



The Safety and Efficacy of Mineralocorticoid Receptor Antagonists in Patients Who Require Dialysis: A Systematic Review and Meta-analysis

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Background: Patients who require dialysis are at high risk for cardiovascular mortality, which may be improved by mineralocorticoid receptor antagonists (MRAs).

Study Design: Systematic review and meta-analysis of randomized controlled trials.

Setting & Population: Adults undergoing long-term hemodialysis or peritoneal dialysis with or without heart failure.

Selection Criteria for Studies: Randomized controlled trials evaluating an MRA in dialysis and reported at least one outcome of interest.

Intervention: Spironolactone (8 trials) or eplerenone (1 trial) compared to placebo (7 trials) or standard of care (2 trials).

Outcomes: Cardiovascular and all-cause mortality, hyperkalemia, serum potassium level, hypotension, change in blood pressure, and gynecomastia.

Results: We identified 9 trials including 829 patients. The overall quality of evidence was low due to methodologic limitations in most of the included trials. The relative risk (RR) for cardiovascular mortality was 0.34 (95% CI, 0.15-0.75) for MRA-treated compared with control patients. The RR for all-cause mortality was 0.40 (95% CI, 0.23-0.69). The RR for hyperkalemia for MRA treatment was 3.05 (95% CI, 1.21-7.70). Sensitivity analyses demonstrated wide variability in RRs for cardiovascular mortality, all-cause mortality, and hyperkalemia, suggesting further uncertainty in the confidence of the primary results.

Limitations: Trial quality and size insufficient to robustly and precisely identify a treatment effect.

Conclusions: Given the uncertainty of both the benefits and harms of MRAs in dialysis, large high-quality trials are required.

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INDEX WORDS: Mineralocorticoid receptor antagonist (MRA); spironolactone; eplerenone; hemodialysis; peritoneal dialysis; cardiovascular death; all-cause mortality; hyperkalemia; blood pressure; adverse events; randomized controlled trials; aldosterone; end-stage renal disease (ESRD); systematic review; meta-analysis.

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Worldwide, approximately 2 million people receive dialysis for end-stage renal disease.¹ The annual mortality for patients who require dialysis is up to 20%, and cardiovascular (CV) disease

is the most common cause of death.² A high burden of atherosclerotic disease, hypertension, and pressure-volume overload may precipitate cardiac remodeling, which in turn causes heart failure and arrhythmias.³

The mineralocorticoid aldosterone appears to play an important role in mediating cardiac remodeling.^{4,5} In the nondialysis population, mineralocorticoid

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receptor antagonists (MRAs), such as spironolactone or eplerenone, reduce mortality and hospitalizations in patients with heart failure with reduced ejection fraction.^{6,7} However, there is less certainty about whether MRAs are beneficial in patients with heart failure with preserved ejection fraction.⁸ Given that patients who require dialysis may develop heart failure with or without preserved ejection fraction and that the mechanism by which heart failure occurs in patients who require dialysis may differ from that in non-dialysis-dependent patients, it is unclear whether MRAs will benefit patients who require dialysis. Furthermore, the use of MRAs is frequently limited by hyperkalemia in patients with non-dialysis-dependent chronic kidney disease and it is uncertain whether patients who require dialysis are similarly affected.⁹

Given that the potential benefits and risks of the use of MRAs in patients who require dialysis are unclear, we synthesized data from randomized controlled trials (RCTs) of MRAs in dialysis patients in a systematic review and meta-analysis. The primary outcome for our systematic review was CV mortality, with secondary outcomes of all-cause mortality, hyperkalemia, blood pressure, and adverse events.

