Safety and efficacy of steroidal mineralocorticoid receptor antagonists in patients with kidney failure requiring dialysis: a systematic review and meta-analysis of randomised controlled trials

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Summary

Background Mineralocorticoid receptor antagonists can prevent cardiovascular events in patients with heart failure and non-severe chronic kidney disease, but their effects in patients with kidney failure requiring dialysis are uncertain. We aimed to assess the efficacy and safety of mineralocorticoid receptor antagonists in this patient population.

Methods In this systematic review and meta-analysis, we updated our previous systematic review by searching MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature for randomised controlled trials published between database inception and March 18, 2025. Trials comparing a mineralocorticoid receptor antagonist with placebo or standard of care in adults (aged ≥18 years) receiving maintenance dialysis were eligible. Studies that did not report an outcome of interest (cardiovascular mortality, heart failure hospitalisation, all-cause mortality, all-cause hospitalisation, hyperkalaemia, gynaecomastia or breast pain, or hypotension) were excluded. Two reviewers independently identified studies, extracted data, and assessed the risk of bias using the Cochrane risk-of-bias tool. The main outcome was cardiovascular mortality assessed using the empirical Bayes random-effects models, stratified by risk-of-bias. The protocol is registered with PROSPERO (CRD420251008119).

Findings 19 trials of steroidal mineralocorticoid receptor antagonists including 4675 participants met eligibility criteria. Effect estimates differed trials with low and high risk of bias. In four trials with a low risk of bias (n=3562), 264 cardiovascular deaths occurred in 1785 patients in the mineralocorticoid receptor antagonist group compared with 276 of 1777 patients in the control group (odds ratio 0·98 [95% CI 0·80–1·20]; I^2=0·0%; τ^2=0·0; moderate certainty) resulting in an absolute risk reduction of 1 fewer event per 1000 patients per year (95% CI 14 fewer to 11 more).

Interpretation Our findings suggest that steroidal mineralocorticoid receptor antagonists have little to no effect on cardiovascular mortality in patients requiring dialysis. There is insufficient information on the effects of steroidal mineralocorticoid receptor antagonists in subgroups of patients requiring dialysis and no information on non-steroidal mineralocorticoid receptor antagonists. Future trials would need to consider the likelihood of only smaller effects or effects limited to patients or events with pathophysiology that is more clearly driven by aldosterone in their design.

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Introduction

The incidence and mortality rate of kidney failure are increasing globally.[1–3] Patients requiring dialysis have annual mortality rates of up to 20%, mostly due to cardiovascular causes.[4–7] The cardiovascular morbidity and mortality that accompanies kidney failure has many similarities with congestive heart failure, such as high rates of hospitalisation for heart failure and high cardiovascular mortality, particularly sudden cardiac death.[5] Mineralocorticoid receptor antagonists have been shown to provide cardiovascular benefits in selected populations with heart failure and chronic kidney disease,[8–11] but their effects and safety in patients with kidney failure requiring dialysis remain uncertain.

Our previous systematic review and meta-analysis on the safety and efficacy of mineralocorticoid receptor antagonists in patients who require dialysis found that there was low-certainty evidence suggesting that mineralocorticoid receptor antagonists reduced cardiovascular mortality (with a relative risk reduction of 66%) in patients requiring dialysis with an increased risk of hyperkalaemia, and concluded that additional large high-quality trials were required.[12] A 2021 Cochrane review reported similar effect estimates, with less focus on the

Research in context

Evidence before this study

Previous meta-analyses of randomised controlled trials suggested a large benefit of mineralocorticoid receptor antagonists, primarily spironolactone, on cardiovascular death (relative risk [RR] 0·34 [95% CI 0·15–0·75]) and all-cause death (0·40 [0·23–0·69]) and a variable increase in the risk of hyperkalaemia (3·05 [1·21–7·70]) in individuals receiving maintenance dialysis. These meta-analyses were limited by a small number of events and a reliance on trials at high risk of bias. Current guidelines recommend the use of non-steroidal mineralocorticoid receptor antagonists in patients with diabetes and chronic kidney disease at risk of progression of chronic kidney disease and steroidal mineralocorticoid receptor antagonists for those with resistant hypertension and chronic kidney disease not receiving dialysis, but no recommendations exist regarding their use in patients with kidney failure receiving dialysis.

Added value of this study

This updated meta-analysis includes ten additional randomised controlled trials, including two recently completed randomised controlled trials at low risk of bias, substantially increasing the number of patients and events to base inferences on.
Our findings suggest that steroidal mineralocorticoid receptor antagonists, predominantly spironolactone, have little to no effect of on cardiovascular death in these patients.
We identified an increase in the risk of hyperkalaemia (defined as a serum potassium concentration ≥6·5 mmol/L) and gynaecomastia or mastodynia, but the absolute risks of these were low in the included randomised controlled trials.

