect of treatment on quality of life. [Time Frame: 25 months]
Starting date	June 2013
Contact information	Prof Patrick ROSSIGNOL University Hospital, Brest, France
Notes	Status: active, not recruiting (28 October 2020)

NCT00277693

Study name	Cardiovascular protective effect of spironolactone in hemodialysis

NCT00277693 *(Continued)*

Methods	Parallel RCT
Participants	Estimated enrolment: not reported Inclusion criteria • 18 to 80 years • Chronic HD (> 3 months) anuria (diuresis < 200 mL/day) Exclusion criteria • Liver failure • Insulin dependent diabetes • Treatment with adrenergic beta blockers or agonists • Treatment with ACEi or ARB • Cancer
Interventions	Intervention • Spironolactone Control • Placebo
Outcomes	Not reported
Starting date	Not reported
Contact information	Antonio Vukusich, MD Faculty of Medicine, University Los Andes, Chile
Notes	Status: unknown (last update posted 16 January 2006)

ACEi - angiotensin-converting enzyme inhibitor; AF - atrial fibrillation; ARB - angiotensin receptor blocker; BP - blood pressure; CRP - C-reactive protein, CV - cardiovascular; DBP - diastolic blood pressure; ECG - echocardiography; EF - ejection fraction; HD - haemodialysis; LVH - left ventricular hypertrophy; LVM - left ventricular mass; PD - peritoneal dialysis; MI - myocardial infarction; NSAID - non-steroidal anti-inflammatory drugs; RCT - randomised controlled trial; SBP - systolic blood pressure

DATA AND ANALYSES

Comparison 1. Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care)

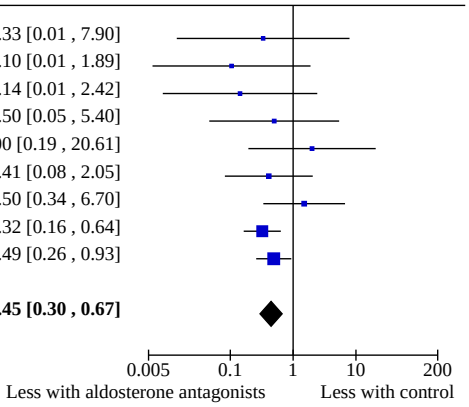
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death (any cause)	9	1119	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.30, 0.67]
1.2 Death: cardiovascular	6	908	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.22, 0.64]
1.3 Cardiovascular and cerebrovascular morbidity	3	328	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.18, 0.76]
1.4 Hyperkalaemia	9	981	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.72, 2.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Gynaecomastia	4	768	Risk Ratio (M-H, Random, 95% CI)	5.95 [1.93, 18.28]
1.6 Left ventricular mass	8	633	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.78, -0.05]
1.7 Left ventricular mass: haemodialysis or peritoneal dialysis	7	435	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.79, 0.04]
1.7.1 Haemodialysis only	6	342	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.92, 0.12]
1.7.2 Peritoneal dialysis only	1	93	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.78, 0.04]
1.8 Ejection fraction	7	458	Mean Difference (IV, Random, 95% CI)	3.15 [-0.74, 7.04]
1.9 Ejection fraction: haemodialysis or peritoneal dialysis	6	260	Mean Difference (IV, Random, 95% CI)	2.57 [-2.34, 7.48]
1.9.1 Haemodialysis only	4	156	Mean Difference (IV, Random, 95% CI)	3.13 [-4.25, 10.51]
1.9.2 Peritoneal dialysis only	2	104	Mean Difference (IV, Random, 95% CI)	2.31 [-1.99, 6.61]
1.10 Serum potassium	7	519	Mean Difference (IV, Random, 95% CI)	0.21 [-0.06, 0.47]
1.11 Serum potassium: haemodialysis or peritoneal dialysis	6	321	Mean Difference (IV, Random, 95% CI)	0.06 [-0.05, 0.18]
1.11.1 Haemodialysis only	5	281	Mean Difference (IV, Random, 95% CI)	0.07 [-0.05, 0.20]
1.11.2 Peritoneal dialysis only	1	40	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.35, 0.33]
1.12 Residual kidney function [urine volume/day]	3	132	Mean Difference (IV, Random, 95% CI)	-36.23 [-114.61, 42.15]

