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REVIEW

Safety evaluation and cardiovascular effect of additional use of spironolactone in hemodialysis patients: a meta-analysis

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Objective: To evaluate the safety and cardiovascular effect of low-dose spironolactone administration in end-stage renal failure patients undergoing hemodialysis coupled with conventional treatment.

Methods: We conducted a systematic search for clinical trials on the safety and cardiovascular effect of additional low-dose spironolactone in hemodialysis patients. The search was performed on PubMed, EMBASE, Cochrane Library, and CBM databases. Relevant references (up to February 2016) were retrieved and subsequent results analyzed with a random-effects model or a fixed-effects model.

Results: We identified nine trials with a total sample size of 765 patients. The results did not indicate significant differences regarding safety and serum potassium levels (mean difference [MD]=0.23, P=0.09) between the two treatment options. However, patients receiving low-dose spironolactone exhibited improvements in left venticular mass index (LVMI) (standardized mean difference= –0.58, P<0.00001) and left ventricular ejection fraction (LVEF) (MD=4.91, P<0.0001) with an additional decrease in systolic blood pressure (MD= –6.97, P=0.0001) and diastolic blood pressure (MD= –4.01, P=0.007). Furthermore, the clinical (OR=0.4, P=0.0003) or cardiovascular and cerebrovascular-related (OR=0.4, P=0.002) mortality was significantly lower among those patients.

Conclusion: These results indicated that additional use of low-dose spironolactone associated with conventional treatment does not have a significant impact on serum potassium levels in hemodialysis patients. What's more, it might exert a protective effect on the cardiovascular system by optimizing LVMI, improving LVEF, decreasing arterial blood pressure and reducing events-related mortality. Further large sample size studies are needed to support these findings.

Keywords: Spironolactone, hemodialysis, safety, cardiovascular protection, meta-analysis

Introduction

Heart disease is extremely recurrent in dialysis patients and coronary artery disease, hypertension and left ventricular failure account for the majority of cases in this subgroup of patients.[1–5] Patients with end-stage renal failure (ESRF) and on hemodialysis often die of heart disease at a much higher rate (20 to 40 times) than the general population.[6–8] According to the United States Renal Data System, cardiovascular disease accounts for more than 44% of all mortalities.[6–8]

Several studies conducted on ESRD patients indicated a significant increase in aldosterone.[3,9,10] Aldosterone is thought to play a role in the development of

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hypertension, vascular structure alteration, vascular smooth muscle hypertrophy, endothelial dysfunction, renal injury, proteinuria, left ventricular remodeling, collagen synthesis, and myocardial fibrosis. With excess aldosterone, both renal and extrarenal mineralocorticoid receptors are activated further exacerbating the effect of angiotensin II and other products of the renin-angiotensin-aldosterone system (RAAS).[11,12] Excessive activation of RAAS contributes to the development of cardiac hypertrophy and myocardial fibrosis[13] and leads to complex pathophysiological effects that may result in hypertension, heart failure, and other cardiovascular disorders.[11,12,14–26]

Currently, the most relevant pharmacological agents that block the RAAS are angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers (ARBs). Aldosterone has been overlooked as a consequential RAAS mediator and a relevant factor in target organ injury in spite of the widespread usage of RAAS blockers.[11,27] Consequently, mineralocorticoid receptor antagonist（MRA） might have benefits for target organ injury mitigation.

Prior studies[28–31] on the impact of spironolactone, a potent competitive mineralocorticoid receptor, on patients with heart failure and myocardial infarction without renal insufficiency have shown favorable outcomes. Nevertheless, safety risks still exist due to its effect on sodium and potassium levels. To date, several clinical studies have actively explored the safety and protective effects of spironolactone in dialysis patients. However, significant differences in outcome indicators and limitations such as small sample size or a limited follow-up period can be observed among those studies. Therefore, it is difficult to form a unified conclusion. Subsequently, the current study applied a systematic evaluation approach and meta-analysis methods to evaluate the safety and protective effect of spironolactone in hemodialysis patients aiming to provide clinical evidence for the optimization of patients prognosis.

Methods

Data sources and search strategy

The present meta-analysis was performed according to The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[32,33] PubMed, EMBASE, Cochrane Library, and CBM databases were searched using the following keywords: Spironolactone, Antisterone, Renal Dialysis, Renal Replacement, End Stage Renal Disease, Renal Insufficiency, and Kidney Failure. No restrictions were imposed on language and date of publication. The final search was run on February 01, 2016. Additional searches were performed based on retrieved articles to identify studies omitted by our primary search strategy.

Study selection

The study selection diagram is shown in Figure 1. All randomized controlled trials (RCTs) and quasi RCTs conducted on a population of adult CKD patients requiring dialysis and with a dialysis period of more than one month were included. Randomized, crossover studies were also considered for inclusion.

Exclusion criteria were as follows: studies with kidney transplant recipients (ESRD), RCTs with different outcomes than the ones of interest, studies lacking a comparable control or placebo, reviews, meeting abstracts, and case-only studies.

Endpoint definition

Endpoints of this study included serum potassium levels (mmol/L), changes in heart structure and function, blood pressure levels, All-cause mortality, cardiovascular and cerebrovascular (CCV) mortalities, Heart failure, Stroke, New or recurrent Acute myocardial infarction (AMI), Aortic dissection and sudden death.