METHODS

Search Strategy and Selection Criteria

We developed a comprehensive search strategy to identify all relevant studies regardless of publication status or language (Table S1, available as online supplementary material). Using the Ovid portal, we searched MEDLINE (inception to May 2015), Embase (1974 to May 2015), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) from 1982 to May 2015. Further, reference lists of published studies were screened for citations of interest. Clinical trial registries (ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register, and Japan Controlled Trials) were reviewed to include any relevant trials that were unpublished. Web of Science and BIOSIS databases were also reviewed. Titles and abstracts of all studies identified by our search strategy were screened in parallel by 2 reviewers (K.Q. and L.L.). Eligible studies included human participants in RCTs that compared any MRA to a placebo or standard of care and reported any of the following outcomes: CV mortality, all-cause mortality, hyperkalemia, serum potassium level, blood pressure, and adverse events. Eligible studies or studies in which eligibility criteria were unclear after title and abstract screening underwent full-text review. Two reviewers (K.Q. and L.L.) assessed eligibility criteria for all studies identified for full-text review. Any disagreements in eligibility were resolved through consensus or by a third author (M.W.) if consensus was not reached.

Data Extraction and Quality Assessment

Two authors (K.Q. and L.L.) abstracted data in parallel. Study characteristics (design and duration), participant characteristics (age, sex, dialysis vintage, dialysis modality, and comorbid conditions), therapeutic intervention characteristics (MRA type, dose, and frequency), outcome characteristics (definition of

hyperkalemia and definition of CV mortality), and results were recorded. In crossover trials, only data from the first period were collected due to limitations in data reporting. The quality of individual RCTs was evaluated using the Cochrane risk of bias instrument, which assesses randomization and allocation concealment, blinding of individuals involved in the trial, completeness of follow-up, and reporting of outcomes. Each study outcome was assigned as “low risk of bias,” “unclear,” or “high risk of bias.”¹⁰

Statistical Analysis

Individual-study relative risks (RRs) and 95% confidence intervals (CIs) were calculated for each study (including one study that reported hazard ratios [HRs] because the HRs were not materially different from the RRs) using the full trial population, consistent with the intention-to-treat principle. Participants with incomplete follow-up were assumed to not have had an event after loss to follow-up in the primary analyses. A summary RR estimate was calculated using the Mantel-Haenszel test and a DerSimonian and Laird random-effects model.¹¹ The degree of between-study variability attributable to heterogeneity beyond chance was calculated using the I^2 statistic and Q statistic. Outcomes with I^2 levels from 0% to 40% were considered minimally heterogeneous, consistent with Cochrane Collaboration guidance.¹² The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was used to assess risk of bias across studies to provide a level of confidence in estimates of the effect in 4 levels (high, moderate, low, and very low).¹³

Sensitivity analyses were conducted to explore the potential impact of losses to follow-up on study outcomes by imputing event rates for patients with missing outcome status using 2 methods. We imputed the observed risk for the outcome from the control arms pooled across all trials for all missing outcomes in each trial. As an alternative approach, we performed a worst-case scenario that assumed all patients with missing outcome in the intervention group experienced the outcomes and those in the control group did not.¹⁴ We also repeated meta-analyses excluding the trial at the highest risk of bias to determine its effects on overall estimates. This trial was thought at highest risk of bias due to unclear allocation methodology and concealment, imbalanced baseline characteristics, and lack of blinding.^{15,16} Finally, we also estimated effect estimates using the profile likelihood method, which considers the uncertainty of the between-studies variance and may be more reliable than DerSimonian and Laird models in meta-analyses of small trials.¹⁷ A 2-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using RevMan, version 5.2 (The Nordic Cochrane Centre, Cochrane Collaboration) and profile likelihood analyses were completed with Stata, version 12 (StataCorp LP).

RESULTS

Figure 1 shows the steps in study selection for review. Nine RCTs including 829 participants were ultimately eligible from 1,085 screened citations.^{15,16,18-24}

Risk-of-Bias and Quality Assessment

Mortality and hyperkalemia were both graded with low quality of evidence due to imprecision and the risk-of-bias assessment imparted by incomplete ascertainment of outcomes and incomplete follow-up (Table S2). Across all studies, 17% of patients discontinued medication. In the 2 largest and longest trials, discontinuation of medication and subsequent