Analysis 1.1. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 1: Death (any cause)

Study or Subgroup	Aldosterone antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Vukusich 2010	0	33	1	33	1.6%	0.33 [0.01 , 7.90]
MiREnDa 2014	0	50	4	47	1.9%	0.10 [0.01 , 1.89]
Taheri CAPD 2012	0	9	3	9	2.0%	0.14 [0.01 , 2.42]
PHASE 2015	1	77	2	77	2.9%	0.50 [0.05 , 5.40]
Ziaee 2019	2	24	1	24	3.0%	2.00 [0.19 , 20.61]
Ito 2014	2	78	5	80	6.3%	0.41 [0.08 , 2.05]
Taheri HD 2009	3	8	2	8	7.3%	1.50 [0.34 , 6.70]
Matsumoto 2014	10	157	30	152	35.3%	0.32 [0.16 , 0.64]
Lin 2016a	12	125	25	128	39.6%	0.49 [0.26 , 0.93]
Total (95% CI)		**561**		**558**	**100.0%**	**0.45 [0.30 , 0.67]**
Total events:	30		73			

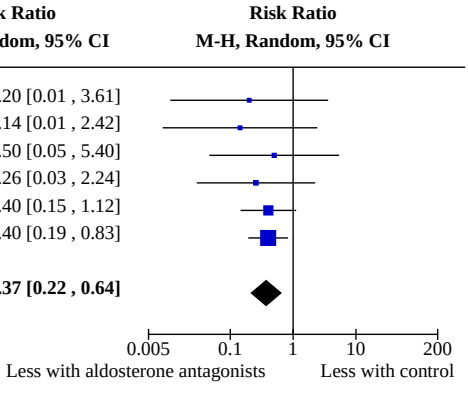
Heterogeneity: Tau² = 0.00; Chi² = 6.78, df = 8 (P = 0.56); I² = 0%
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 2: Death: cardiovascular

Study or Subgroup	Aldosterone antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Taheri HD 2009	0	8	2	8	3.4%	0.20 [0.01 , 3.61]
Taheri CAPD 2012	0	9	3	9	3.6%	0.14 [0.01 , 2.42]
PHASE 2015	1	77	2	77	5.1%	0.50 [0.05 , 5.40]
Ito 2014	1	78	4	80	6.1%	0.26 [0.03 , 2.24]
Matsumoto 2014	5	157	12	152	27.7%	0.40 [0.15 , 1.12]
Lin 2016a	9	125	23	128	54.0%	0.40 [0.19 , 0.83]
Total (95% CI)		**454**		**454**	**100.0%**	**0.37 [0.22 , 0.64]**
Total events:	16		46			

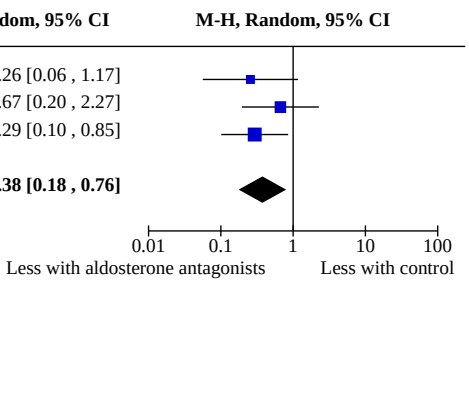
Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 5 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.61 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 3: Cardiovascular and cerebrovascular morbidity

Study or Subgroup	Aldosterone antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ito 2014	2	78	8	80	21.9%	0.26 [0.06 , 1.17]
PHASE 2015	4	77	6	77	33.6%	0.67 [0.20 , 2.27]
Taheri HD 2009	2	8	8	8	44.5%	0.29 [0.10 , 0.85]
Total (95% CI)		**163**		**165**	**100.0%**	**0.38 [0.18 , 0.76]**
Total events:	8		22			