Data extraction and quality assessment

Data from all included studies were extracted by two independent reviewers using a standardized data-extraction protocol. Disagreements were resolved by consensus. Data extracted from the study included: 1. study characteristics (title, first author name, year of publication, design, and duration); 2. participant characteristics (age, sex, the presence of other chronic diseases (hypertension, cardiac insufficiency, diabetes), the frequency of dialysis treatment, type of medication); 3. the nature of treatment and intervention (MRA type, dose, frequency, and follow-up duration); 4. the outcome (serum/plasma potassium levels, changes in heart structure and function, blood pressure, All-cause mortality, Cardiovascular mortality). The quality of each RCT was evaluated using the Cochrane risk of bias instrument which primarily assesses the randomization and allocation concealment, the blinding process of individuals involved in the trial, the completeness of follow-up, and the outcome. Each study outcomes were classified as low risk of bias, unclear, or high risk of bias. The quality assessments of the two none-randomized

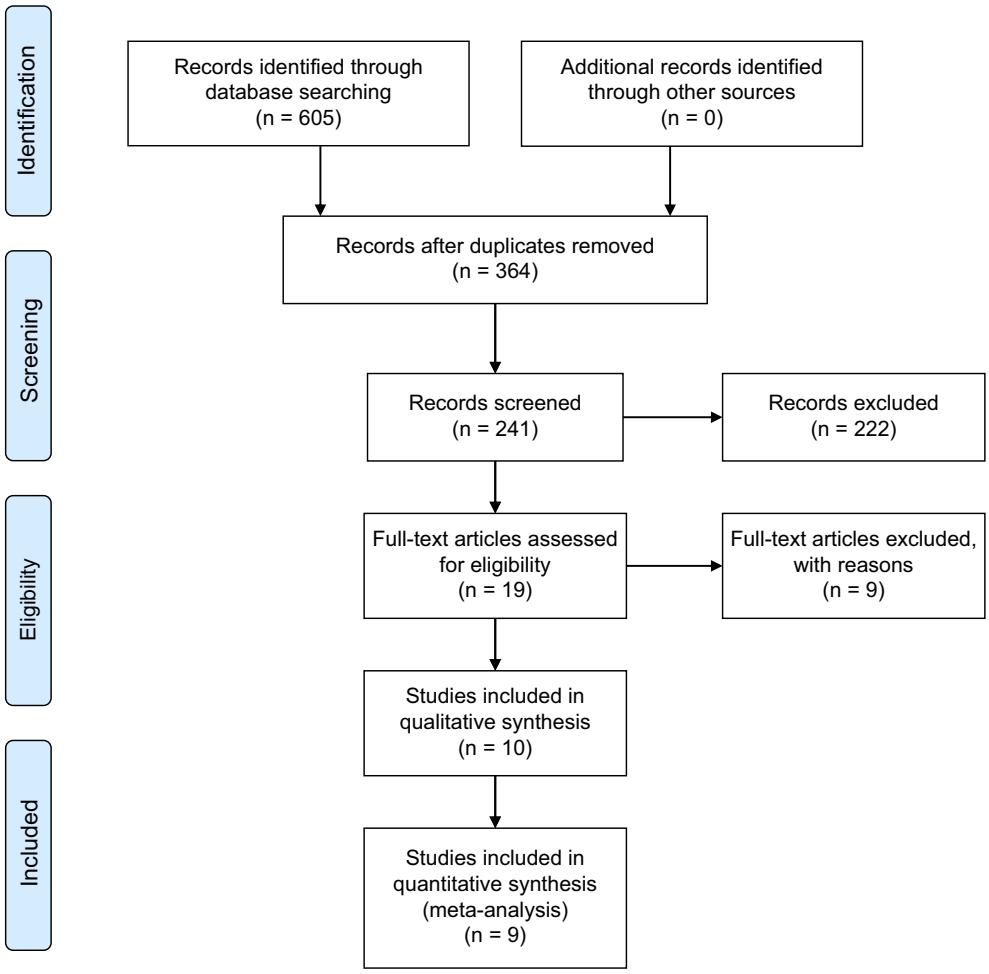

Figure 1 Selection process of studies included in the meta-analysis.

studies were performed using The Newcastle-Ottawa Scale with few modifications to match the needs of this meta-analysis.[34,35] This scoring system uses the following aspects of study design to assess quality: patient selection, comparability of study groups, and assessment of outcome. High-quality studies were defined as studies that have achieved five or more stars on the modified Newcastle-Ottawa Scale.

Data synthesis and statistical analysis

The statistical analysis was conducted on the Cochrane Review Manager (RevMan version 5.3). Continuous outcomes were analyzed using mean differences (MDs), standardized mean differences (SMDs) and dichotomous outcomes were analyzed using pooled odds ratio (OR) to combine different tests and measurement scales within each domain. Overall effect estimates were calculated for all analyses using inverse variance weighted fixed-effects analysis with 95% confidence intervals (CIs). Standard deviations (SDs) were calculated using the following formula: SD = square root [(SD pretreatment)2+ (SD post-treatment)2–(2R × SD pre-treatment× SD post-treatment)], assuming a correlation coefficient of (R)=0.5.

Heterogeneity among studies was identified using a standard $\chi 2$ test and a *P*-value (two-sided) based on the Cochran Q statistic.[36] I^2 index, as the percentage of variation across studies, was used to assess heterogeneity with an I^2 value of 25%, 50% or 75% representing low, moderate, or high heterogeneity, respectively.[37] The fixed effect model was used for analysis in cases where the heterogeneity analysis indicated an $I^2<25\%$. The source of heterogeneity and the stability of the results were further evaluated for an I^2 value of $25\%\leq I2<50\%$. The random effect model was used for analysis when

$I^2 \geq 50\%$. Subgroup analysis or sensitivity analysis methods further explored the sources of heterogeneity and explained possible causes. We planned to construct a funnel plot to evaluate the risk of publication bias provided that the number of included studies was sizeable (more than ten).

Results

Study selection and characteristics

Of the 605 studies identified by our primary search, 19 articles were retrieved after initial assessment for detailed evaluation. Nine of those met the inclusion criteria and were incorporated in the final analysis (Figures 1 and 2). Tables 1 and 2 summarizes the characteristics of those studies. In summary, seven randomized controlled trials and two non-randomized controlled trials with a sample size of 765 patients and an average follow-up period of 2 weeks to 3 years were included in this meta-analysis. The risk of bias among included trials was generally low. Two studies[38,39] scored 5 or more stars on the modified Newcastle-Ottawa Scale.

