STATE OF THE ART REVIEWS

Safety and cardiovascular effects of mineralocorticoid receptor antagonists for patients receiving hemodialysis: a systematic review and meta-analysis

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ABSTRACT

Introduction

Cardiovascular disease is an important factor in the mortality and morbidity of patients with end-stage renal disease receiving hemodialysis. Although mineralocorticoid receptor antagonists may have potential benefits on the cardiovascular system, their safety for patients on hemodialysis remains unclear, considering the differences between the results of already performed clinical trials. Methods MEDLINE, EMBASE, Cochrane, ClinicalTrials.gov and PubMed databases were searched for relevant clinical trials. The Cochrane Collaboration assessment tool was employed to evaluate the quality of the randomized controlled trials. Revman 5.3 was used to perform the meta-analysis. Results Eleven studies (n=379) were included in the systematic review and five randomized controlled trials were included in the meta-analysis (n=248). Mineralocorticoid antagonists (MRAs) did not increase predialysis potassium levels significantly (0.11, 95% confidence interval 0.03 to 0.25, p = 0.11). However, the studies included in this review reported inconsistently with respect to effects of mineralocorticoid receptor antagonists on blood pressure, left ventricular ejection fraction and left ventricular hypertrophy, and quantitative analysis was not performed due to insufficient data. One trial showed that the mineralocorticoid receptor antagonists were associated with decreased carotid intima-media thickness and other articles concluded that mineralocorticoid receptor antagonists had no effect on aortic stiffness. Conclusion It is safe to use low dose mineralocorticoid receptor antagonists on patients receiving hemodialysis, at the end of each session of hemodialysis, and close monitoring of serum potassium levels and possible side effects is necessary. The cardiovascular actions still need to be explored and large scale RCTs are in progress.

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Introduction

Cardiovascular (CV) disease is an important factor of the mortality and morbidity of patients with end-stage renal disease receiving hemodialysis and accounts for about half of all fatalities.1–3 Hypertension is a common yet frequently uncontrolled complication in hemodialysis,4 which is an important risk factor for left ventricular hypertrophy (LVH), cardiac failure, coronary artery disease (CAD), arrhythmia, and heart failure.5 LVH is highly prevalent in individuals with ESRD and a risk factor for death in the ESRD population, and presence of LVH over time is strongly associated with the risk of death during follow-up.6 Heart failure, defined as a reduction in the left ventricular ejection fraction (LVEF), occurs in a considerable proportion of patients on hemodialysis and impacts morbidity and mortality.7

Aldosterone and mineralocorticoid receptors (MRs) have been recognized for their significant role in potassium excretion and sodium and water retention.8,9 Recent researches have revealed that they are also responsible for hypertension, congestive heart failure and ventricular hypertrophy in patients receiving hemodialysis.5,10–12 To prevent these negative impacts, the inhibition of renin-angiotensin-aldosterone system (RAAS) should be considered in the treatment of patients undergoing hemodialysis.

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Nevertheless, it has been reported that angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) alone may not effectively inhibit aldosterone production in all patients,\(^7\),\(^10\) and consequently, the mineralocorticoid antagonists (MRAs) should be considered for complete blockade of RAAS.

MRAs, including spironolactone and eplerenone, have been proven effective in the treatment of patients with heart failure and hypertension.\(^13\)–\(^15\) However, the use of MRAs on patients receiving hemodialysis is still controversial, considering the possibility of an elevated serum potassium level or even fatal hyperkalemia due to a patient’s compromised ability to maintain electrolyte balance.\(^16\) Therefore, we performed this systematic review and meta-analysis to evaluate the effect of MRAs on the serum potassium level and CV system for patients undergoing hemodialysis.

**Methods**

**Search strategy**

We searched MEDLINE, EMBASE, Cochrane, ClinicalTrials.gov and PubMed databases for relevant literature until August 2015. The following terms were used for searching: MR antagonist, MR blocker, aldosterone receptor blocker, aldosterone receptor blocker, aldosterone blocker, spironolactone, eplerenone, canrenone, hemodialysis, extracorporeal dialysis, renal replacement therapy, renal dialysis, ESRD, renal failure, kidney failure and end-stage kidney disease. Additionally, we searched articles in magazines by hand as a supplement and contacted the authors for unpublished data if necessary. All of the searches were limited to human studies. There was no restriction regarding language.