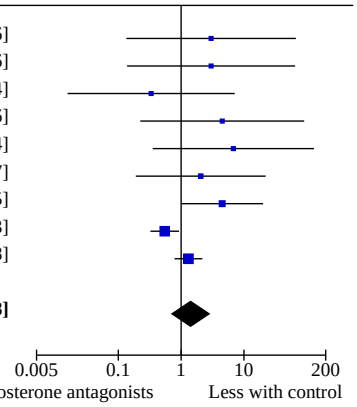
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 4: Hyperkalaemia

Study or Subgroup	Aldosterone antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Yongsiri 2015	1	12	0	12	4.2%	3.00 [0.13 , 67.06]
Taheri CAPD 2012	1	9	0	9	4.3%	3.00 [0.14 , 65.16]
Taheri HD 2009	0	8	1	8	4.3%	0.33 [0.02 , 7.14]
Ni 2014	2	40	0	36	4.4%	4.51 [0.22 , 90.96]
Matsumoto 2014	3	157	0	152	4.6%	6.78 [0.35 , 130.14]
Ito 2014	2	78	1	80	6.6%	2.05 [0.19 , 22.17]
PHASE 2015	9	77	2	77	12.9%	4.50 [1.00 , 20.15]
MiREnDa 2014	14	50	24	47	29.2%	0.55 [0.32 , 0.93]
SPIN-D 2019	30	78	15	51	29.5%	1.31 [0.79 , 2.18]
Total (95% CI)		**509**		**472**	**100.0%**	**1.41 [0.72 , 2.78]**
Total events:	62		43			

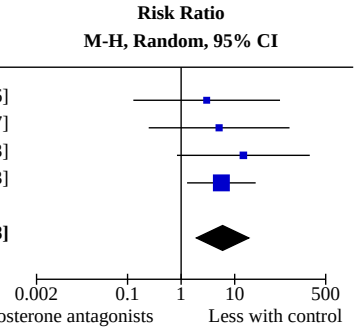
Heterogeneity: Tau² = 0.34; Chi² = 14.96, df = 8 (P = 0.06); I² = 47%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 5: Gynaecomastia

Study or Subgroup	Aldosterone antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ziaee 2019	1	24	0	24	12.7%	3.00 [0.13 , 70.16]
Lin 2016a	2	125	0	128	13.8%	5.12 [0.25 , 105.57]
Matsumoto 2014	7	157	0	152	15.5%	14.53 [0.84 , 252.13]
Ito 2014	11	78	2	80	58.1%	5.64 [1.29 , 24.63]
Total (95% CI)		**384**		**384**	**100.0%**	**5.95 [1.93 , 18.28]**
Total events:	21		2			

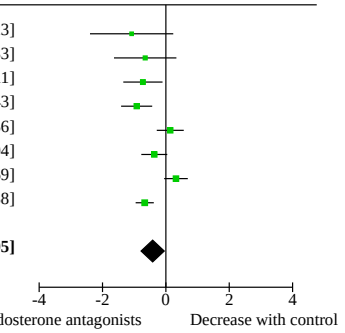
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 3.11 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 6: Left ventricular mass