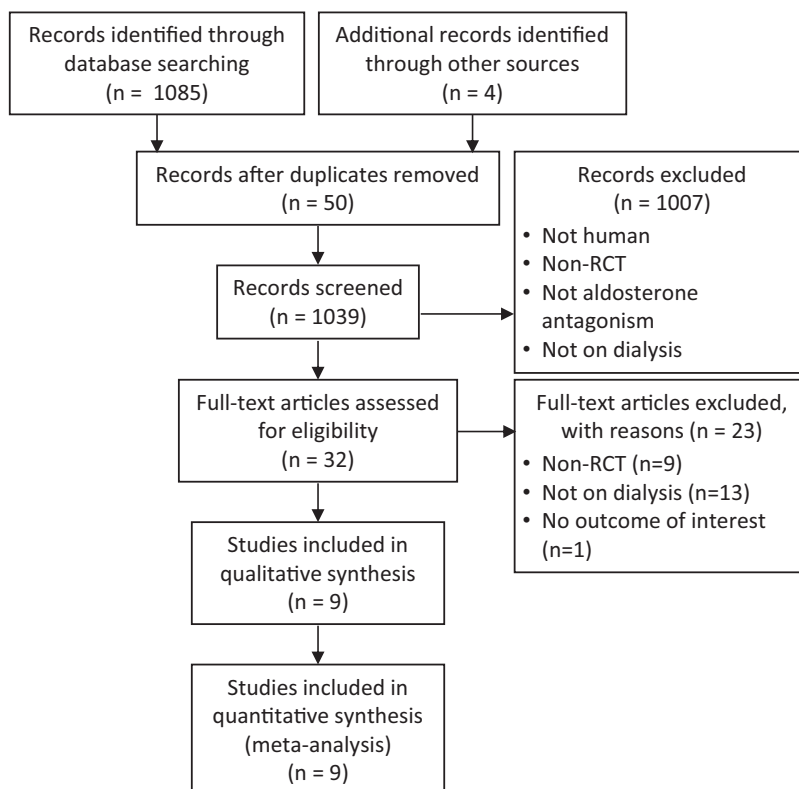


Figure 1. Flow diagram of search selection. Abbreviation: RCT, randomized controlled trial.

incomplete follow-up accounted for 32% and 22% of all patients.^{15,16} Transfer of participants between dialysis centers, changes in dialysis modality, and malignancy were major reasons for discontinuation. Methods for random sequence generation and allocation concealment were unclear in all except 3 trials.^{21,22,24} Furthermore, baseline characteristics of patients in the largest trial were not equally distributed between groups.¹⁵ Seven of the 9 studies were double blinded,¹⁸⁻²⁴ whereas 2 did not use a placebo in their comparison group.^{15,16} One trial reported receiving funding from an industry partner, but no studies reported industry involvement in protocol development, analyses, or reporting of results.²²

Trial Characteristics

A summary of study characteristics is shown in Table 1. All 9 trials were published in the English language in 2005 to 2015. Seven RCTs used a parallel design,^{15,16,19-22,24} whereas 2 RCTs used a crossover design.^{18,23} Spironolactone was the MRA in 8 trials,^{15,16,18-21,23,24} and eplerenone, in one.²² Sample sizes ranged from 8 to 309. Average age and percent of males of all study participants was 60.2 years and 63.1%, respectively. Five trials included only hemodialysis patients,^{15,18,20-22} and 4 included only patients undergoing peritoneal dialysis.^{16,19,23,24} The target population varied between trials, with one trial enrolling only patients with reduced ejection

fraction,¹⁹ one excluding patients with symptomatic heart failure,²⁵ one including only patients already using 3 antihypertensives,²⁴ and one excluding patients with diabetes or vascular disease.²¹ Patients received dialysis from 3 to 128 months prior to enrollment. Median duration of follow-up was 6 (range, 0.5-36) months. Use of β -blockers, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors was permitted in all except one study.²¹