**Inclusion and exclusion criteria**

1. **Type of studies.** Randomized controlled trials (RCTs) or clinical trials in which (a) an intervention arm and a control arm were designed or (b) participants served as their own control. Crossover studies were also accepted if there was evidence of a sufficient washout period without carry-over effect. Only RCTs were included for the meta-analysis.

2. **Subjects.** Participants were on hemodialysis for at least 1 month with predialysis serum potassium <6.5 mmol/L. Patients with a history of kidney transplantation were excluded.

3. **Interventions.** Spironolactone or eplerenone administered for at least 2 weeks.

4. **Outcome.** The primary outcome was the serum potassium level and the secondary outcome was CV effects.

**Quality assessment**

The assessment tool developed by the Cochrane Collaboration\(^17\) was applied to evaluate all potentially relevant sources of bias, including the selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases of RCTs. The assessment was performed by two independent authors and disagreements were resolved by discussion with a third author.

**Funding source of included RCTs**

As recommended by Roseman et al.,\(^18\) funding sources of included RCTs were reported.

**Data extraction**

The data were extracted independently by two different investigators using a collection form that we designed (Supplementary data 1). Data presented only in graphs and figures were extracted whenever possible, but they were included only if the two reviewers had the same results. Data not published were acquired by contact with the original investigators and, if that failed, calculated with available data.

**Statistical analysis**

Considering the high potential risk of bias in non-RCTs, we only included RCTs in the meta-analysis. We employed Revman 5.3 software (the Cochrane Collaboration, UK)\(^19\) to perform the meta-analysis to estimate the serum potassium level after intervention. The results were presented as the mean difference with 95% confidence intervals. Additionally, we calculated the Chi square and \(I^2\) values to evaluate the heterogeneity among the studies according to the Cochrane Handbook.\(^20\)

**Results**

**Search results**

A total of 193 articles were retrieved, among which 147 were duplicates or reviews. Forty six articles were screened based on the titles and abstracts, and 12 studies met the criteria for inclusion. After full-text screening, one article was excluded as no data of serum potassium for the control group was provided.\(^21\)
Eleven studies were reported in this systematic review, among which five studies were RCTs22–26 and six were non-randomized studies27–32 (Figure 1).

Characteristics of the included trials

The characteristics of the included trials are summarized in Table 1. Five studies were RCTs, one of which was a crossover study. Six were prospective non-randomized studies, three of which assigned a placebo group as the control, and the other studies considered the participants at baseline as their own control. All of the trials reported the serum potassium level before dialysis. Blood pressure, LVEF, left ventricular mass (LVM) and other parameters used for assessing the CV effects were reported in seven articles.

All potentially relevant sources of bias of included RCTs were evaluated and are demonstrated in Figure 2. It should be noted that, due to the lack of the original study protocol and insufficient information provided in the literatures, most sources of bias were assessed as ‘Unclear’. No particular source of bias was present in the studies reviewed.

Funding sources of included RCTs

The RCT conducted by Feniman-De-Stefano et al.25 was funded by FUNDUNESP (Foundation for the Development of UNESP, Process 0090910) and FAPESP (Foundation for Research Support of São Paulo, Process 2010/10439–1). The authors declared no conflicts of interests.

The RCT conducted by Walsh et al.26 was funded by Canadian Institutes of Health Research, the Canadian Network and Center for Trials Internationally, the Canadian Kidney Knowledge Translation and Generation Network, and the Pfizer Investigator Initiated Research program. No funder had any role in the design, conduct, or reporting of the trial. One of the authors was supported by a New Investigator Award from the Kidney Research Scientist Core Education and National Training (KRESCENT) Program, and received