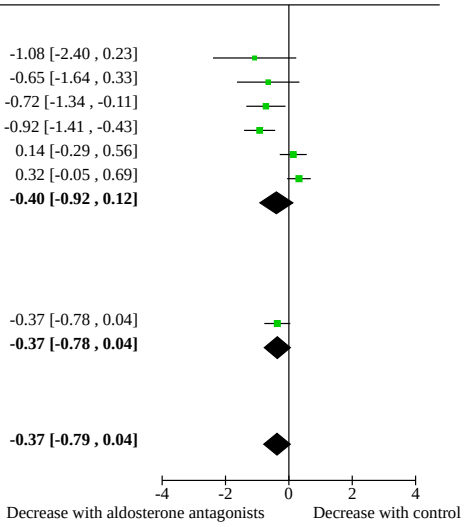
Study or Subgroup	Aldosterone antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Taheri HD 2009	142	15.4	5	159	13.5	6	5.4%	-1.08 [-2.40 , 0.23]
Feniman De Stefano 2015	236	36.1	8	273	65.5	9	7.8%	-0.65 [-1.64 , 0.33]
Ziaee 2019	205.3	40.5	22	274.6	127.8	21	12.0%	-0.72 [-1.34 , -0.11]
Zaripova 2012	132.2	13.4	36	145.5	15.1	35	13.7%	-0.92 [-1.41 , -0.43]
MiREnDa 2014	153.3	42.4	44	147.3	43.6	41	14.6%	0.14 [-0.29 , 0.56]
Ito 2014	45.2	16.3	46	51.3	16.8	47	14.8%	-0.37 [-0.78 , 0.04]
SPIN-D 2019	103	27.6	67	94.8	22.4	48	15.3%	0.32 [-0.05 , 0.69]
Lin 2016a	43.8	13.7	100	54.4	17.7	98	16.4%	-0.67 [-0.95 , -0.38]
Total (95% CI)			**328**			**305**	**100.0%**	**-0.42 [-0.78 , -0.05]**

Heterogeneity: Tau² = 0.19; Chi² = 30.29, df = 7 (P < 0.0001); I² = 77%
Test for overall effect: Z = 2.24 (P = 0.03)
Test for subgroup differences: Not applicable



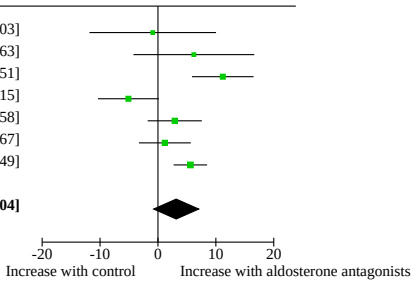
Analysis 1.7. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 7: Left ventricular mass: haemodialysis or peritoneal dialysis

Study or Subgroup	Aldosterone antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.7.1 Haemodialysis only								
Taheri HD 2009	142	15.4	5	159	13.5	6	6.8%	-1.08 [-2.40 , 0.23]
Feniman De Stefano 2015	236	36.1	8	273	65.5	9	9.7%	-0.65 [-1.64 , 0.33]
Ziaee 2019	205.3	40.5	22	274.6	127.8	21	14.4%	-0.72 [-1.34 , -0.11]
Zaripova 2012	132.2	13.4	36	145.5	15.1	35	16.3%	-0.92 [-1.41 , -0.43]
MiREnDa 2014	153.3	42.4	44	147.3	43.6	41	17.3%	0.14 [-0.29 , 0.56]
SPIN-D 2019	103	27.6	67	94.8	22.4	48	18.0%	0.32 [-0.05 , 0.69]
Subtotal (95% CI)			**182**			**160**	**82.5%**	**-0.40 [-0.92 , 0.12]**
Heterogeneity: Tau² = 0.30; Chi² = 23.46, df = 5 (P = 0.0003); I² = 79%								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.7.2 Peritoneal dialysis only								
Ito 2014	45.2	16.3	46	51.3	16.8	47	17.5%	-0.37 [-0.78 , 0.04]
Subtotal (95% CI)			**46**			**47**	**17.5%**	**-0.37 [-0.78 , 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.75 (P = 0.08)								
Total (95% CI)			**228**			**207**	**100.0%**	**-0.37 [-0.79 , 0.04]**
Heterogeneity: Tau² = 0.22; Chi² = 24.02, df = 6 (P = 0.0005); I² = 75%								
Test for overall effect: Z = 1.76 (P = 0.08)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%								