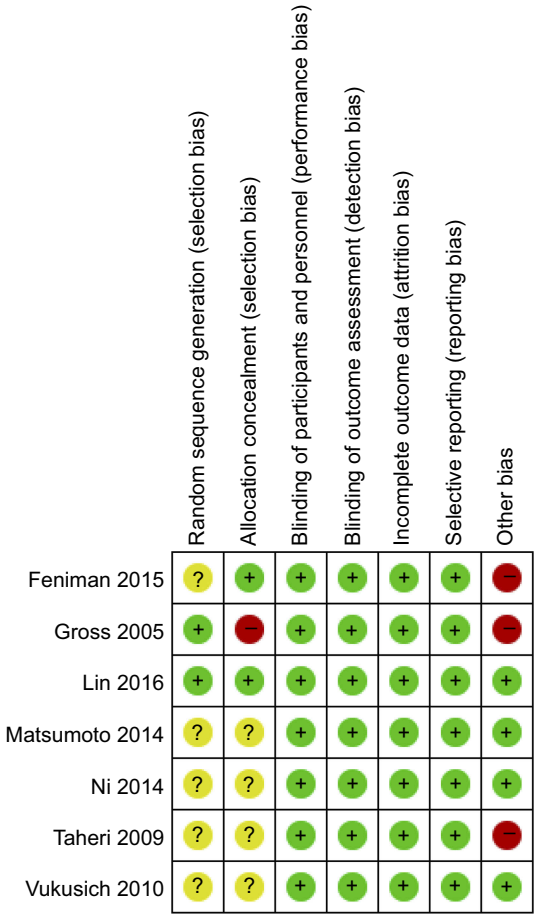

Figure 2 Quality of studies included in the meta-analysis. Red, high risk of bias; green, low risk of bias; yellow, unknown risk of bias.

More detailed informations on the number of studies involved and sample sizes for each outcome are as follows: serum potassium levels, 7 studies (spironolactone, 200 patients; control,202 patients);[38–43] LVMI, 4 studies (spironolactone, 138 patients; control, 137 patients);[39,40,43,44] LVEF, 4 studies (spironolactone, 138 patients; control, 137 patients);[39,40,43,44] BP, 5 studies (spironolactone, 101 patients; control, 105 patients);[39,42,44–46] All-cause mortality, 3 studies (spironolactone, 285 patients; control, 293 patients);[40,41,43] CCV events, 2 studies (spironolactone, 277 patients; control, 285 patients).[40,41]

Serum potassium levels

Substantial heterogeneity in serum potassium levels was observed among studies with a significant effect seen in the spironolactone group (MD=0.23, 95%CI [–0.03, 0.49], P=0.09) (Figure 3). We carefully checked the extracted data, reviewed the characteristics of included studies, and concluded that heterogeneity might be partly due to two studies: Taheri 2009[43] and Lin 2016.[42] Therefore, we conducted a fixed-effect subgroup analysis by removing those two studies.[42,43] As demonstrated in Figure 4, no significant treatment effect was observed in the spironolactone group (MD=0, 95%CI [–0.18, 0.18], P=0.98).

LVMI

Compared with control, the addition of spironolactone significantly decreased the LVMI (SMD=–0.58, 95%CI [–0.82, –0.334], $P<0.00001$) (Figure 5).

LVEF

As indicated by the results, additional spironolactone treatment elevated the LVEF significantly (MD=4.91, 95%CI [2.58, 7.24], $P<0.0001$). No significant heterogeneity was observed (Figure 6).

Blood pressure

The results indicated that additional spironolactone significantly decreased the systolic blood pressure (MD=−6.97, 95%CI [−10.56,−3.37], P=0.0001) (Figure 7) and diastolic blood pressure (MD=−4.01, 95%CI [−6.90,−1.12], P=0.007) of the treatment group (Figure 11). Secondary analysis of the data using a random effects model showed a downward trend in SBP in the spironolactone group (MD=−5.34, 95%CI [−11.36, 0.68], P=0.08) (Figure 8).

Table 1 Characteristics of 9 clinical trials included in the meta-analysis

Study , year	Study design	Spironolactone usage	Hemodialysis frequency	Follow time	Cardiac function III-IV	Oliguria, no urine	Outcome
Feniman, 2015[44]	Random, placebo control, double blind	12.5 mg daily (2 weeks) then 25 mg daily	None	6 months	0%	None	Serum potassium levels, LVMI, LVEF, BP
Gross, 2005[45]	Random, placebo control, cross	50 mg semiweekly	Triweekly	2 weeks	None	100%	Serum potassium levels, BP
Lin, 2016[40]	Random, placebo control, double blind	25 mg daily	Triweekly	2 years	0%	Spironolacton 68% control 64%	Serum potassium levels, LVMI, LVEF, All-cause mortality, CCV mortality
Matsumoto, 2014[41]	Random, crontrol	25 mg daily	Triweekly	3 years	None	None	All-cause mortality, CCV mortality
Ni, 2014[42]	Random, placebo control, double blind	25 mg daily	Triweekly	12 weeks	None	100%	Serum potassium levels, BP
Sandan, 2003[38]	Non-random, unblind	12.5 mg triweekly (2 weeks) 25 mg triweekly	Triweekly	4 weeks	0%	Spironolacton 86% control 0%	Serum potassium levels
Taheri, 2009[43]	Random, placebo control, double blind	25 mg triweekly	Triweekly	6 months	100%	None	Serum potassium levels, LVMI, LVEF
Vukusich, 2010[46]	Random, placebo control	50 mg triweekly	Triweekly	2 years	None	None	BP, CIMT
Liang, 2011[39]	Non-random, unblind	25 mg triweekly	Triweekly	3 months	100%	None	Serum potassium levels, LVMI, LVEF, BP

Abbreviations: CCV, cardiovascular and cerebrovascular; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction.