Figure 1. Study flow diagram.
| Study                      | Study design                   | Subjects | ACEI/ARB | No. of subjects | Intervention                                      | Control  | Duration | Outcome measured |
|----------------------------|--------------------------------|----------|----------|-----------------|--------------------------------------------------|----------|----------|------------------|
| Saudan et al., 2003        | Prospective, single-arm        | HD patients | ACEI      | 19/35           | Spironolactone 12.5 mg thrice weekly for 2 weeks, 25 mg thrice weekly for 2 weeks | Baseline | 8 weeks  | Serum K⁺         |
| Hussain et al., 2003       | Prospective, single-arm        | HD > 4 months, serum K⁺ ≤5.5 mmol/L | ACEI      | 6/15            | Spironolactone 25 mg daily for 28 days           | Baseline | 4 weeks  | Serum K⁺, serum renin and aldosterone, incidence rate of hyperkalemia |
| Michea et al., 2004        | Sequential, doubled-blind, placebo-controlled | HD > 18 months | ACEI      | 0/9             | Spironolactone 25 mg thrice weekly for 2 weeks, washout for 2 weeks, placebo for 2 weeks | Placebo  | 8 weeks  | Serum K⁺         |
| Gross et al., 2005         | RCT, double-blinded, crossover | HD > 3 months, predialysis serum K⁺<6.5 mmol/L, not using ACEI/ARB | ACEI      | 0/8             | Spironolactone, 50 mg twice daily for 2 weeks | Placebo  | 2 weeks  | BP, serum K⁺, weight, PRA, 24-h urine volume, urine sodium, K⁺, creatinine |
| Taheri et al., 2009        | RCT, double-blind              | HD > 1 month, heart failure, LVEF ≤45%, treated with an ACEI or ARB | ACEI      | 16/16           | Spironolactone 25 mg thrice weekly for 6 months | Placebo  | 6 months  | LVEF, LVM, serum K⁺ |
| Matsumoto et al., 2009     | Prospective, single-arm        | HD > 2 years, predialysis serum K⁺<6.5 mmol/L, treated with an ACEI or ARB | ACEI      | 29/50           | Spironolactone 25 mg daily for 6 months          | Baseline | 6 months  | Serum K⁺         |
| Vukusic et al., 2010       | RCT, double-blind              | HD > 18 months, predialysis serum K⁺<6.5 mmol/L, not using ACEI/ARB | ACEI      | 0/53            | Spironolactone 50 mg thrice weekly for 24 months | Placebo  | 24 months | BP, CIMT, serum K⁺ |
| Shavit et al., 2011        | Prospective, single-arm        | HD > 3 months, predialysis serum K⁺<6.5 mmol/L, not using ACEI/ARB | ACEI      | 2/8             | Eplerenone 25 mg twice daily for 4 weeks         | Baseline | 8 weeks  | BP, serum K⁺      |
| Flevari et al., 2013       | Sequential, placebo-controlled | HD > 12 months, predialysis serum K⁺<6.5 mmol/L | ACEI      | 11/14           | Placebo for 4 weeks, spironolactone 50 mg thrice weekly | Placebo  | 4 months  | BP, serum K⁺, IVS, LVM, LVDD, LSVD, FS, RWT, E/A, RVD |
| Feniman-De-Stefano et al., 2015 | RCT, double-blind             | HD, no previous hyperkalemia | ACEI      | 14/17           | Spironolactone 12.5 mg daily for 2 weeks, then adjusted according to K⁺ | Placebo  | 6 months  | BP, serum K⁺, LVM, LVDD, LSVD, EF, PWT, DA, ABPM, PWV, AI |
| Walsh et al., 2015          | RCT, double-blind              | HD > 90 days | ACEI      | 65/154          | Eplerenone 25 mg daily for 7 days, then adjusted according to K⁺ | Placebo  | 13 weeks | Change of BP, serum K⁺ |

Notes: Abbreviations: ABPM: ambulatory blood pressure monitoring; AI: augmentation index; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; BP: blood pressure; CIMT: carotid intima-media thickness; DA: diastolic dimension of the atrium; E/A: ratio of early-to-late diastolic filling; EF: ejection fraction; FS: fractional shortening; HD: hemodialysis; IVS: interventricular septum; K⁺: potassium; LSVD: left ventricular diastolic diameter; LVM: left ventricular mass; LVMi: left ventricular mass index; LVSD: left ventricular systolic diameter; PRA: plasma renin activity; PWT: posterior wall thickness; PWV: pulse wave velocity; RCT: randomized controlled trial; RVD: right ventricular diameter; RWT: relative wall thickness.

*If serum K⁺ <5.5 mmol/L, spironolactone 25 mg daily; if serum K⁺ between 5.5 and 5.9 mmol/L, spironolactone 12.5 mg daily; if serum K⁺ ≥6.0 mmol/L, drop.

**NYHA class 3 and 4.**

*If serum K⁺<6 mmol/L, eplerenone 50 mg daily; if serum K⁺>6 mmol/L, the dose was titrated down.

*Baseline* indicates that the baseline status of participants was used as control.
Effect of MRA on the predialysis potassium level

Reported serum potassium data are summarized in Table 2. The dose of the MRAs administered varied dramatically and the serum potassium level changed accordingly.