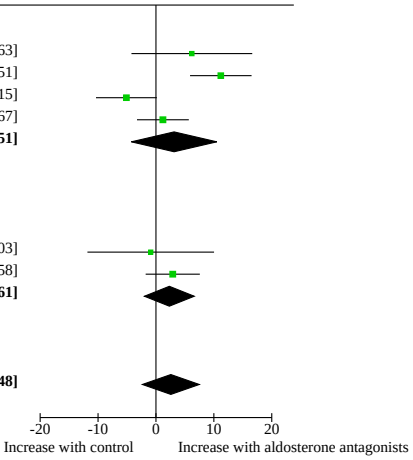
Analysis 1.8. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 8: Ejection fraction

Study or Subgroup	Aldosterone antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Taheri CAPD 2012	33.3	7.8	7	34.2	11.6	6	8.0%	-0.90 [-11.83 , 10.03]
Taheri HD 2009	41.2	9.6	5	35	7.7	6	8.5%	6.20 [-4.23 , 16.63]
Ziaee 2019	60	7.1	22	48.8	10.3	21	15.4%	11.20 [5.89 , 16.51]
MiREnDa 2014	56.7	13.9	44	61.8	10.7	41	15.5%	-5.10 [-10.35 , 0.15]
Ito 2014	65.6	9.4	45	62.7	13.1	46	16.5%	2.90 [-1.78 , 7.58]
Feniman De Stefano 2015	70.9	4.2	8	69.7	5.2	9	16.8%	1.20 [-3.27 , 5.67]
Lin 2016a	64.3	11	100	58.7	9.7	98	19.3%	5.60 [2.71 , 8.49]
Total (95% CI)			**231**			**227**	**100.0%**	**3.15 [-0.74 , 7.04]**
Heterogeneity: Tau² = 18.17; Chi² = 22.32, df = 6 (P = 0.001); I² = 73%								
Test for overall effect: Z = 1.59 (P = 0.11)								
Test for subgroup differences: Not applicable								



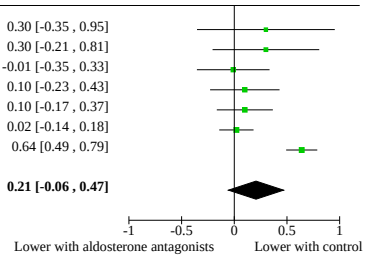
Analysis 1.9. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 9: Ejection fraction: haemodialysis or peritoneal dialysis

Study or Subgroup	Aldosterone antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 Haemodialysis only								
Taheri HD 2009	41.2	9.6	5	35	7.7	6	11.5%	6.20 [-4.23 , 16.63]
Ziaee 2019	60	7.1	22	48.8	10.3	21	18.8%	11.20 [5.89 , 16.51]
MiREnDa 2014	56.7	13.9	44	61.8	10.7	41	18.9%	-5.10 [-10.35 , 0.15]
Feniman De Stefano 2015	70.9	4.2	8	69.7	5.2	9	20.1%	1.20 [-3.27 , 5.67]
Subtotal (95% CI)			**79**			**77**	**69.3%**	**3.13 [-4.25 , 10.51]**
Heterogeneity: Tau² = 45.97; Chi² = 19.16, df = 3 (P = 0.0003); I² = 84%								
Test for overall effect: Z = 0.83 (P = 0.41)								
1.9.2 Peritoneal dialysis only								
Taheri CAPD 2012	33.3	7.8	7	34.2	11.6	6	11.0%	-0.90 [-11.83 , 10.03]
Ito 2014	65.6	9.4	45	62.7	13.1	46	19.8%	2.90 [-1.78 , 7.58]
Subtotal (95% CI)			**52**			**52**	**30.7%**	**2.31 [-1.99 , 6.61]**
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%								
Test for overall effect: Z = 1.05 (P = 0.29)								
Total (95% CI)			**131**			**129**	**100.0%**	**2.57 [-2.34 , 7.48]**
Heterogeneity: Tau² = 26.06; Chi² = 19.55, df = 5 (P = 0.002); I² = 74%								
Test for overall effect: Z = 1.03 (P = 0.30)								
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%								