The subgroup analysis indicated that the SBP of the spironolactone group was considerably lowered in Subgroup1 [MD= –10.51, 95%CI (−15.04, −5.97), $P<0.00001$](Figure 9); meanwhile, there was no significant treatment effect in the subgroup 2 [MD=−1.00, 95%CI (−6.89, 4.89), $P=0.74$] (Figure 10).

All-cause mortality

Treatment with spironolactone was associated with a significant reduction in all-cause mortality [OR=0.4, 95%CI (0.24, 0.66), $P=0.0003$] (Figure 12).

CCV mortality

The spironolactone group showed a significant reduction in CCV mortality [OR=0.4, 95%CI (0.22, 0.72), $P=0.002$] (Figure 13).

Discussion

Our analysis included a total of 765 patients in nine studies, with seven being randomized controlled trials and two non-randomized controlled trials. The results indicated that additional use of low-dose spironolactone associated with conventional treatment does not significantly increase serum potassium levels in hemodialysis patients. Conversely, it might exert a protective effect on their cardiovascular system by optimizing LVMI and improving LVEF.

Mineralocorticoid receptors are present in major organs such as the brain, heart, blood vessels and kidneys, and interestingly, there is evidence suggesting the production of aldosterone within their tissues.[1] Therefore, the activation of local mineralocorticoid receptors by aldosterone has a significant effect on the cardiovascular system.[1,2] The existence of "aldosterone escape phenomenon" has been clarified with the widespread usage of ACEI/ARB in clinical settings.[11,27] Several studies[28–31,47,48] have confirmed that the addition of MRA coupled with conventional treatments (including ACEI/ARB drugs) can significantly improve the long-term survival rate of patients with heart failure and myocardial infarction.

Table 2 Characteristics of patients from 9 clinical trials included in the meta-analysis

	Subjects (man)		**Age (year)**		**Sex (man, %)**		**LVEF (%)**		**Hypertension (%)**		**Diabetes (%)**		**ACEI/ARB (%)**	
Study, year	Test group	Control group	Test group	Control group	Test group	Control group	Test group	Control group	Test group	Control group	Test group	Control group	Test group	Control group
Feniman-De-Stefano, 2015[44]	8	10	52	56	50	56	70.3	68.9	NR	NR	50	56	37.5	88.9
Gross, 2005[45]	8	8	53	53	37.5	37.5	NR	NR	37.5	37.5	37.5	37.5	0	0
Lin, 2016[40]	125	128	70.3	70.6	58.4	62.5	61.78	62.29	4.8	4.7	20.8	20.7	100	99
Matsumoto, 2014[41]	157	152	67.4	67.7	72	59.2	NR	NR	12.7	4.6	31.8	30.9	50	48
Ni, 2014[42]	40	36	55.7	54.9	60	58.3	NR	NR	5	5.5	15	19.4	55	53
Sandan, 2003[38]	14	21	54	59	NR	NR	NR	NR	NR	NR	14.3	23.8	57.1	52.4
Taheri, 2009[43]	8	8	59.5	56.8	62.5	75	31.25	33.75	75	100	62.5	62.5	100	100
Vukusich, 2010[46]	30	23	60.1	55.6	66.7	61	61.9	62.5	60	56.5	0	0	0	0
Liang, 2011[39]	22	22	60	59.8	72.7	68.2	30.49	28.66	NR	NR	27.3	31.8	100	100

Abbreviations: LVEF, left ventricular ejection fraction.

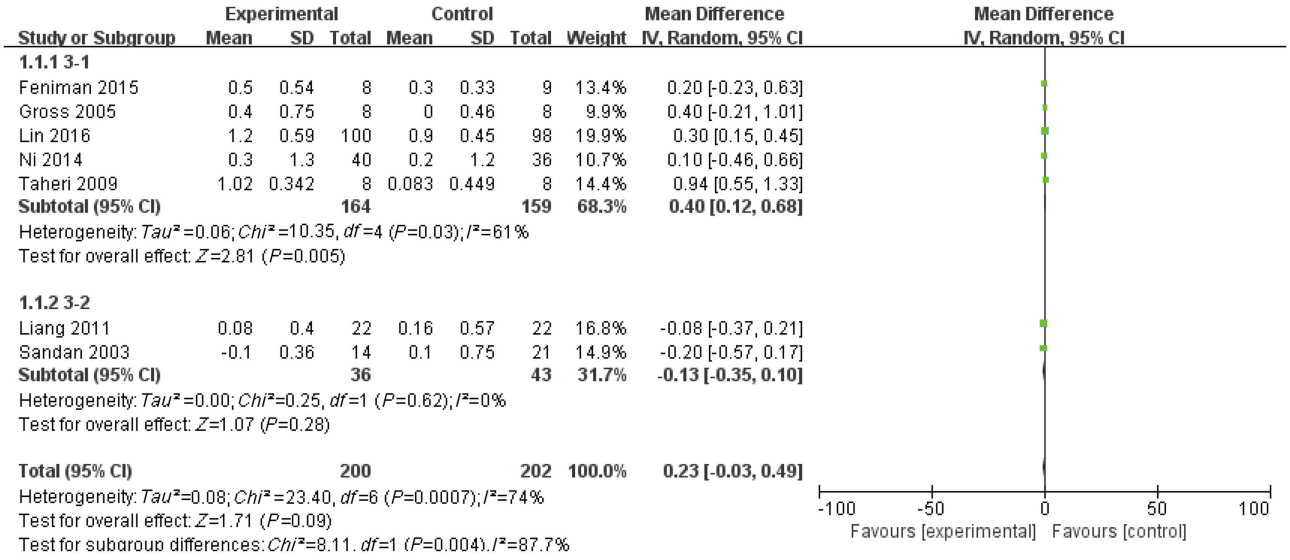

Figure 3 Forest plot for changes of serum potassium level.