CV and All-Cause Mortality

Of 9 trials, 6 contributed mortality data (721 patients)^{15,16,19-22} and one had no CV mortality events and thus was excluded from CV mortality analyses.¹⁸ Effects of MRA on CV and all-cause mortality for the primary and sensitivity analyses are summarized in Table 2. Compared with controls, the RR of CV mortality for MRA-treated patients was 0.34 (95% CI, 0.15-0.75; $P = 0.008$; Fig 2). There was no significant heterogeneity observed for CV mortality ($I^2 = 0\%$; $P = 0.9$) and no significant evidence of publication bias (fig a of Item S1). However, the effect of MRAs was attenuated and results were not statistically significant in our sensitivity analyses. Imputation of the pooled control group event rate for patients lost to follow-up resulted in an RR of 0.54 (95% CI, 0.28-1.02; $P = 0.06$; fig a of Item S1), whereas the worst-case scenario resulted in an RR of 2.04

Table 1. Baseline Characteristics of Included Trials

Study	Design	Sample Size ^a	Complete F/U	Intervention	Control	F/U, mo	Mean Age, y	Male Sex, %	CHF	Dialysis Type	Funding
Gross et al ¹⁸ (2005)	Crossover	8	8 (100)	Spironolactone 50 mg 2×/d	Placebo	0.5	53 ± 10	38	I: 0%; C: 0%	HD	Not disclosed
Ito et al ¹⁶ (2014)	Parallel	I: 78; C: 80	I: 50 (64); C: 58 (73)	Spironolactone 25 mg/d or eplerenone 50 mg/d	None ^b	24	I: 57.4 ± 12.3; C: 55.6 ± 14.4	I: 71; C: 73	I: 0%; C: 0%	PD	Ministry of Health, Labor and Welfare of Japan
Matsumoto et al ¹⁵ (2014)	Parallel	I: 157; C: 152	I: 112 (71); C: 128 (84)	Spironolactone 25 mg/d	None ^b	36	I: 67.4 ± 12.3; C: 66.7 ± 11.2	I: 71.9; C: 59.2	I: 0%; C: 0%	HD	Not disclosed
Ni et al ²⁴ (2014)	Parallel	I: 40; C: 36	I: 36 (90); C: 34 (94)	Spironolactone 25 mg/d	Placebo	12	I: 55.7 ± 12.3; C: 54.9 ± 14.2	I: 60; C: 58	Not reported	HD/PD	Not disclosed
Taheri et al ²⁰ (2009)	Parallel	I: 8; C: 8	I: 8 (100); C: 8 (100)	Spironolactone 25 mg 3×/wk	Placebo	6	I: 59.5 ± 6.5; C: 56.8 ± 9.3	I: 63; C: 75	I: 100%; C: 100%	HD	Not disclosed
Taheri et al ¹⁹ (2012)	Parallel	I: 9; C: 9	I: 7 (78); C: 9 (100)	Spironolactone 25 mg every other day	Placebo	6	I: 50.7 ± 17.4; C: 57.2 ± 13.1	I: 56; C: 56	I: 100%; C: 100%	CAPD	Isfahan University of Medical Sciences
Vukusich et al ²¹ (2010) ^c	Parallel	I: 33; C: 33	I: 30 (91); C: 23 (70)	Spironolactone 50 mg 3×/wk	Placebo	24	I: 60.1 ± 5.2; C: 55.6 ± 3.6	I: 67; C: 61	I: 10%; C: 4%	HD	Fondo Ayuda Investigacion Universidad Los Andes
Walsh et al ²² (2015)	Parallel	I: 77; C: 77	I: 77 (100); C: 77 (100)	Eplerenone 50 mg/d	Placebo	3	I: 62.1 ± 14.6; C: 63.1 ± 13.7	I: 61; C: 64	I: 10%; C: 8%	HD	CIHR, CANNeCTIN, CANN-NET, Pfizer Canada
Yongsiri et al ²³ (2015)	Crossover	24	20 (83)	Spironolactone 25 mg/d	Placebo	4	52.4 ± 12.4	40	Not reported	CAPD	Commission of Thailand and Faculty of Medicine, Burapha University, Thailand

Note: Values for categorical variables are given as number (percentage) or percentage; for continuous variables, as mean ± standard deviation.