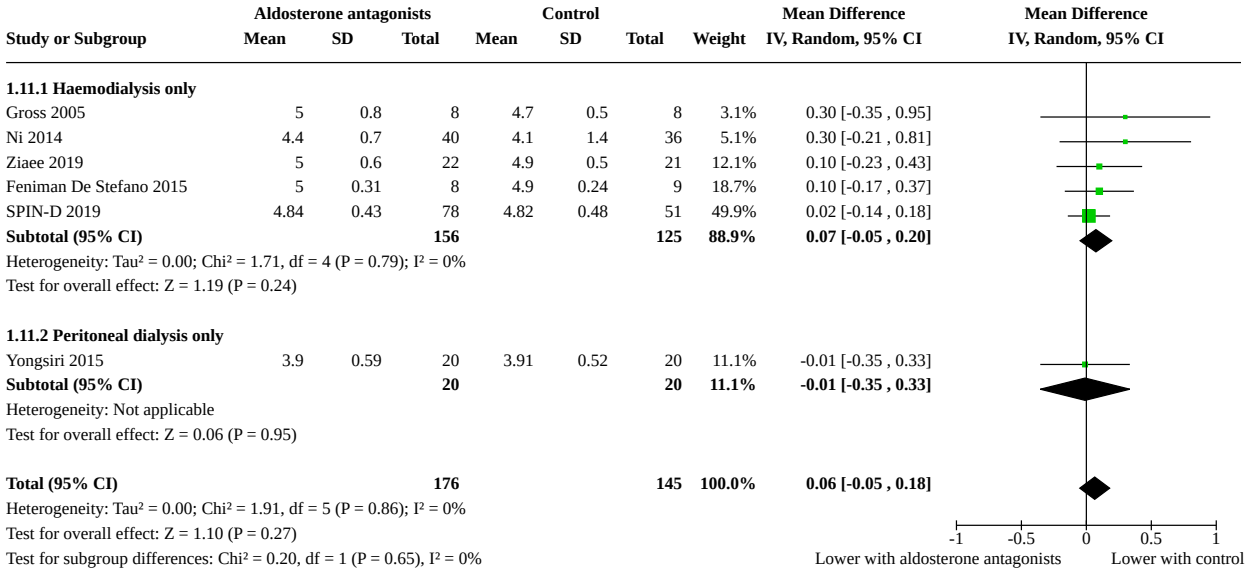


Analysis 1.10. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 10: Serum potassium

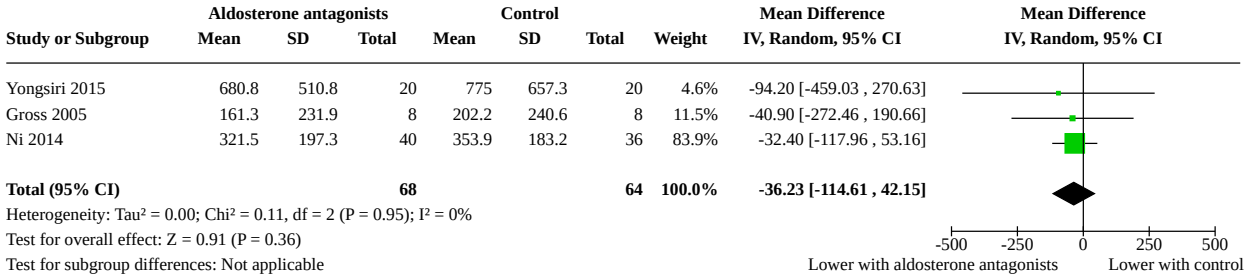
Study or Subgroup	Aldosterone antagonists Mean [mmol/L]	SD [mmol/L]	Total	Control Mean [mmol/L]	SD [mmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [mmol/L]
Gross 2005	5	0.8	8	4.7	0.5	8	8.7%	0.30 [-0.35 , 0.95]
Ni 2014	4.4	0.7	40	4.1	1.4	36	11.1%	0.30 [-0.21 , 0.81]
Yongsiri 2015	3.9	0.59	20	3.91	0.52	20	14.3%	-0.01 [-0.35 , 0.33]
Ziaee 2019	5	0.6	22	4.9	0.5	21	14.6%	0.10 [-0.23 , 0.43]
Feniman De Stefano 2015	5	0.31	8	4.9	0.24	9	15.9%	0.10 [-0.17 , 0.37]
SPIN-D 2019	4.84	0.43	78	4.82	0.48	51	17.7%	0.02 [-0.14 , 0.18]
Lin 2016a	5.32	0.68	100	4.68	0.32	98	17.9%	0.64 [0.49 , 0.79]
Total (95% CI)			**276**			**243**	**100.0%**	**0.21 [-0.06 , 0.47]**
Heterogeneity: Tau² = 0.09; Chi² = 38.31, df = 6 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 1.55 (P = 0.12)								
Test for subgroup differences: Not applicable								