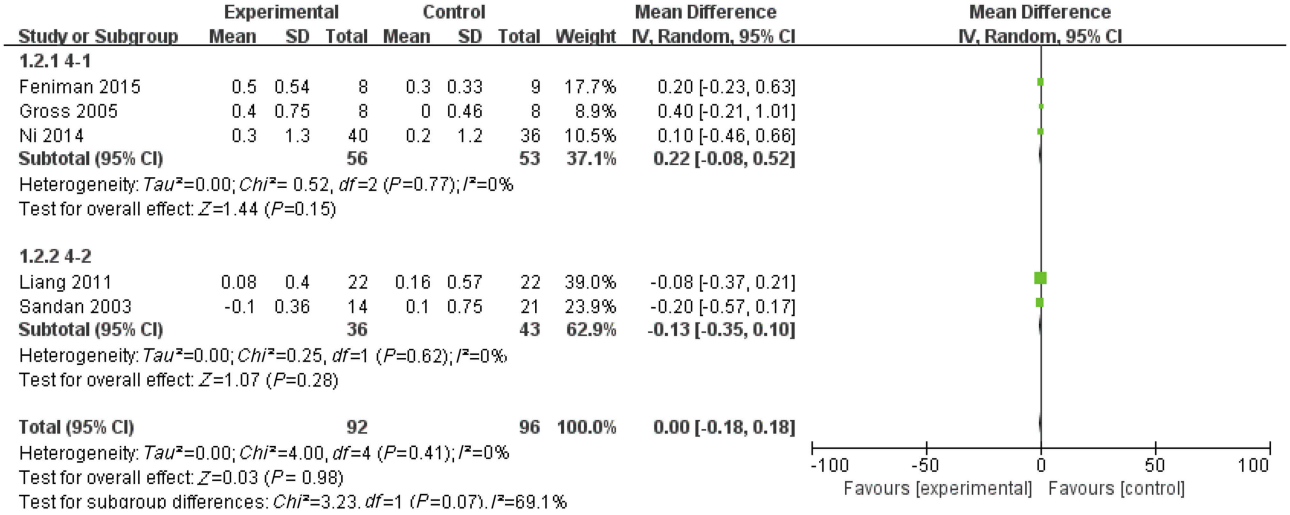

Figure 4 Forest plot for changes of serum potassium level after sensitivity analysis.

However, fluctuations in blood potassium levels and hyperkalemia are likely to occur in patients with renal insufficiency.[49] Another study showed that the blood potassium balance relied primarily on regular dialysis and timely adjustment of dialysate ion concentration in the ESRD hemodialysis population.[50]

In earlier studies,[38,39,43,45,46] the administration of spironolactone was timely adjusted, and it was usually administered after hemodialysis to avoid a short-term increase in blood potassium due to oral spironolactone. However, recent studies[40–42,44] on regular hemodialysis patients with a daily dosage of 25 mg of spironolactone did not indicate a significant increase in mean potassium levels after a follow-up period of 3 months to 2 years. These findings are consistent with the results of the RALES study[29] suggesting that daily usage of 25 mg of spironolactone is safe in this subgroup.

A previous meta-analysis with 28 eligible studies[49] found that the use of MRA is associated with a higher risk of hyperkalemia. Meanwhile, another study[51] indicated that a higher potassium intake might significantly increase the risk of death in long-term HD patients. Therefore, education on risks related to potassium intake is crucial for hemodialysis patients especially those taking spironolactone.

The estimated prevalence of hypertension in patients with chronic kidney disease but not undergoing dialysis is 70%. Of these, 75% are treated with antihypertensive medications with only 36% achieving a blood pressure

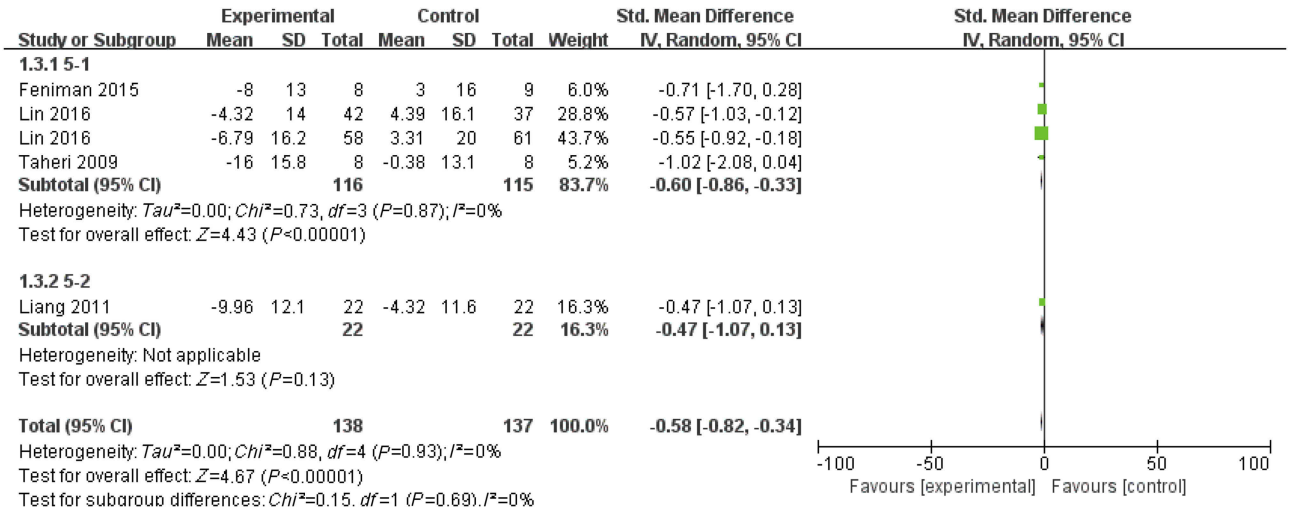

Figure 5 Forest plot for LVMI.
Abbreviation: LVMI, left ventricular mass index.