Among the studies included in our review, eight studies reported no significant change in the serum potassium level. Saudan et al.27 enrolled 35 patients who were treated with either placebo or sequentially 12.5 mg of spironolactone thrice weekly for 2 weeks and 25 mg of spironolactone thrice weekly for 2 weeks. The serum potassium level at study completion was 4.9 ± 0.3 in the spironolactone group and 4.9 ± 0.7 in the control group, with no significant difference. Hussain et al.,31 Shavit et al.,29 Michea et al.,28 Gross et al.,22 Vukusich et al.,24 Feniman-De-Stefano et al.25 and Walsh et al.26 also found no significant change in the serum potassium level. These trials used relatively small doses of MRAs (no more spironolactone or eplerenone than 25 mg daily).

Other investigators reported different results. Matsumoto et al.32 reported that after administration of spironolactone at a dose of 25 mg daily for 6 months, there was a significant rise in serum potassium after spironolactone treatment (5.18 ± 0.72 vs. 4.96 ± 0.72 mmol/L, \( p < 0.05 \)). Taheri et al.,23 Flevari et al.30 and Gross et al.22 reported a significant rise in the serum potassium level after administration of MRAs. These investigators administered MRAs at larger doses (no less than 50 mg thrice a week).

To evaluate the influence of MRA comprehensively, data from five RCTs were pooled to provide an overall estimate of the predialysis potassium level after intervention (Figure 3). There was no significant difference between the MRA group and the placebo group (mean difference 0.11, 95% CI −0.03, 0.25 mmol/L, \( p = 0.11 \)), and there was low heterogeneity (\( \chi^2 = 2.65, \ p = 0.62, \ I^2 = 0\% \)).

Other side effects of MRA

Several side effects of MRAs were reported, including gastrointestinal side effects, dizziness, hyperemia,
gynecomastia, dry mouth, nose bleed, mild pruritus, gynecomastia, leg numbness, sleepiness and unpleasant feelings. Only eleven patients withdrew from the study because of these side effects.\(^{31,32}\)

**CV effects of MRA**

The outcome of the CV effects explored in the trials was blood pressure, parameters of ventricular hypertrophy, carotid intima-media thickness (CIMT) and pulse wave velocity (PWV). A meta-analysis of these outcomes was impossible due to insufficient subjects from the RCTs.

**Blood pressure (BP)**

BP was measured and reported in six trials, five\(^{22,24,25,29,30}\) of which provided systolic blood pressure (SBP) and diastolic pressure (DBP), and the other trial reported the change of BP after intervention\(^{26}\) (Table 3). Patients with hypertension and receiving

![Image](https://via.placeholder.com/150)

**Figure 3.** Effect of mineralocorticoid receptor antagonists on the predialysis serum level. Abbreviations: CI: confidence interval; IV: inverse variance; MRA: mineralocorticoid receptor antagonist.