Analysis 1.11. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 11: Serum potassium: haemodialysis or peritoneal dialysis



Analysis 1.12. Comparison 1: Aldosterone antagonists (spironolactone or eplerenone) versus control (placebo or usual care), Outcome 12: Residual kidney function [urine volume/day]



ADDITIONAL TABLES

Table 1. Comparison of included studies between previous non-Cochrane systematic reviews and current Cochrane systematic review

Systematic reviews	Quach 2016	Li 2019	Hasegawa 2021 [a]
Number of included studies	9	10	16
Number of analysed participants	829	1172	1446
Included studies	-	Feniman De Stefano 2015	Feniman De Stefano 2015
	Gross 2005	-	Gross 2005

Table 1. Comparison of included studies between previous non-Cochrane systematic reviews and current Cochrane systematic review *(Continued)*

Ito 2014	Ito 2014	Ito 2014
-	Lin 2016a	Lin 2016a
Matsumoto 2014	Matsumoto 2014	Matsumoto 2014
-	-	MiREnDa 2014
Ni 2014	-	Ni 2014
PHASE 2015	PHASE 2015	PHASE 2015
-	Song 2017 [b]	-
-	-	SPIN-D 2019
Taheri CAPD 2012	Taheri CAPD 2012	Taheri CAPD 2012
Taheri HD 2009	Taheri HD 2009	Taheri HD 2009
-	-	Vazquez-Rangel 2014 [c]
Vukusich 2010	-	Vukusich 2010
-	Wang 2018 [b]	-
Yongsiri 2015	-	Yongsiri 2015
-	Zaripova 2012	Zaripova 2012
-	-	Ziaee 2019

[a] Current Cochrane review
[b] No data available for this review
[c] Not meta-analysed

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Renal Replacement Therapy] this term only 2. MeSH descriptor: [Renal Dialysis] this term only 3. MeSH descriptor: [Peritoneal Dialysis] explode all trees 4. MeSH descriptor: [Hemodiafiltration] this term only 5. MeSH descriptor: [Hemodialysis, Home] this term only 6. (hemodialysis or haemodialysis):ti,ab,kw (Word variations have been searched) 7. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched) 8. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched)

(Continued)