Implications of all the available evidence

The available evidence does not support the use of mineralocorticoid receptor antagonists to reduce the risk of cardiovascular death in patients with kidney failure receiving maintenance dialysis.

certainty of the evidence.[13] On completion of two additional randomised controlled trials, ALCHEMIST[14] and ACHIEVE,[15] we found it timely to update our previous meta-analysis.[12] Our updated systematic review and meta-analysis includes the results of randomised controlled trials published in the subsequent 10 years, to assess the totality of available evidence on the safety and efficacy of mineralocorticoid receptor antagonists in patients with kidney failure requiring dialysis.

Methods

Search strategy and selection criteria

We based our dataset on a previous systematic review and meta-analysis,[12] which included studies published between 1974 and 2015 (search details are shown in the appendix [p 2]). We updated our previous systematic review and meta-analysis by searching MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature database without any language restrictions for randomised controlled trials published between Jan 1, 2015, and March 18, 2025, and added terms for finerenone to our previous search strategy (appendix p 2). We added two newly completed randomised controlled trials, the ALCHEMIST trial[14] and the ACHIEVE trial,[15] to the identified titles and abstracts and reviewed their eligibility alongside all other studies.

See Online for appendix

Two authors (CG and MJ) independently assessed all articles from the first systematic review and the abstracts from the results of the updated search for eligibility. Abstracts identified as ineligible by both assessors were excluded and all other studies underwent a full-text review by the same two assessors. Inclusion criteria were: study design (randomised controlled trial), population (adults [aged ≥18 years] with kidney failure, receiving maintenance haemodialysis or peritoneal dialysis), intervention (any mineralocorticoid receptor antagonist), comparator (placebo or standard of care), and outcome (one or more outcomes of interest [cardiovascular mortality, heart failure hospitalisation, all-cause mortality, all-cause hospitalisation, hyperkalaemia, gynaecomastia or breast pain, or hypotension]). We excluded studies that did not meet all the inclusion criteria. Disagreements were resolved via discussion and involvement of a third reviewer (LP). Following data extraction, we found significant variability in reported definitions of hyperkalaemia, and decided to separately analyse the two most common definitions, potassium of 6·0 mmol/L or higher and potassium of 6·5 mmol/L or higher.

The systematic review was registered at PROSPERO (CRD420251008119).

Data analysis

Two reviewers (CG and LP) independently extracted the following data from eligible studies: study characteristics (design and duration); participant baseline characteristics (age, sex, dialysis type, history of heart failure); intervention (mineralocorticoid receptor antagonist type and dose); comparator; outcome characteristics (definition of relevant outcomes); and results. We extracted cardiovascular death and heart failure hospitalisations as efficacy outcomes, and all-cause mortality, hyperkalaemia, gynecomastia or breast pain, and hypotension as safety outcomes. Disagreements were resolved via discussion or involvement of a third reviewer (MW). Corresponding authors were contacted by email to clarify data points on which any uncertainty was apparent.

Two reviewers (CG and LP) independently assessed study quality using the revised Cochrane risk-of-bias tool, which assesses sources of bias in various domains

(random sequence generation; allocation concealment; masking of participants, personnel, or outcome assessors; incomplete outcome data; and selective reporting).[16] Each study outcome was categorised as of low risk of bias if there were no concerns; all other studies were considered as being at high risk of bias. We assessed publication bias with a funnel plot, Egger's test, and Begg's test of the primary outcome.

We used the GRADE approach to summarise our results and evaluate the certainty of evidence using a minimally contextualised approach rating the certainty in relation to the null effect.[17,18] The rating of certainty included consideration of risk of bias, inconsistency, indirectness, and imprecision.[17]

The primary outcome of this study was cardiovascular death. We summarised treatment effects using odds ratios (ORs) and 95% CIs for each available outcome in each study using the full trial population, consistently with the intention-to-treat principle. We chose ORs because they can be consistently applied across various study designs; their logarithms often approximate a normal distribution (facilitating meta-analysis); and unlike risk ratios, they are mathematically invariant to baseline event rates, making them broadly comparable across studies with differing baseline risks. We explored the use of hazard ratios (HRs), but because HRs and their standard errors often had to be estimated indirectly (even in studies that reported HRs), we chose to report only ORs, which can approximate HRs reasonably well when event rates are low and the proportional hazards assumption holds. For each outcome, we used a Bayesian random-effects model to estimate the overall effects and heterogeneity variance, given that this approach has generally shown lower bias than other estimators that account for between-study heterogeneity.[19,20] The empirical Bayes model estimates a prior distribution for the true effects informed by the observed data and allows for shrinkage of individual study effect estimates towards the overall mean, providing more stable estimates than other models in meta-analyses with smaller trials or higher variance. The proportion of total variability due to between-study heterogeneity was calculated using the I^2 statistic and the estimated between-study variance (τ^2). We plotted the results for each outcome in forest plots that included the number of participants with and without events (as required for the calculation of ORs), the OR and 95% CI for each study, the weight of each study and the effects for studies at low and high risk of bias, and an overall effect when low and high risk of bias studies were consistent.

We calculated the absolute reduction for each outcome on the basis of the estimated annualised risk from epidemiological data where available (for cardiovascular mortality and all-cause mortality), and from the pooled control group event rate where epidemiological data were not available (for heart failure hospitalisation, all-cause hospitalisation, hyperkalaemia, gynaecomastia or breast pain, and hypotension).