Abbreviations: C, control; CANNeCTIN, Canadian Network and Centre for Trials Internationally; CANN-NET, Canadian Kidney Knowledge Translation and Generation Network; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; CIHR, Canadian Institutes of Health Research; F/U, follow-up; HD, hemodialysis; I, intervention; PD, peritoneal dialysis.

^aBaseline.

^bStandard of care.

^cBaseline characteristics reported on 30 I and 23 C patients.

Table 2. Summary of Efficacy and Safety Outcomes Analyses

Outcome	MRA	Control	RR (95% CI)
CV mortality, n = 5			
Intention-to-treat population	7/329	23/326	0.34 (0.15-0.75)
Control risk scenario	13/329	26/326	0.54 (0.28-1.02)
Worst-case scenario	81/329	23/326	2.04 (0.75-5.56)
Excluding highest risk of bias	1/94	7/94	0.27 (0.06-1.24)
Profile likelihood	7/329	23/326	0.34 (0.14-0.75)
All-cause mortality, n = 6			
Intention-to-treat population	16/362	43/359	0.40 (0.23-0.69)
Control risk scenario	26/362	49/359	0.56 (0.36-0.87)
Worst-case scenario	93/362	43/359	2.01 (1.09-3.70)
Excluding highest risk of bias	4/127	8/127	0.71 (0.24-2.09)
Profile likelihood	16/362	43/359	0.40 (0.22-0.90)
Hyperkalemia, n = 7			
Intention-to-treat population	18/381	4/374	3.05 (1.21-7.70)
Control risk scenario	18/381	4/374	3.05 (1.21-7.70)
Worst-case scenario	97/381	4/374	9.35 (3.37-25.93)
Excluding highest risk of bias	13/146	3/142	2.97 (1.02-8.67)
Profile likelihood	18/381	4/374	3.54 (1.95-5.04)

Note: Control risk scenario imputes the overall control group outcome risk for all participants with missing outcome follow-up, whereas worst-case scenario imputes an event for all participants with missing outcome follow-up in the MRA group and no event for all participants in the control group.

Abbreviations: CI, confidence interval; CV, cardiovascular; MRA, mineralocorticoid receptor antagonists; RR, relative risk.

(95% CI, 0.75-5.56; $P = 0.02$; fig *b* of Item S1). Furthermore, exclusion of the 2 trials at highest risk of bias resulted in an RR of 0.27 (95% CI, 0.06-1.24; $P = 0.09$; fig *c* of Item S1). Profile likelihood estimates found the RR for CV mortality to be 0.34 (95% CI, 0.14-0.75).

Compared with controls, the RR of all-cause mortality for MRA-treated patients was 0.40 (95% CI, 0.23-0.69; $P = 0.001$; Fig 3). There was no statistical heterogeneity in all-cause mortality observed

($I^2 = 0\%$; $P = 0.6$). As with CV mortality, the effect of MRAs on all-cause mortality and statistical significance was significantly attenuated in sensitivity analyses that imputed either the control group event rate or worst-case scenario for patients lost to follow-up, as did removal of the 2 studies at highest risk of bias (figs *a-c* of Item S2). The RR estimated using the profile likelihood method was 0.40 (95% CI, 0.22-0.90).

Hyperkalemia

Hyperkalemia was defined as potassium level > 5 mEq/L in one study,²⁴ ≥ 5.5 mmol/L in one study,¹⁹ > 5.5 mmol/L in 2 studies,^{20,23} ≥ 6.0 mmol/L in 2 studies,^{18,21} > 6.0 mmol/L in one study,¹⁶ ≥ 6.5 mmol/L in one study,¹⁵ and > 6.5 mmol/L in one study.²² Two trials did not report any hyperkalemic events and were excluded from analyses.^{18,21} In the 7 RCTs including 755 patients, MRA use was significantly associated with hyperkalemia (RR, 3.05; 95% CI, 1.20-7.71; $P = 0.04$; Fig 4). No significant heterogeneity was observed ($I^2 = 0\%$; $P = 0.8$). One study reported a mean serum potassium level increase of 0.16 (95% CI, 0.04-0.28) mmol/L ($P = 0.008$) compared to placebo over 13 weeks,²² whereas another reported an increase of 0.012 mmol/L per month ($P < 0.001$) over 24 months.²¹ Worst-case scenario suggested that if all patients lost to follow-up in the MRA group developed hyperkalemia, the RR of hyperkalemia would be 9.35 (95% CI, 3.37-25.93; $P < 0.001$; Fig S1).