	9. "end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal":ti,ab,kw (Word variations have been searched) 10.ESKD or ESKF or ESRD or ESRF:ti,ab,kw (Word variations have been searched) 11.CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched) 12.{or #1-#11} 13.MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees 14.spironolactone:ti,ab,kw (Word variations have been searched) 15.eplerenone:ti,ab,kw (Word variations have been searched) 16.canrenone:ti,ab,kw (Word variations have been searched) 17.{or #13-#16} 18.{and #12, #17}
MEDLINE	1. Renal Replacement Therapy/ 2. Renal Dialysis/ 3. exp Peritoneal Dialysis/ 4. (CAPD or CCPD or APD).tw. 5. Hemodiafiltration/ 6. Hemodialysis, home/ 7. dialysis.tw. 8. (hemodialysis or haemodialysis).tw. 9. (hemofiltration or haemofiltration).tw. 10.(hemodiafiltration or haemodiafiltration).tw. 11.(end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw. 12.(ESKD or ESKF or ESRD or ESRF).tw. 13.or/1-12 14.exp Mineralocorticoid Receptor Antagonists/ 15.Diuretics, Potassium Sparing/ 16.spironolactone.tw. 17.eplerenone.tw. 18.canrenone.tw. 19.or/14-17 20.and/13,19
EMBASE	1. Kidney Failure/ 2. renal replacement therapy/ 3. end stage renal disease/ 4. renal replacement therapy-dependent renal disease/ 5. extended daily dialysis/ 6. hemodiafiltration/ 7. hemofiltration/ 8. exp hemodialysis/ 9. exp peritoneal dialysis/ 10.(hemodialysis or haemodialysis).tw. 11.(hemofiltration or haemofiltration).tw. 12.(hemodiafiltration or haemodiafiltration).tw. 13.dialysis.tw. 14.peritoneal dialysis.tw. 15.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 16.(CAPD or CCPD or APD).tw. 17.(ESRF or ESKF or ESRD or ESKD).tw. 18.or/1-17 19.exp mineralocorticoid antagonist/

(Continued)

	20.spironolactone.tw. 21.canrenone.tw. 22.eplerenone.tw. 23.or/19-22 24.and/18,23

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; minimisation (minimisation 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).
	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

(Continued)

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 standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 8, 2018
Review first published: Issue 2, 2021

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: TH, EO, WL
2. Study selection: TH, H Nishiwaki
3. Extract data from studies: TH, H Nishiwaki
4. Enter data into RevMan: TH, H Nishiwaki, EO, WL, H Noma
5. Carry out the analysis: TH, EO, WL, H Noma
6. Interpret the analysis: TH, H Nishiwaki

7. Draft the final review: TH, H Nishiwaki, EO, WL, H Noma
8. Disagreement resolution: TH, H Nishiwaki, EO
9. Update the review: TH, H Nishiwaki, EO, WL, H Noma

DECLARATIONS OF INTEREST

- TH: has a grant by JSPS KAKENHI Grant Number 19K03092 and consultancy agreement with Kyowa Kirin and has received speaker honoraria from Kyowa Kirin, Astellas, Baxter, Terumo, and Torii Pharmaceutical for activities unrelated to this review
- H Nishiwaki: has declared that they have no conflict of interest
- EO: has declared that they have no conflict of interest
- WL: has declared that they have no conflict of interest
- H Noma: has received consultant fees from Kyowa Kirinand lecture fees from Boehringer Ingelheim and Kyowa Kirin

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- JSPS KAKENHI, Japan

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Non-selective (spironolactone) and selective (eplerenone) interventions were combined and not analysed separately as planned in the protocol because only one study compared eplerenone to a control intervention. Death was set as a composite outcome for all-cause and cardiovascular In the protocol. Because the cause of death was not distinguished in each case in the included studies, we set the outcomes for death (any cause) and death (cardiovascular) separately in the review. We kept the various definition of hyperkalaemia together due to the small number of the eligible included studies. Information on blood pressure as an outcome was insufficient and lacked a standardised method of reporting (e.g. pre-dialysis systolic or diastolic blood pressure or mean 24 hours blood pressure or mean morning systolic or diastolic blood pressure), we therefore were not able to carry out a meta-analysis on these data as planned. Additionally, we could not conduct prespecified subgroup analyses including residual kidney function, diabetic kidney disease, and concomitant use of RAS inhibitors except for dialysis modality due to the small number of the eligible included studies and the lack of information reported.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Cardiovascular Diseases [chemically induced]; Cause of Death; Cerebrovascular Disorders [chemically induced]; Eplerenone [adverse effects] [therapeutic use]; Gynecomastia [chemically induced]; Hyperkalemia [chemically induced]; Mineralocorticoid Receptor Antagonists [adverse effects] [*therapeutic use]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; *Renal Dialysis; Renal Insufficiency, Chronic [mortality] [*therapy]; Spironolactone [adverse effects] [therapeutic use]

MeSH check words

Humans