For studies with no events in a 2×2 contingency table, we added the value 0·1 to all cells as a continuity correction factor to reduce potential bias in estimates. We explored the possible effects of this correction factor using sensitivity analyses in which we used a smaller continuity correction of 0·01. Studies with no events in both groups were excluded.

We mitigated the potential effects of studies at high risk of bias by examining the Q statistic for differences between subgroups of low risk of bias and high risk of bias and the degree to which the overall pooled estimate and precision of the estimate differed by inclusion and exclusion of high risk of bias studies. When the p value for the Q statistic was less than 0·05, or if inclusion of studies

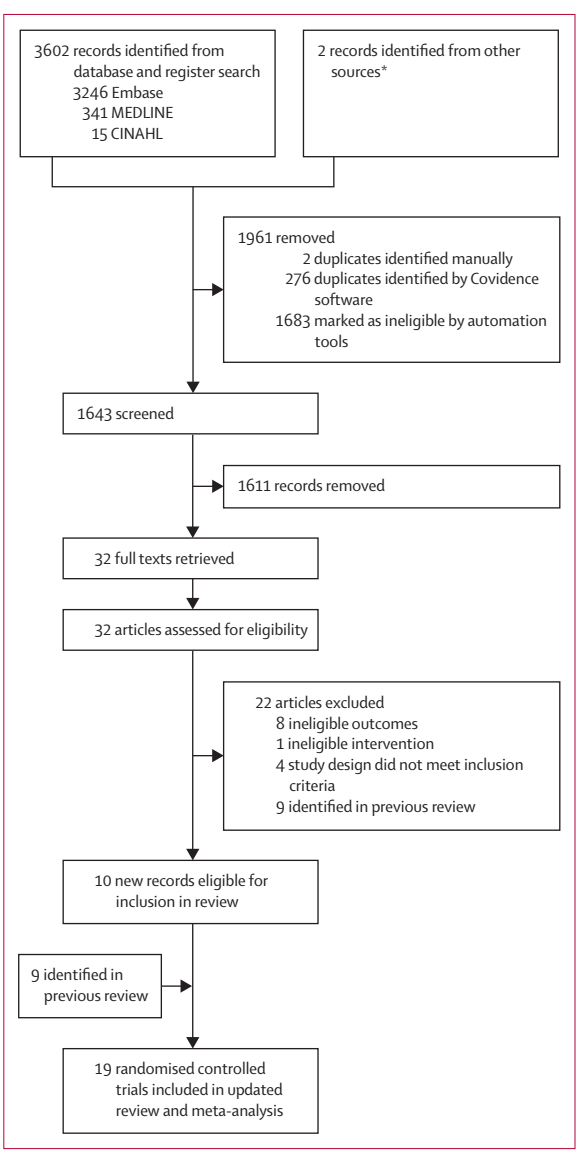

Figure 1: **Study selection**
CINAHL=Cumulative Index to Nursing and Allied Health Literature database. *ALCHEMIST[14] and ACHIEVE[15] trials.