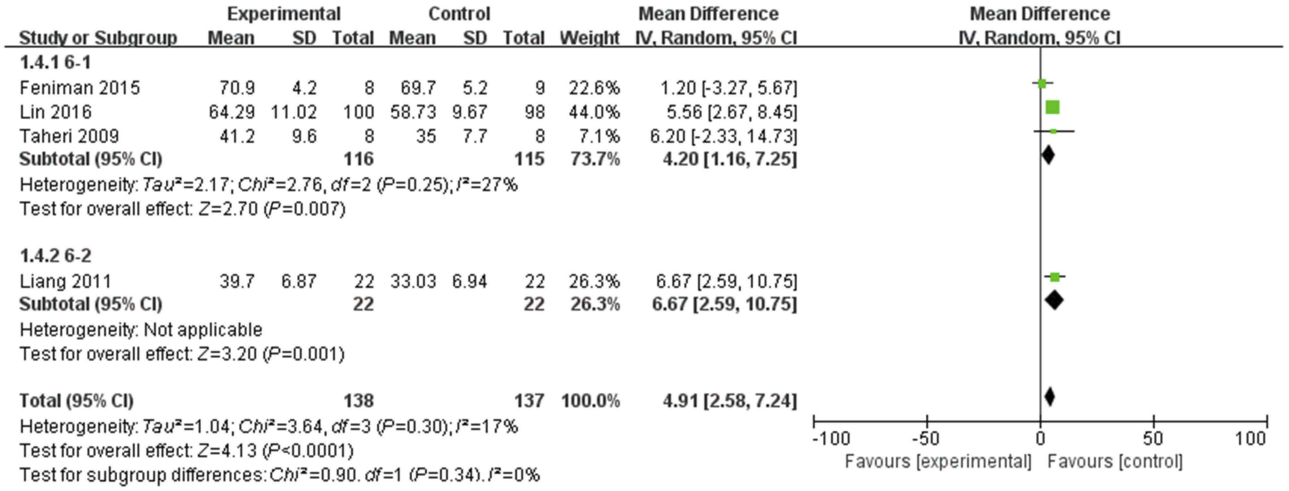

Figure 6 Forest plot for LVEF.
Abbreviation: LVEF, left ventricular ejection fraction.

goal of 140/90 mmHg.[52] Several studies[42,45] indicated that administration of spironolactone utilizes a non-diuretic mechanism to decrease pre-dialysis systolic blood pressure in oligo-anuric hemodialysis patients.

Increased common carotid artery intima-media thickness (CCA-IMT) has been associated with an increase in myocardial infarction and stroke risks. Interestingly, fifty milligrams of spironolactone thrice weekly has been shown to significantly reduce the progression of CIMT in HD patients.[53–55] Here, we indicate that blocking MR has a direct effect on vascular remodeling independent of BP.

The Hammer[56] trial is a prospective, randomized, placebo-controlled, double-blind, parallel group, and a multi-centered study investigating the effect of spironolactone (50 mg daily) on maintenance hemodialysis patients. The endpoints included changes in LV geometry and function, office and 24-h ambulatory blood pressure, cardiac arrhythmias, vascular function parameters, and measurements of heart failure and quality of life. MiREnDa will provide highly relevant insights into the cardiac and vascular effects as well as the safety of spironolactone in dialysis patients.

The present meta-analysis has several limitations. Firstly, the small sample size and a limited number of clinical trials might make our results susceptible to bias. The second limitation is the lack of long-term studies.

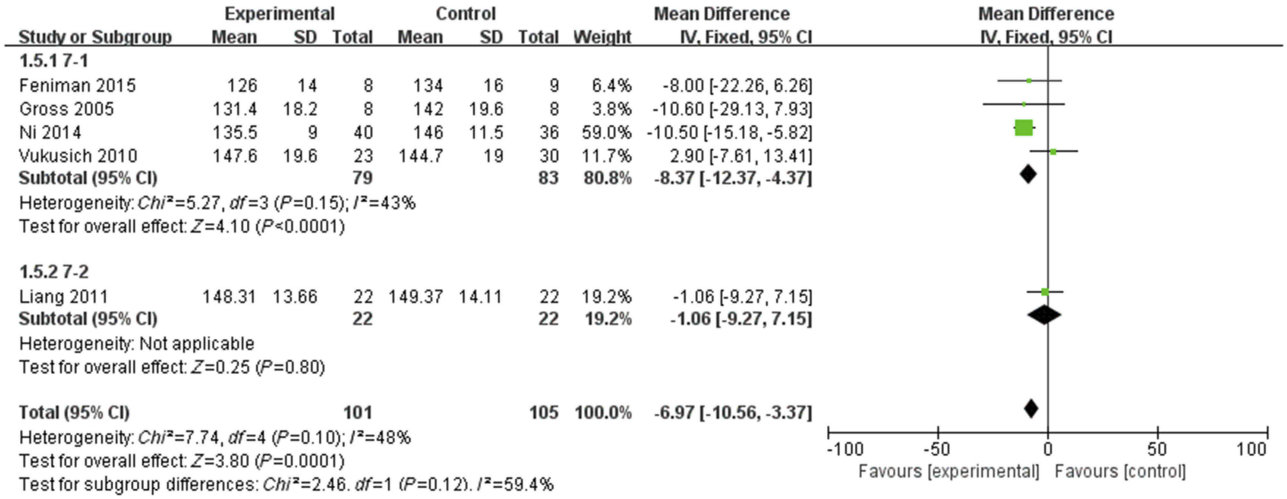

Figure 7 Forest plot for SBP with fixed-effect model.
Abbreviation: SBP, systolic blood pressure.