Blood Pressure

Differences in reporting methods precluded meta-analysis of blood pressure results. Trials noted a decrease in predialysis systolic blood pressure in MRA-treated patients that ranged from 1.7 to 11 mm Hg and from 2 to 5.2 mm Hg in control patients. One trial that measured mean ambulatory blood pressure observed a significant decrease in systolic (-12.5 mm Hg) and diastolic (-7.0 mm Hg) blood pressure after 12 weeks.²⁴ In the 2 trials that reported hypotensive events, no significant difference was detected between the MRA and placebo groups.^{16,22}

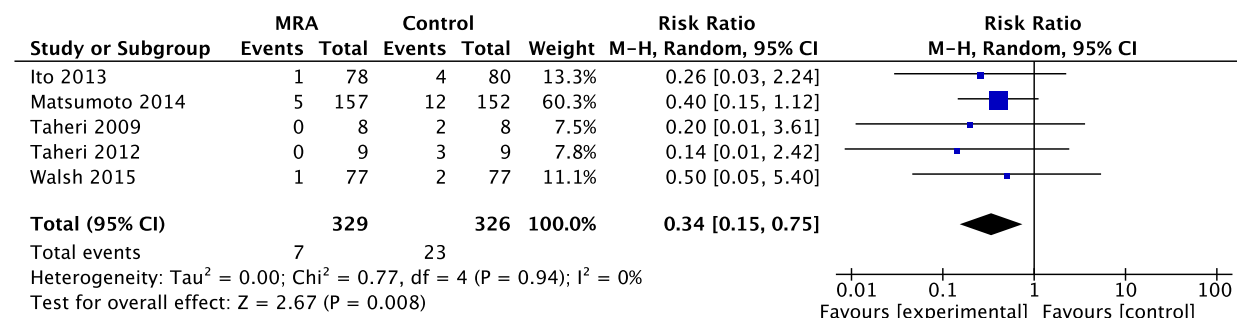


Figure 2. Forest plot of the effects of mineralocorticoid receptor antagonists (MRAs) on cardiovascular mortality in dialysis patients. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

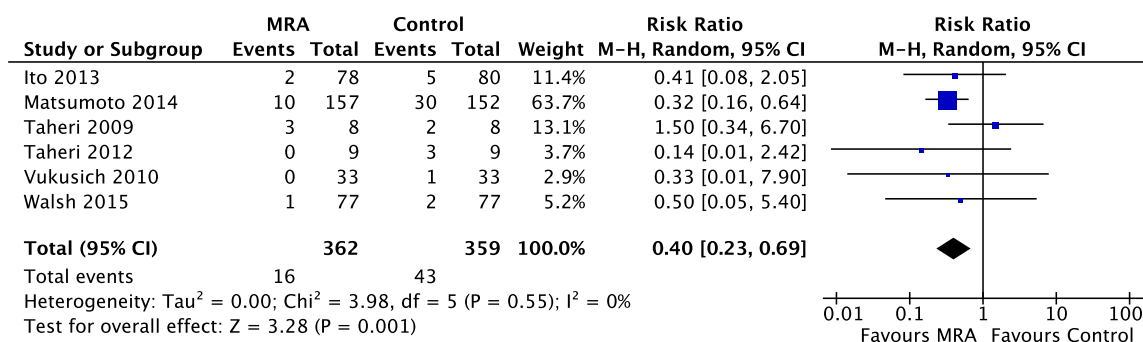


Figure 3. Forest plot of the effect of mineralocorticoid receptor antagonists (MRAs) on all-cause mortality in dialysis patients. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Other Adverse Effects