	Design	Mineralocorticoid receptor antagonist	Regimen*	Control	Patients, n	Female n (%)	Male n (%)	Age, years (mean [SD])	Heart failure n (%)	Dialysis type	Length of follow-up
Gross et al (2005)[21]	Crossover	Spironolactone	50 mg twice daily	Placebo	8	5 (62·5%)	3 (37·5%)	53 (10)	Not reported	Haemodialysis	4 weeks
Taheri et al (2009)[22]	Parallel	Spironolactone	25 mg after haemodialysis	Placebo	Intervention n=8; control n=8	Intervention 3 (37·5%); control 2 (25%)	Intervention 5 (62·5%); control 6 (75·0%)	Intervention 59·5 (6·5); control 56·8 (9·3)	Intervention 8 (100%); control 8 (100%)	Haemodialysis	6 months
Vukusich et al (2010)[23]	Parallel	Spironolactone	50 mg three times weekly after haemodialysis	Placebo	Intervention n=33; control n=33	Intervention 10 (33·3%); control 9 (39%)	Intervention 20 (66·7%); control 14 (61·0%)	Intervention 60·1 (5·2); control 55·6 (3·6)	Not reported	Haemodialysis	24 months
Taheri et al (2012)[24]	Parallel	Spironolactone	25 mg every other day	Placebo	Intervention n=9; control n=9	Intervention 4 (44·4%); control 4 (44·4%)	Intervention 5 (55·6%); control 5 (55·6%)	Intervention 50·7 (17·4); control 57·2 (13·1)	Intervention 9 (100%); control 9 (100%)	Peritoneal dialysis	6 months
Ito et al (2014)[25]	Parallel	Spironolactone or eplerenone	Spironolactone 25 mg daily or eplerenone 50 mg daily	NA	Intervention n=78; control n=80	Intervention 23 (29·5%); control 22 (27·5%)	Intervention 55 (70·5%); control 58 (72·5%)	Intervention 57·4 (12·3); control 55·6 (14·4)	Not reported	Peritoneal dialysis	24 months
Matsumoto et al (2014)[26]	Parallel	Spironolactone	25 mg daily	NA	Intervention n=157; control n=152	Intervention 44 (28%); control 62 (40·8%)	Intervention 113 (72·0%); control 90 (59·2%)	Intervention 67·4 (12·3); control 67·7 (11·2)	Not reported	Haemodialysis	36 months
Ni et al (2014)[27]	Parallel	Spironolactone	25–50 mg daily	Placebo	Intervention n=40; control n=36	Intervention 16 (40%); control 15 (41·7%)	Intervention 24 (60·0%); control 21 (58·3%)	Intervention 55·7 (12·3); control 54·9 (14·2)	Not reported	Haemodialysis and peritoneal dialysis	12 weeks
Feniman-De-Stefano et al (2015)[28]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=10; control n=9	Intervention 4 (50%); control unclear	Intervention 4 (50·0%); control unclear	Unclear reporting	Not reported	Haemodialysis	6 months
Walsh et al (2015)[29]	Parallel	Eplerenone	50 mg daily	Placebo	Intervention n=77; control n=77	Intervention 30 (39%); control 28 (36·4%)	Intervention 47 (61·0%); control 49 (63·6%)	Intervention 62·1 (14·6); control 63·1 (13·7)	Intervention 8 (10·4%) control 6 (7·8%)	Haemodialysis	13 weeks
Yongsiri et al (2015)[30]	Crossover	Spironolactone	25 mg daily	Placebo	20	12 (60%)	8 (40·0%)	52·4 (12·4)	Not reported	Peritoneal dialysis	4 weeks
Lin et al (2016)[31]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=125; control n=128	Intervention 52 (41·6%); control 48 (37·5%)	Intervention 73 (58·4%); control 80 (62·5%)	Intervention 70·3 (10·9); control 70·6 (8·4)	Intervention 0 (0·0%); control 0 (0·0%)	Haemodialysis and peritoneal dialysis	24 months
Charytan et al (2019)[32]	Parallel	Spironolactone	12·5, 25, or 50 mg daily	Placebo	Intervention n=78; control n=51	Intervention 25 (32·1%); control 19 (37·3%)	Intervention 53 (67·9%); control 32 (62·7%)	Intervention 54·6 (12·5); control 56·8 (11·5)	Intervention 13 (14·1%); control 10 (19·6%)	Haemodialysis	36 weeks

(Table 1 continues on next page)

	Design	Mineralocorticoid receptor antagonist	Regimen*	Control	Patients, n	Female n (%)	Male n (%)	Age, years (mean [SD] or median [IQR])	Heart failure n (%)	Dialysis type	Length of follow-up
(Continued from previous page)											
Gueiros et al (2019)[33]	Parallel	Spironolactone	25 mg daily	NA	Intervention n=16; control n=17	Intervention 4 (57·1%); control 4 (44·4%)	Intervention 3 (42·9%); control 5 (55·6%)	Intervention 69·7 (8·9); control 61·3 (8·6)	Not reported	Peritoneal dialysis	12 months
Hammer et al (2019)[34]	Parallel	Spironolactone	50 mg daily	Placebo	Intervention n=50; control n=47	Intervention 10 (20·0%); control 12 (25·5%)	Intervention 40 (80·0%); control 35 (74·5%)	Intervention 60·6 (13·1); control 59·9 (13·4)	Intervention 3 (6%); control 1 (2%)	Haemodialysis	40 weeks
Ziaee et al (2019)[35]	Parallel	Spironolactone	25 mg after haemodialysis	NA	Intervention n=24; control n=24	Intervention 10 (45·5%); control 8 (38·1%)	Intervention 12 (54·5%); control 13 (61·9%)	Intervention 69·2 (13·5); control 67·5 (10)	Not reported	Haemodialysis	9 months
Thanaponsatorn et al (2022)[38]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=20; control n=20	Intervention 6 (35·3%); control 6 (35·3%)	Intervention 11 (64·7%); control 11 (64·7%)	Intervention 46 (15·9); control 54·7 (11·9)	Not reported	Peritoneal dialysis	6 months
Walsh et al (2025)[15]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=1260; control n=1275	Intervention 466 (37·0%); control 465 (36·4%)	Intervention 794 (63·0%); control 810 (63·5%)	Intervention 61·5 (11); control 62·1 (11)	Intervention 155 (12·3%); control 135 (10·6%)	Haemodialysis and peritoneal dialysis	Median 1·8 years
Rossignol et al (2025)[14]	Parallel	Spironolactone	25 mg daily	Placebo	Intervention n=320; control n=324	Intervention 110 (34·4%); control 90 (27·8%)	Intervention 210 (65·6%); control 234 (72·2%)	Intervention 71·1 (64·3–77·4);† control 71·5 (63·2–79·0)†	Intervention 37 (11·6%); control 37 (11·4%)	Haemodialysis	Median 32·6 months
Vongchaiudomchoke et al (2025)[37]	Crossover	Spironolactone	50 mg before haemodialysis	Placebo	49	19 (39%)	30 (61·0%)	54 (14)	Not reported	Haemodialysis	24 weeks

NA=not applicable. *Route of administration was oral for all study drugs . †Median (IQR).