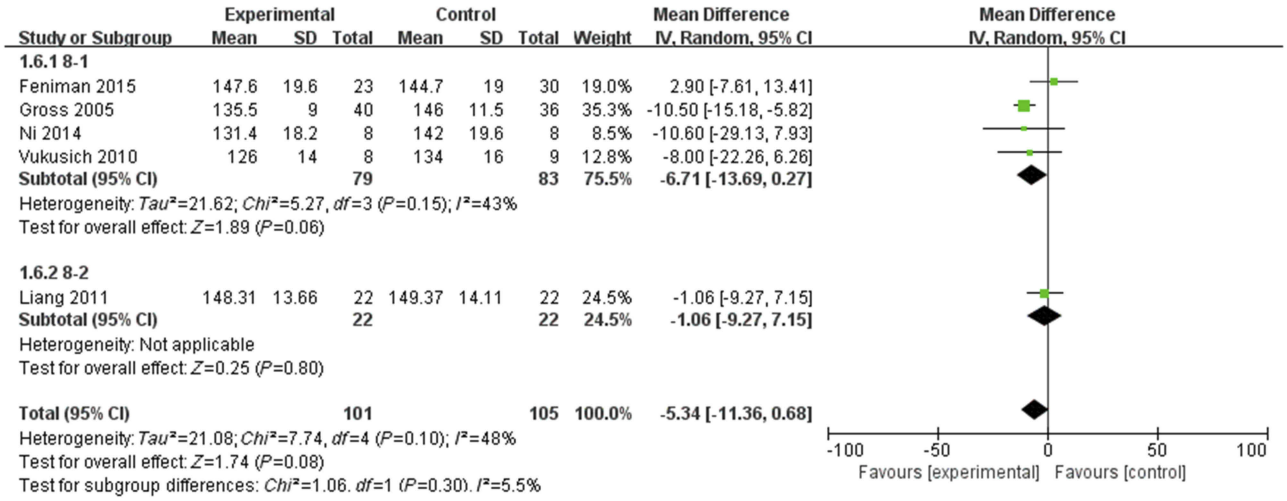

Figure 8 Forest plot for SBP with random-effect model.
Abbreviation: SBP, systolic blood pressure.

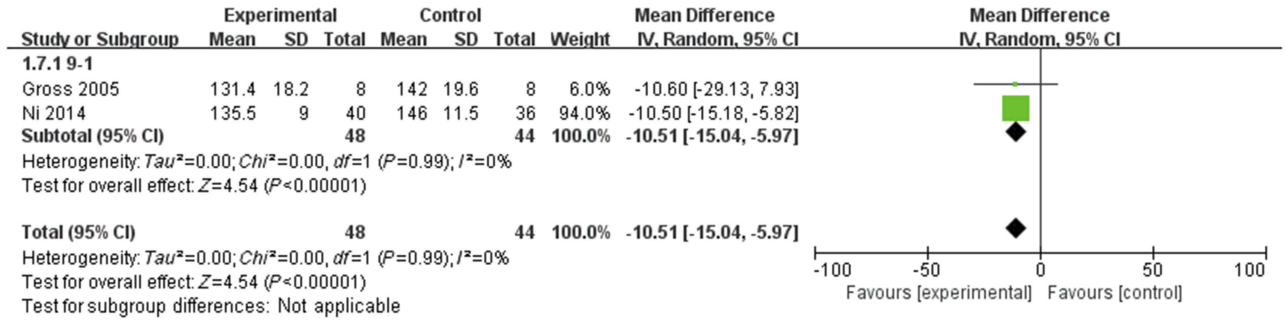

Figure 9 Forest plot for subgroup1 analysis of SBP.
Abbreviation: SBP, systolic blood pressure.

For example, only 5 included studies were long-term studies (>6 months), among which, three concluded that spironolactone provided a long-term beneficial effect. Thirdly, the dosage of spironolactone varied between studies making the establishment of a maximum safe dose much harder. Fourthly, even

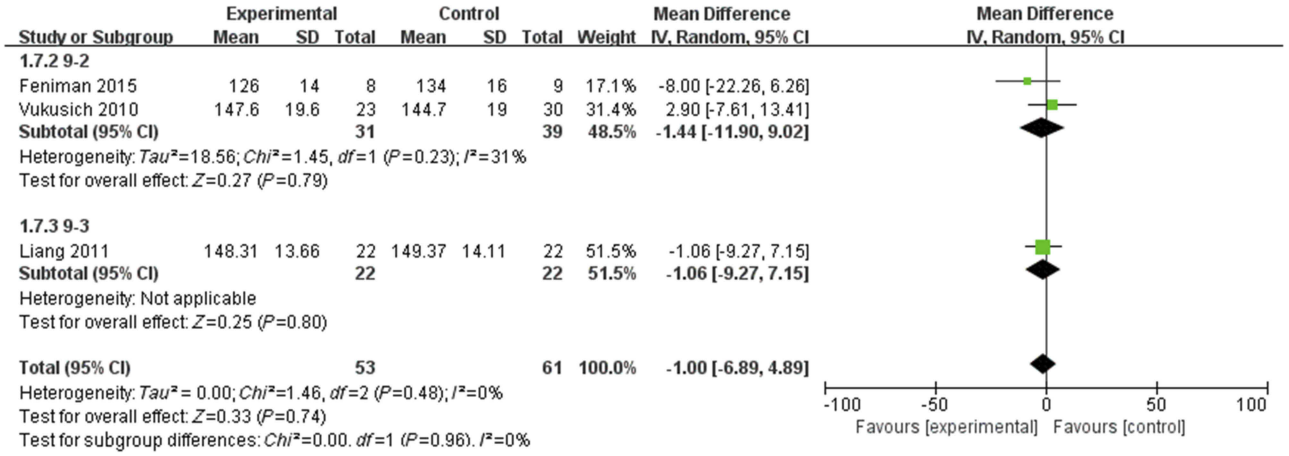

Figure 10 Forest plot for subgroup2 analysis of SBP.
Abbreviation: SBP, systolic blood pressure.