Four studies reported 30 patients who developed gynecomastia or breast pain in spironolactone-treated patients, with an overall incidence of 11% in the MRA groups.^{15,16,21,24} Only one study compared events of gynecomastia in the spironolactone compared to the control group (RR, 5.64; 95% CI, 1.29-24.63; $P = 0.03$).¹⁶

DISCUSSION

Our systematic review and meta-analysis identifies MRAs as a potentially beneficial treatment to reduce CV mortality for dialysis patients. Although risk lowering appears substantial, data are insufficient to robustly determine whether MRAs are truly beneficial for dialysis patients. Furthermore, due to high risk of bias, losses to follow-up, and inadequate number of outcomes, there is a substantial risk for hyperkalemia that may limit widespread use of MRAs in dialysis patients.

RR reductions for major CV events in non-dialysis-dependent patients with heart failure treated with an MRA are 10% to 30% in large RCTs and meta-analyses.⁶⁻⁸ Our meta-analysis suggested a 66% RR reduction in dialysis patients, only some of whom

had heart failure. There are several possibilities for the difference in effect between dialysis-dependent and non-dialysis-dependent patients.

First, one must acknowledge the likelihood that the current meta-analysis misestimates the effect of MRAs in dialysis patients. The misestimation may arise from either bias or imprecision. The issue of potential bias is particularly important given that the 2 largest trials are considered at the highest risk of bias due to unclear allocation methods, lack of blinding, and incomplete follow-up. The potential for bias is further underscored by the lack of reported data for some outcomes in some studies and the degree to which our results depend on how losses to follow-up are handled.

The possibility that imprecision has resulted in an overestimate of the effect of MRAs must also be acknowledged despite the statistical significance of our results. Our estimates are based on only 30 CV mortality events, whereas simulation studies suggest that at least 300, if not 600, events are necessary to provide stable estimates of effect.²⁶ A useful way to approach this issue is to consider the required sample size of a single trial to detect a plausible treatment effect under assumptions similar to those observed in the trials conducted to date. The control event rate is approximately 3.5 CV deaths per 100 patient-years of

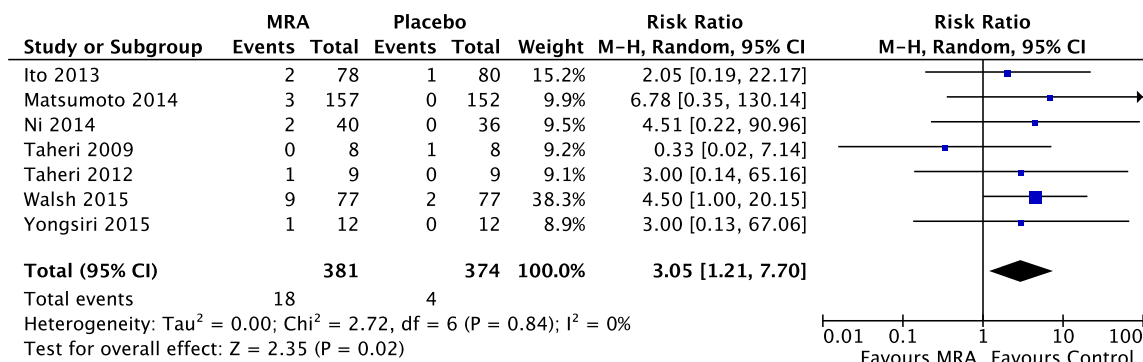


Figure 4. Forest plot of the effect of mineralocorticoid receptor antagonists (MRAs) on hyperkalemia in dialysis patients. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

follow-up in a prevalent cohort with all-cause mortality of 6.1 per 100 patient-years (and therefore a risk for non-CV death of 2.6 per 100 patient-years). Assuming an HR of 0.75 for CV death, consistent with MRA use in other trials, and using non-CV death as a competing risk as suggested by other trials of CV event reduction in dialysis, one would require at least 2,380 patients (1,190 per group) with a resulting 380 events to achieve 80% power with 2-sided α of 0.05.²⁷ This calculation does not factor in the effects of nonadherence, loss to follow-up, crossover, and loss to transplantation.²⁷ Furthermore, detecting an HR of 0.8 under similar conditions would require at least 3,853 patients (1,926 per group) with a resulting 630 events. Given that most monotherapies for chronic CV disease are expected to yield only moderate treatment effects, our current meta-analysis is less than one-third the required size to make credible inferences despite the statistical significance of the results.