### Table 2. Effect of mineralocorticoid receptor antagonists on serum potassium level.

| Study             | Study design                        | No. of subjects | Intervention                                                                 | Predialysis serum potassium level (mmol/L) |
|-------------------|-------------------------------------|-----------------|-----------------------------------------------------------------------------|---------------------------------------------|
| Saudan et al., 2003 | Prospective, single-arm             | 35              | Spironolactone 12.5 mg thrice weekly for 2 weeks, 25 mg thrice weekly       | After the 25 mg phase, spironolactone group: 4.9 ± 0.3, control group: 4.9 ± 0.7, \(p\) values not reported |
| Hussain et al., 2003 | Prospective, single-arm             | 15              | Spironolactone 25 mg daily for 28 days                                      | 4.6 ± 0.6 at baseline, 4.7 ± 0.6 at study completion, \(p = 0.19\) |
| Michea et al., 2004 | Sequential, double-blind, placebo-controlled | 9               | Spironolactone 25 mg thrice weekly for 2 weeks, washout for 2 weeks, placebo for 2 weeks | Baseline: 4.5 ± 0.54, after spironolactone: 4.56 ± 3.39, after placebo: 4.67 ± 0.33, no significant differences |
| Gross et al., 2005  | RCT, double-blinded, crossover      | 8               | Spironolactone 50 mg twice daily for 2 weeks                               | Spironolactone group: 5.0 ± 0.8, placebo group: 4.7 ± 0.5, \(p > 0.05\) |
| Taheri et al., 2009 | RCT, double-blinded                 | 16              | Spironolactone 25 mg thrice weekly for 6 months                            | Differences of serum potassium concentration at the end of the study compared with the start: spironolactone: 1.02 ± 0.34, placebo: 0.083 ± 0.449, 95% CI (0.381–1.491), \(p = 0.004\) |
| Matsumoto et al., 2009 | Prospective, single-arm           | 50              | Spironolactone 25 mg daily for 6 months                                     | Baseline: 4.96 ± 0.72, end of study: 5.18 ± 0.76, \(p < 0.05\) |
| Vukusich et al., 2010 | RCT, double-blinded               | 53              | Spironolactone 50 mg thrice weekly for 24 months                           | End of study, spironolactone: 4.9 ± 0.66, placebo: 4.6 ± 0.53, no significant differences; spironolactone increase serum potassium level by 0.012 per months (\(p < 0.001\)) |
| Shavit et al., 2011  | Prospective, single-arm             | 8               | Eplerenone 25 mg twice daily for 4 weeks                                   | Baseline: 4.67 ± 0.2, week 4: 4.86 ± 0.38, \(p = 0.48\) |
| Flevari et al., 2013 | Sequential, placebo-controlled     | 14              | Spironolactone 50 mg thrice weekly                                        | Baseline: 4.4 ± 0.72, after placebo: 4.7 ± 0.75, after spironolactone: 4.5 ± 0.75, \(p < 0.05\) |
| Feniman-De-Stefano et al., 2015 | RCT, double-blinded       | 17              | Spironolactone 12.5 mg daily for 2 weeks, then adjusted according to K\(^+\)\(^a\) | End of study, spironolactone: 5.0 ± 0.31, placebo: 4.9 ± 0.24, \(p = 0.244\) |
| Walsh et al., 2015  | RCT, double-blinded                 | 154             | Eplerenone 25 mg daily for 7 days then adjusted according to K\(^+\)\(^b\)  | End of study, eplerenone: 4.9 ± 0.7, placebo: 4.9 ± 0.7, no significant difference; eplerenone increased serum potassium level by 0.16 (95% CI, 0.04–0.28) |

\(^a\)If serum K\(^+\) < 5.5 mmol/L, spironolactone 25 mg daily; if serum K\(^+\) between 5.5 and 5.9 mmol/L, spironolactone 12.5 mg daily; if serum K\(^+\) > 6.0 mmol/L, drop.

\(^b\)If serum K\(^+\) < 6 mmol/L, eplerenone 50 mg daily; if serum K\(^+\) > 6.0 mmol/L, the dose was titrated down.
antihypertensive treatment continued their therapy during the trial. Gross and colleagues\textsuperscript{22} reported a significant decrease of SBP after spironolactone administration (131.4 ± 18.2 vs. 142.0 ± 19.6, p < 0.05), while there was no significant difference in DBP. Shavit et al.\textsuperscript{29} also noticed a significant drop in the SBP after eplerenone administration (from 166 ± 14 to 153 ± 10, p < 0.021), but no significance in the DBP was observed. In the sequential placebo-controlled study conducted by Flevari et al.,\textsuperscript{30} there were significant differences in both the SBP and DBP in the spironolactone group and placebo group (121 ± 8.6/66 ± 2.5 vs. 147 ± 13.8/76 ± 2.6, p < 0.05). Other investigators reported no significant effect of MRA on BP.

**Left ventricular ejection fraction**

Taheri et al.\textsuperscript{23} evaluated the cardiac function of hemodialysis patients treated with spironolactone. Compared with the placebo group, LVEF improves significantly after spironolactone administration (6.2%±1.6% vs. 0.8%±4.9%, p = 0.046). Feniman-De-Stefano\textsuperscript{25} and colleagues observed different results. No significant difference in the LVEF between the spironolactone group and placebo group was observed (70.9%±4.2% vs. 69.7 ± 5.2, p = 0.89).

**Left ventricular hypertrophy**

LVH can be evaluated by LVM, left ventricular mass index (LVM), and thickness of the left ventricular walls. In the study conducted by Taheri and his team,\textsuperscript{23} the change in the LVM of the spironolactone group was significantly different from the placebo group (−8.4 g/m²±4.72 vs. 3 g/m²±7.97 g/m², p = 0.021). Feniman-De-Stefano\textsuperscript{25} reported similar results (LVM at the end of study, 236 g±36.1 g vs. 273 g±65.5 g, p = 0.046). Their study also showed a significant decrease in posterior wall thickness in the spironolactone group compared with the placebo group (11.9 mm±0.8 mm vs. 12.7 mm±1.0 mm, 0.021), but no significance in the DBP was observed.