Table 1: **Characteristics of included trials**

at high risk of bias resulted in a wider overall CI for the treatment effect, inferences were drawn from the studies at low risk of bias only. We performed sensitivity analyses by applying Sidik–Jonkman random effects models and maximum likelihood models, given these models can reduce bias in some situations when there are few events or τ^2 values are close to zero.[20] We planned subgroup effects on the basis of age, sex, dialysis type, and heart failure history, but none of the included studies reported these data. Statistical analyses were performed using Stata (version 18.5).

Role of the funding source

There was no funding source for this study.

Results

The updated search identified 3604 records, of which 1961 were removed due to duplication or automated identification as not being a randomised controlled trial. After screening of 1643 titles and abstracts, 32 randomised controlled trials[14,15,21–37] were selected for full-text review (appendix pp 16–18). Of those, ten records were eligible for inclusion, in addition to the nine identified by our previous review (figure 1). The characteristics of the included studies are summarised in table 1. Studies excluded after full-text review are listed in the appendix (p 16). 17 trials[14,15,21–24, 26–28, 30–37] studied spironolactone, one trial[29] studied eplerenone, and one trial[25] studied spironolactone or eplerenone (in participants unable to tolerate spironolactone). No trials studying finerenone or other mineralocorticoid receptor antagonists were identified.

The risk of bias of the included studies is summarised in the appendix (p 6). Of the 19 eligible trials, five were considered at low risk of bias. Unclear random sequence generation, allocation methods, absence of masking, and loss to follow-up were prevalent among studies at high risk of bias.

The findings for all outcomes are summarised in table 2. The certainty of each assessment and the absolute risk differences expected are summarised in table 3. No publication bias was identified in the funnel plot analysis (all studies were within the pseudo 95% CI, with no obvious asymmetry), Egger's test (p=0·11), or Begg's test (p=0·88; appendix p 10). We did not repeat these assessments for the low risk of bias stratum due to the limited number of studies remaining.

The assessment of cardiovascular mortality comprised 11 trials (n=4349), of which five (n=3562) were at low risk of bias and six (n=787) were at high risk of bias. Effect estimates from trials at low risk of bias trials differed from trials at high risk of bias (figure 2). In trials with low risk of bias, 264 cardiovascular deaths occurred in 1785 patients (14·8%) in the mineralocorticoid receptor antagonist group, compared with 276 (15·5%) of 1777 patients in the control group (OR 0·98 [95% CI 0·80–1·20]; I^2=2·9; τ^2=0·0; moderate certainty). Sensitivity analyses showed no substantial differences in these results (appendix p 9).

Heart failure hospitalisation was assessed in two trials[14,15] (n=3182), both of which were at low risk of bias. 94 heart failure hospitalisations occurred in 1580 patients (5·9%) in the mineralocorticoid receptor antagonist group, compared with 106 (6·6%) of 1602 patients in the control group (OR 0·70 [95% CI 0·30–1·65]; I^2=71·1, τ^2=0·29; low certainty; appendix p 11).

14 trials[14,15,22–26,29,31,32–36] (n=4503) reported all-cause mortality. Effect estimates from trials with low risk of bias differed substantially from those from trials at high risk of bias (appendix p 12). For low risk of bias trials, 553 all-cause mortality events occurred in 1805 patients (30·6%) in the mineralocorticoid receptor antagonist group compared with 574 (31·9%) of 1797 patients in the control group (OR 0·97 [95% CI 0·84–1·12]; I^2=0, τ^2=0; moderate certainty).

One trial[15] (n=2538) reported all-cause hospitalisation. All-cause hospitalisation occurred in 728 (57·8%) of 1260 patients in the mineralocorticoid receptor antagonist group compared with 748 (58·5%) of 1278 patients in the control group (OR 0·97 [95% CI 0·83–1·14]; moderate certainty). Hyperkalaemia, defined as a serum potassium concentration of 6·0 mmol/L or greater, was reported in

	All studies			Studies with a low risk of bias			Studies with a high risk of bias		
	Participants, n	OR (95% CI)	I^2	Participants, n	OR (95% CI)	I^2	Participants, n	OR (95% CI)	I^2
Cardiovascular mortality	4349	0·73 (0·46–1·16)	42·7	3562	0·98 (0·80–1·20)	2·9	787	0·33 (0·17–0·67)	0·0
Heart failure hospitalisations	3182	0·70 (0·30–1·65)	71·1	3182	0·70 (0·30–1·65)	71·1	..	..	..
All-cause mortality	4503	0·73 (0·53–1·01)	34·1	3602	0·97 (0·84–1·12)	0·0	901	0·40 (0·25–0·65)	0·0
All hospitalisations	2538	0·96 (0·87–1·06)	NA	2538	0·96 (0·87–1·06)	NA	..	..	..
Hyperkalaemia (≥6·0 mmol/L)	1104	1·07 (0·82–1·40)	0·0	927	1·06 (0·81–1·38)	0·0	177	2·54 (0·26–24·6)	0·0
Hyperkalaemia (≥6·5 mmol/L)	2918	1·50 (1·11–2·03)	0·0	2918	1·50 (1·11–2·03)	0·0	..	..	..
Gynaecomastia or breast pain	4292	3·66 (2·02–6·62)	0·0	3448	3·02 (1·57–5·81)	0·0	844	8·69 (2·17–34·8)	0·0
Hypotension	3012	1·04 (0·61–1·78)	0·0	2821	0·99 (0·54–1·83)	0·0	191	1·22 (0·39–3·78)	0·0

OR=odds ratio. NA=not applicable.