Despite these issues, MRAs are a promising therapy with a strong rationale for efficacy in dialysis patients and there is reason to believe that MRAs may be at least as effective in dialysis patients as in patients with heart failure. Patients with heart failure after myocardial infarction may have only a short duration of elevated aldosterone activity, resulting in a limited time for MRAs to have an effect. In dialysis, long-term elevations of aldosterone levels (triggered by the rapid cycling of volume status and serum potassium) in dialysis patients may create an ongoing benefit of MRAs.²⁸ It is also possible that dialysis-dependent patients may tolerate hyperkalemia better than non-dialysis-dependent patients because of the frequent monitoring and routine dialysis, which the latter do not receive and which may mitigate the potential harms of MRAs.

Although evidence suggesting that MRAs benefit dialysis patients is promising, the potential to cause harm must be considered. MRA use in non-dialysis-dependent patients is often limited by hyperkalemia caused by reduced renal potassium excretion.⁹ In the dialysis population, it is unclear how quantitatively important aldosterone-mediated renal excretion of potassium might be. Given that potassium excretion by renal tubules requires tubular flow of urine, it seems unlikely, though not impossible, that it is of major quantitative importance in most dialysis patients. Aldosterone may also affect extrarenal potassium excretion (eg, gastrointestinal, salivary, and perspiration), and the degree to which this is important in the absence of kidney function is uncertain.²⁹ Therefore, MRA-mediated hyperkalemia in dialysis patients may arise from reduced extrarenal excretion. Given concerns over harm from other drugs that act on the renin-angiotensin-aldosterone system in dialysis patients, further studies are required to understand the

safety of MRAs in dialysis patients and how to best monitor their use.³⁰

Our meta-analysis has several strengths, including a thorough and comprehensive assessment of the available literature's risks of bias and sensitivity analyses to ensure the findings were robust. We demonstrated that qualitative results of the meta-analysis are highly dependent on the potential outcomes of participants with incomplete follow-up. However, the true event rates of participants lost to follow-up are unpredictable and unlikely to be at either extreme of our assumptions (ie, no participants had events or only participants in the treatment group had events). It is therefore unclear where in the spectrum of potential results the true treatment effect may lie. In addition, we demonstrated a substantial difference between total meta-analysis sample size and optimal sample size. As such, despite statistical significance, the clinical significance of these data remains uncertain and therefore further studies are needed to substantiate or refute these results before any changes to clinical practice or guidelines are made.

In summary, although small studies suggest that MRAs may improve patient-important outcomes for patients who require dialysis, there is insufficient evidence to support their widespread use. Furthermore, MRAs likely increase the risk for serious hyperkalemia. Larger trials are required to clarify the benefit-risk ratio for this potentially important class of medications in dialysis patients.

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Contributions: The research idea and study design: KQ, CB, JB, AXG, CH, RH, BM, VP, CGR, RW, MW; data acquisition: KQ, LL, MW; statistical analyses: KQ, MW; supervision: MW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. MW takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Search strategies used for Embase and Ovid MEDLINE.

Table S2: Risk-of-bias assessment of included trials.

Figure S1: Worst-case scenario analysis forest plot of effect of MRAs on risk of hyperkalemia.

Item S1: Forest plots of effects of MRAs on CV mortality in dialysis patients.

Item S2: Forest plots of effects of MRAs on all-cause mortality in dialysis patients.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2016.04.011>) is available at www.ajkd.org

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