### Table 3. Effect of mineralocorticoid receptor antagonists on blood pressure.

| Study               | Study design                  | No. of subjects | Intervention                                      | Predialysis serum potassium level (mmol/L) |
|---------------------|-------------------------------|-----------------|--------------------------------------------------|-------------------------------------------|
| Saudan et al., 2003 | Prospective, single-arm       | 35              | Spironolactone 12.5 mg thrice weekly for 2 weeks, 25 mg thrice weekly for 2 weeks | After the 25 mg phase, spironolactone group: 4.9 ± 0.3, control group: 4.9 ± 0.7, p values not reported 4.6 ± 0.6 at baseline, 4.7 ± 0.6 at study completion, p = 0.19 |
| Hussain et al., 2003| Prospective, single-arm       | 15              | Spironolactone 25 mg daily for 28 days            |                                          |
| Michea et al., 2004 | Sequential, double-blind, placebo-controlled | 9               | Spironolactone 25 mg thrice weekly for 2 weeks, washout for 2 weeks, placebo for 2 weeks | Baseline: 4.53 ± 0.54, after spironolactone: 4.56 ± 3.39, after placebo: 4.67 ± 0.33, no significant differences |
| Gross et al., 2005  | RCT, double-blinded, crossover| 8               | Spironolactone, 50 mg twice daily for 2 weeks    | Spironolactone group: 5.0 ± 0.8, placebo group: 4.7 ± 0.5, p > 0.05 |
| Taheri et al., 2009 | RCT, double-blinded           | 16              | Spironolactone 25 mg thrice weekly for 6 months  | Differences of serum potassium concentration at the end of the study compared with the start: spironolactone: 1.02 ± 0.342, placebo: 0.98 ± 0.449, 95% CI (0.381–1.491), p = 0.004 |
| Matsumoto et al., 2009 | Prospective, single-arm      | 50              | Spironolactone 25 mg daily for 6 months          | Baseline: 4.96 ± 0.72, end of study: 5.18 ± 0.76, p < 0.05 |
| Vukusich et al., 2010| RCT, double-blinded           | 53              | Spironolactone 50 mg thrice weekly for 24 months | End of study, spironolactone: 4.9 ± 0.66, placebo: 4.6 ± 0.53, no significant differences; spironolactone increase serum potassium level by 0.012 per months (p < 0.0001) |
| Shavit et al., 2011 | Prospective, single-arm       | 8               | Eplerenone 25 mg twice daily for 4 weeks          | Baseline: 4.67 ± 0.2, week 4: 4.86 ± 0.38, p = 0.48 |
| Flevari et al., 2013| Sequential, placebo-controlled | 14             | Spironolactone 50 mg thrice weekly                | Baseline: 4.4 ± 0.72, after placebo: 4.7 ± 0.75, after spironolactone: 5.5 ± 0.75, p < 0.05 |
| Feniman-De-Stefano et al., 2015 | RCT, double-blinded | 17             | Spironolactone 12.5 mg daily for 2 weeks, then adjusted according to K⁺ | End of study, spironolactone: 5.0 ± 0.31, placebo: 4.9 ± 0.24, p = 0.244 |
| Walsh et al., 2015  | RCT, double blindered         | 154             | Eplerenone 25 mg daily for 7 days then adjusted according to K⁺ | End of study, eplerenone: 4.9 ± 0.7, placebo: 4.9 ± 0.7, no significant difference; eplerenone increased serum potassium level by 0.16 (95% CI, 0.04–0.28) |

Notes: Abbreviations: DBP: diastolic blood pressure; SBP: systolic blood pressure.
\[\text{If serum K⁺}<5.5 \text{mmol/L}, \text{spironolactone 25 mg daily; if serum K⁺ between 5.5 and 5.9 mmol/L, spironolactone 12.5 mg daily; if serum K⁺≥6.0 mmol/L, drop.}\]
\[\text{If serum K⁺<6 mmol/L, eplerenone 50 mg daily; if serum K⁺≥6 mmol/L, the dose was titrated down.}\]
Discussion

The safety of MRAs for patients receiving hemodialysis has been a controversial topic with two systematic reviews already published. A clear conclusion regarding safety and its positive effect, however, remains unclear.