Table 2: **Pooled clinical outcomes in trials of mineralocorticoid receptor antagonists (*vs* control) in patients receiving dialysis**

Studies, n	Certainty assessment				Risk of outcome	Summary effect		
	Risk of bias	Inconsistency	Indirectness	Imprecision	Control group	Odds ratio (95% CI)	Absolute difference in number of events per 1000 patients (95% CI)	Certainty
Cardiovascular death								
5	No concerns	Not serious	Not serious	Serious	6·0%*	0·98 (0·80 to 1·20)	−1 (−14 to 11)	Moderate
Heart failure hospitalisation								
2	No concerns	Serious	Not serious	Serious	6·6%	0·70 (0·30 to 1·65)	−19 (−45 to 38)	Low
All-cause death								
6	No concerns	Not serious	Not serious	Serious	12·0%*	0·97 (0·84 to 1·21)	−3 (−17 to 22)	Moderate
All-cause hospitalisation								
1	No concerns	Not applicable	Not serious	Not serious	58·0%	0·97 (0·83 to 1·14)	−7 (−46 to 32)	Moderate
Hyperkalaemia (≥6·5 mmol/L)								
4	No concerns	Not serious	Serious	Not serious	5·0%†	1·50 (1·11 to 2·03)	23 (5 to 47)	Moderate
Gynaecomastia or breast pain								
10	Some concerns	Not serious	Not serious	Not serious	0·5%	3·66 (1·82 to 7·36)	13 (4 to 31)	Moderate
Hypotension								
5	Some concerns	Not serious	Serious	Serious	2·0%	1·04 (0·61 to 1·78)	1 (15 to −8)	Low

All included studies were randomised controlled trials. Risk of each outcome was based on the aggregate control group risk, with the exception of cardiovascular and all-cause death, which were estimated as annual risks from epidemiological data. *Estimated annual risk. †Due to heterogeneity in control event rates, an annual rate of 5·0% was assumed; however, this value should be considered uncertain.

***Table 3*: Summary of findings according to the Grading of Recommendations Assessment, Development and Evaluation approach, by outcome**

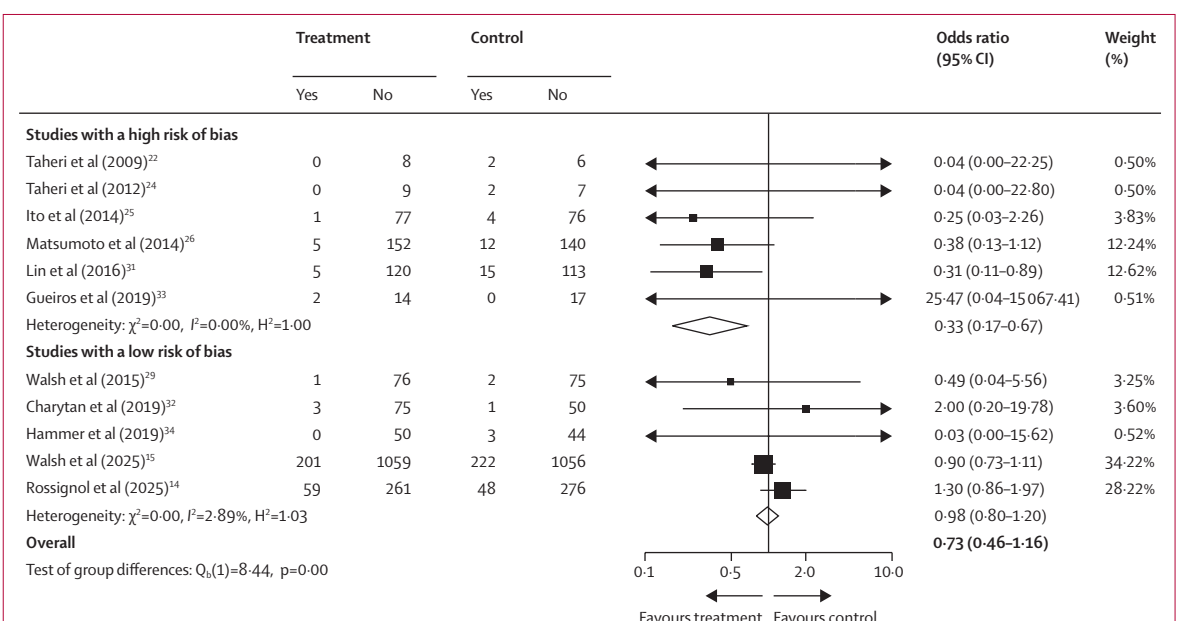

***Figure 2*: Effect of mineralocorticoid receptor antagonists on cardiovascular mortality in patients with kidney failure receiving maintenance dialysis**
The empirical Bayes random-effects model was used. Yes=number of individuals with an event. No=number of individuals without an event.