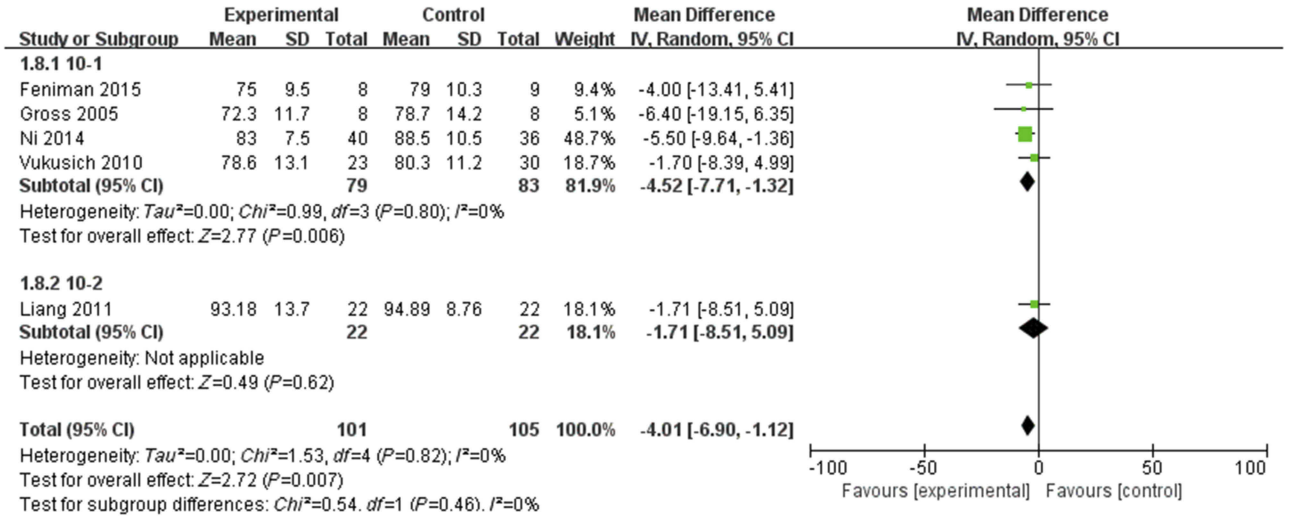

Figure 11 Forest plot for DBP.
Abbreviation: DBP, diastolic blood pressure.

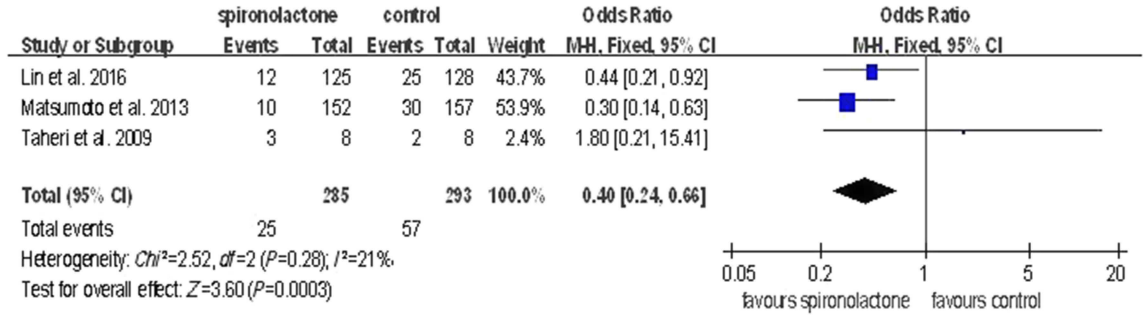

Figure 12 Forest plot for mortality caused by any clinical event.

though some studies have reported changes in blood pressure before and after follow-up, blood pressure was not considered as a primary outcome. Therefore, there may be differences in the control of external factors affecting blood pressure in each group, which in turn might impact the final result. In summary, meta-analysis conclusions still need to be demonstrated by additional high-quality, large-sampled clinical studies.

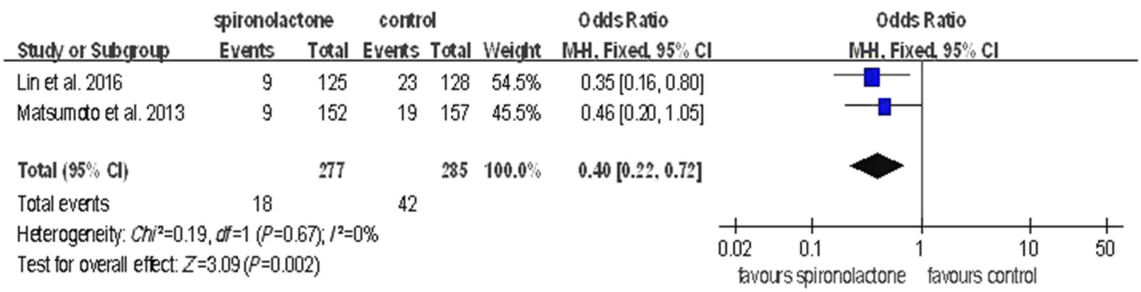

Figure 13 Forest plot for mortality caused by CCV events.
Abbreviation: CCV, cardiovascular and cerebrovascular.

Conclusion

This study indicated that the additional use of low-dose spironolactone exerts a protective effect on the cardiovascular system of hemodialysis patients by optimizing LVMI, improving LVEF, decreasing arterial blood pressure and reducing clinical or CCV-related mortality. Additionally, its usage did not significantly increase serum potassium levels in those patients.

Disclosure

The authors report no conflicts of interest in this work.

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