Although the overall conclusion of the quantitative analysis suggests that the MRA exerts no significant effect on the predialysis serum potassium level compared with the placebo, the differences between the results should be explored. The studies that reported no significant difference between the MRA and placebo group used a rather low-dose of the MRA (no more than 25 mg daily of spironolactone or eplerenone). In the trials that found a significant increase in the serum potassium level after administration of MRAs, large doses (50 mg thrice a week) of MRAs were used. There was an exception, the trial conducted by Gross et al., in which patients took spironolactone 50 mg twice daily for 2 weeks, and no significant increase in the serum potassium level was observed. The underlying explanation for this may lie in the exclusion criteria – patients using ACEI or ARB were excluded, therefore lowering the potential effect on the serum potassium level. Interestingly, Ng et al. found in their meta-analysis of 28 studies that the use of MR antagonists was associated with increased serum potassium and a higher risk ratio of hyperkalemia. A possible explanation is that Ng included patients with chronic kidney disease (CKD) of stage I to stage V, while this review only included patients receiving hemodialysis. For patients with CKD of stage I–IV, residual renal function is the main approach for potassium excretion. In patients with ESRD and undergoing hemodialysis, however, regular hemodialysis plays the most important role in potassium balance, and by adjusting the potassium concentration in the dialysate, the serum potassium level can be controlled more easily.

The incidence of hyperkalemia was reported in a few studies with little consistency. Only Walsh et al. reported a significant increase in the incidence rate of hyperkalemia in the MRA group, and that might have been the result of increasing the dose of eplerenone during the trial. Nevertheless, it must be noted that the subjects included in all of the trials had no previous history of hyperkalemia and remained compliant to therapy. Meanwhile, we need to learn a lesson from the RALES studies. After the results were published, the prescription rate rose significantly and the incidence of hyperkalemia was much higher than that reported in the studies, indicating the necessity of surveillance of the serum potassium level. Additionally, an appropriate timetable for administration of MRAs is crucial to avoid hyperkalemia, and particularly, the relationship between MRAs and dialysis and meal must be considered. In three RCTs, MRAs were administered after each dialysis, when the serum potassium level was relatively low. Noori et al. found that the more potassium intake was associated with higher serum potassium level. Consequently, the ideal window for MRAs administration may be at the end of the dialysis and far away from meals to avoid hyperkalemic episodes. Conclusively, we may safely consider using MRAs on patients receiving hemodialysis at a low dose at the end of the dialysis and far away from meal, but serum potassium levels need to be monitored closely, and the patients should be cautiously observed for potential side effects, which can be easily accomplished due to the regular visits to the hospital or dialysis center.

Hypertension is the initial factor of other severe CV conditions, including LVH, arterial damage, cardiac ischemia, arrhythmia and, ultimately, heart failure, and therefore controlling blood pressure is critical in the management of patients on hemodialysis. It is suggested by three studies that there was a significant drop in blood pressure after the administration of MRAs. In these studies, relatively large doses of spironolactone were used (from 25 mg twice daily to 50 mg twice daily). Those studies that found no significant drop in BP used rather low dose of MRAs (no more than 50 mg thrice weekly). It is possible that MRAs may serve an important part in the future treatment paradigm, provided that the dose is accurately titrated.

LVH, as the consequence of increased afterload, humoral and cellular factors, altered myocardial
metabolism and rheostatic factors, progresses rapidly without intervention and is an important risk factor in end-stage renal disease. Taheri and Feniman-De-Stefano\textsuperscript{23,25} observed a decrease in the LVM after low doses of spironolactone. Flevari et al.\textsuperscript{30} found that spironolactone had no effect on the LVM, which may be explained by the fact that only patients without heart failure or hypertension and, therefore, a lower possibility of LVH, were included. If future studies confirm the necessity of intervention, low-dose MRA might be considered as a potential choice. However, whether targeting LVH is appropriate is still uncertain. Despite the promising results of several trials, whether therapeutic improvement in LVMI reduces mortality remains unclear.\textsuperscript{6}

Heart failure, the eventual outcome of all CV events, volume overload between dialyses and anemia,\textsuperscript{40} presents primarily as a decrease in the LVEF. Despite the fact that MRAs have already been proven effective in the treatment of heart failure in patients without kidney disease,\textsuperscript{13,41} whether they are beneficial for patients on hemodialysis and the ‘safe dose’ remains to be determined. We suppose the difference between the results from Taheri and Feniman-De-Stefano may derive from the difference between the inclusion criteria. Taheri only enrolled patients with a LVEF no more than 45\%,\textsuperscript{23} but Feniman-De-Stefano put no restriction on LVEF.\textsuperscript{25} These trials were not quite convincing, considering the small sample size. Large-scale trials are needed.