five trials[14,25,28,29,32] (n=1104; appendix p 13). Hyperkalaemia (serum potassium concentration ≥6·0 mmol/L) occurred in 190 (33·7%) of 563 patients in the mineralocorticoid receptor antagonists group compared with 172 (31·8%) of 541 patients in the control group (OR 1·07 [95% CI 0·81–1·40]; I^2=0·0%, τ^2=0·0; low certainty). Hyperkalaemia, defined as a serum potassium concentration of 6·5 mmol/L or greater, was reported in four trials[15,29,32,34] (n=2918). Hyperkalaemia (serum potassium concentration ≥6·5 mmol/L) occurred in 120 (8·2%) of 1465 patients in the mineralocorticoid receptor antagonist group compared with 78 (5·7%) of

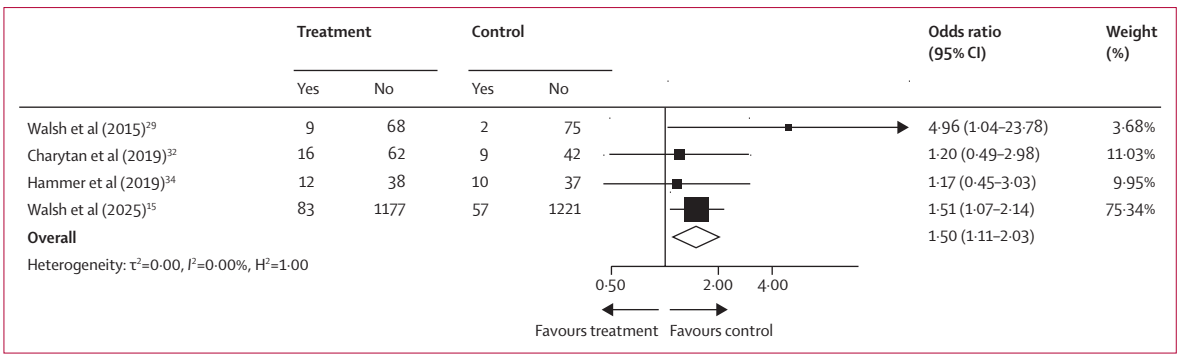

Figure 3: **Effect of mineralocorticoid receptor antagonists on hyperkalaemia in patients with kidney failure receiving maintenance dialysis**
The empirical Bayes random-effects model was used. Hyperkalaemia was defined as a serum potassium concentration of ≥6·5 mmol/L in patients with kidney failure receiving maintenance dialysis. Yes=number of individuals with an event. No=number of individuals without an event.

1375 patients in the control group (OR 1·50 [95% CI 1·11–2·03]; I^2=0·0%, τ^2=0·0; moderate certainty; figure 3).

Gynaecomastia or breast pain was assessed in ten trials [14,15,25–27,31,32,34–36] (n=4292). The 95% CI of the estimate from the five low risk of bias trials (n=3448) became wider after inclusion of the five trials at high risk of bias (n=844; appendix p 14). In the low risk of bias trials, gynaecomastia or breast pain occurred in 40 (2·3%) of 1728 patients in the mineralocorticoid receptor antagonist group compared with 12 (0·7%) of 1720 patients in the control group (OR 3·02 [95% CI 1·57–5·81]; I^2=0·0%, τ^2=0·0; moderate certainty).

Hypotension was assessed in five trials[15,25,29,32,33] (n=3012). Hypotension occurred in 35 (2·3%) of 1509 patients in the mineralocorticoid receptor antagonist group compared with 30 (2·0%) of 1500 patients in the control group (OR 1·04 [95% CI 0·61–1·78]; I^2= 0·0%, τ^2=0·0; low certainty; appendix p 15). Sensitivity analyses of the secondary outcomes had no substantial impact on the results (appendix p 9).

Discussion

This updated systematic review and meta-analysis found that the use of steroidal mineralocorticoid receptor antagonists (mostly spironolactone) has little to no effect on cardiovascular mortality in patients with chronic kidney failure requiring dialysis, and that it potentially increases the risk of hyperkalaemia events and of gynaecomastia or breast pain.

Previous systematic reviews and observational studies suggested that mineralocorticoid receptor antagonists reduce cardiovascular mortality and all-cause mortality in people with kidney failure. This systematic review and meta-analysis, which incorporates data from recent, large trials at low risk of bias (including two new trials that are much larger than previous studies), provides a comprehensive update and enables the assessment of important efficacy and safety outcomes with at least moderate certainty.

The conclusions of this review are, however, limited to spironolactone at doses of approximately 25 mg daily, and extrapolating the results to other mineralocorticoid receptor antagonists should be done with caution. Additionally, although we include cardiovascular mortality and heart failure hospitalisations as potential efficacy outcomes, their aetiologies can be complex and difficult to define, which might reduce their sensitivity to changes caused by mineralocorticoid receptor antagonists. More refined versions of these outcomes or other outcomes might better measure the potential benefits of mineralocorticoid receptor antagonists. Furthermore, we were limited to aggregate data in our meta-analysis and unable to study subgroups.

Our previous review on this topic and a 2021 Cochrane review found that mineralocorticoid receptor antagonist use in patients with kidney failure requiring dialysis resulted in a substantial reduction in cardiovascular and all-cause mortality.[12,13] However, this finding was based primarily on small trials with a high risk of bias, short follow-up, and few events, and was therefore prone to substantial bias in the estimation of treatment effects.[38] Our previous meta-analysis was based on 30 cardiovascular deaths and 69 total deaths. This updated meta-analysis included 540 cardiovascular deaths and 1127 total deaths reported in several large trials at low risk of bias, and illustrates the importance of high-quality, adequately powered trials to provide clear evidence on which to base guidelines and practice.

The absence of benefit from the use of mineralocorticoid receptor antagonists in patients with kidney failure requiring dialysis is inconsistent with the findings of previous trials showing these benefits in patients with heart failure or in patients with diabetic kidney disease not requiring dialysis.[8–11] Mineralocorticoid receptor antagonists might not have these benefits in patients with kidney failure requiring dialysis because the pathophysiology of their cardiac events could differ substantially. Other populations do not experience intradialytic cardiac injury, or to the same degree, chronic pressure–volume overload, and retain functional renal tissue, which enables mineralocorticoid receptor antagonists to induce effects such as diuresis. A similar

inconsistency was found with lipid-lowering therapy: robust effects were observed in patients with normal kidney function but not in patients with chronic kidney failure, and even less so in patients requiring dialysis.[39] Therefore, although our review was unable to identify a benefit of steroidal mineralocorticoid receptor antagonists on cardiovascular mortality, or heart failure, other benefits might exist and the effects of non-steroidal or other methods of aldosterone antagonism could have different results.

In conclusion, the totality of available evidence from randomised controlled trials does not indicate a benefit from the use of steroidal mineralocorticoid receptor antagonists in patients with kidney failure requiring dialysis, and does indicate a risk for potential harm. The risk of cardiovascular death in these patients remains high, and effective therapies continue to be urgently needed.

Contributors

LP and MW drafted the manuscript. LP, PR, CG, MJ, PBM, MG, JRdZ, PJD, and MW contributed to the study design and methodology, and revised the manuscript for important intellectual content. LP, CG, MJ and MW conducted the literature search and data extraction. LP and MW resolved conflicts regarding study inclusion and data extraction. MW conducted the statistical analysis. LP and MW accessed and verified the data. All authors had access to all the included data and agreed to submit the manuscript for publication.

Declaration of interests

PR is the principal investigator of the ALCHEMIST study and reports fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Fresenius, Novartis, Novo-Nordisk, Vera Therapeutics, and Vifor; honoraria for lectures or presentations from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Vifor; support for meeting attendance from Boehringer Ingelheim, Vera Therapeutics, and Vifor; participation in data safety monitoring boards for Bayer, Idorsia, and Sequana Medical; and stock options in G3P; none related to this manuscript. LP, PBM, MG, JRdZ, PJD and MW are investigators of the ACHIEVE study. PBM reports grants from AstraZeneca and Boehringer Ingelheim; consulting fees from AstraZeneca, Boehringer Ingelheim, Pharmacosmos, and Vifor; honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Pharmacosmos, and Vifor; and participation in advisory boards for Vertex and Novartis. JdZ reports honoraria from Otsuka; leadership roles in the Well Foundation, the Royal Australian College of Physicians, and Aotearoa New Zealand Committee; and grants from Three Harbours Trust and Health Research Council New Zealand. PJD reports grants from Abbott Diagnostics, AOP Pharma, Roche Diagnostics, and Siemens; consulting fees from Abbott Diagnostics, AstraZeneca, Roche Canada, and Trimedic; participation in a committee for the MUSC/PEPPER study; participation in an advisory board for Quidel; and receipt of equipment from CloudDX and Philips Healthcare. MW reports grants from the Canadian Institutes of Health Research, the Medical Research Future Fund, Health Research Council New Zealand, the British Heart Foundation, and the Hamilton Academic Health Sciences Organization; consulting fees paid to institution from Otsuka, Visterra, Alexion, Bayer, GlaxoSmith-Kline, and Bayer; serves on committees for studies funded by Otsuka, Visterra, Alexion, Hansa, and NovoNorDisc; holds leadership roles for the Canadian Society of Nephrology, the Glomerular disease Consortium, and the International Society of Nephrology; and is an employee of the Ontario Renal Network. All other authors declare no competing interests.

Data sharing

Data in this systematic review and meta-analysis were extracted from published and referenced studies. All processed data are presented in this Article and the appendix.

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This study built on the methods and data of the previous systematic review and meta-analysis conducted by Quach and colleagues.[12]

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