Elevated CIMT is considered as an indicator of atherosclerosis.\textsuperscript{42,43} The trial conducted by Vukusich et al. showed that MRAs had the potential to reduce CIMT and decrease the incidence of atherosclerosis and further CV thromboembolic events, including myocardial infarction and stroke.\textsuperscript{24}

Most importantly, the effect of MRAs on the mortality of hemodialysis patients remains to be explored. We are pleased that such studies are beginning. Matsumoto et al.\textsuperscript{21} conducted a trial focusing on the mortality and morbidity rate of CV and cerebrovascular (CCV) events of patients on hemodialysis treated with spironolactone. Three hundred and nine patients were recruited, 157 for the spironolactone group and 152 for the placebo group. The death from CCV causes, hospitalization for CCV causes and the death from all causes decreased significantly. However, the article failed to provide the serum potassium level and was therefore excluded from the review. Indeed, this was one trial with a relatively small sample size, yet it marked the first step on the way to full comprehension of the effects of MRAs on hemodialysis patients.

The MRAs administered in the included trials were spironolactone or eplerenone, both of which have been proved efficacious in the treatment of heart failure and hypertension.\textsuperscript{44} Compared to spironolactone, eplerenone is a selective aldosterone antagonist with lower incidence of sexual side effects due to lower affinity for progesterone and androgen receptors.\textsuperscript{45} However, highly polymorphic cytochrome dependent metabolism makes eplerenone susceptible to drug interactions.\textsuperscript{36} Besides, the cost of eplerenone is significantly higher than that of spironolactone (approximately $113 vs. $24 per months) since spironolactone has been off-patent.\textsuperscript{45} Regretfully, there have been no trials comparing spironolactone and eplerenone in patients on hemodialysis.

In clinical practice, the comorbidities of patients and economic conditions should be considered during the decision making of treatment plans.

Meanwhile, the non-steroidal MR antagonists are being evaluated, finerenone being one of them, which has been tested through phase I to phase IIb. The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS)\textsuperscript{47–49} included patients with heart failure and CKD. It was reported that finerenone decreased the concentration of NT-proBNP and BNP. Additionally, although not statistically significant, there was a trend that finerenone was associated with lower urinary albumin to creatinine ratio. Compared to spironolactone, finerenone did not decrease eGFR and increase serum potassium level. Considering the above advantages, finerenone may be a promising candidate MRA in the treatment of patients undergoing dialysis, especially those with heart failure.

It must be noted that this review is a preliminary summarization of clinical trials. The methodology of some trials may increase the risk of bias, especially considering that only five studies were RCTs and the others were not designed to be double-blinded and did not have a parallel control arm as a comparison. Additionally, each study recruited only a limited number of patients and, therefore, the number of patients included in this review is relatively small (379 for systematic review and 248 for quantitative analysis). Meanwhile, the inclusion criteria, study design and intervention method of different studies were not identical, which is a possible source of heterogeneity in the meta-analysis. Large-scale multi-center RCTs are necessary to provide further evidence for the safety and CV benefits of MRAs on patients receiving hemodialysis.

Notably, at least three RCTs investigating the effect of MRAs on patients undergoing hemodialysis are already in process. Hammer et al.\textsuperscript{50} conducted a prospective, randomized, placebo-controlled, double-blind, parallel group, multi-center intervention study (NCT01691053) to investigate the effects of spironolactone (50 mg daily) compared with placebo in maintenance hemodialysis
patients. The outcomes include pre-dialysis potassium levels, incidence of life-threatening hyperkalemia, LVMI, changes in left ventricular geometry and function, 24-h ambulatory blood pressure, cardiac arrhythmias, vascular function parameters, measures of heart failure and quality of life. We are optimistic that with the accumulation of high-quality large-scale RCTs, there will be a sophisticated guide for the use of MRAs in patients receiving hemodialysis. Currently, it is reasonable to use low-dose MRAs safely with cautious monitoring of the serum potassium level, and its potential effect on blood pressure, LVEF and LVH. A second ongoing RCT by Central Hospital and Institut National de la Santé Et de la Recherche Médicale of France (NCT01848639) is recruiting patients undergoing chronic hemodialysis to investigate the effect of spironolactone (25 mg per 2 days, after dialysis). The primary outcome is the time to onset of the first non-fatal MI or acute coronary syndrome or hospitalization for heart failure or nonfatal stroke or CV death, and other outcomes include incidence of hyperkalemia, the cumulative rate of non-fatal MI or acute coronary syndrome, hospitalization for heart failure, nonfatal stroke or CV death, etc. Another similar RCT by Brigham and Women’s Hospital is also recruiting participants (NCT02285920)."}

Disclosure statement

The authors report no conflict of interest.

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