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Original Article

Effects of spironolactone on cardiovascular outcomes in chronic kidney disease and end-stage renal disease patients

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Abstract: Cardiovascular disease causes significant morbidity and mortality among patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Several small clinical trials have shown the beneficial effects of spironolactone therapy on cardiac function in CKD patients. However, the effect of spironolactone on cardiovascular outcomes in CKD and ESRD patients is not clear. The objective of this study was to systematically review data regarding the effects of spironolactone on cardiac morphology, function and mortality in these patient populations. We searched Embase, PubMed, and Cochrane Central Register of Controlled Trials databases up to March 2015 for English-language, human-subjects clinical trials that evaluated cardiovascular outcomes with spironolactone use in CKD and ESRD patients. Data extracted from the literature were analyzed with the Review Manager. Seven randomized controlled trials (RCTs) involving 737 patients were included. Ejection fraction (EF) was not significantly improved with spironolactone treatment (P = 0.78). However, compared with the use of placebo alone, spironolactone therapy decreased left ventricular mass (LVM) (P = 0.03). Spironolactone was superior to placebo in reducing cardiovascular mortality (P = 0.03) and all-cause mortality (P = 0.0005), whereas the occurrence of hyperkalemia was similar between placebo- and spironolactone-treated patients (P = 0.16). These findings suggest that spironolactone has beneficial effects on LVM and reduces the risk of cardiovascular and all-cause mortality without increasing the incidence of hyperkalemia in CKD and ESRD patients, but it does not seem to improve the cardiac function index. The potential effects of spironolactone therapy on cardiovascular outcomes require further study.

Keywords: Spironolactone, chronic kidney disease, end-stage renal disease, cardiovascular outcomes, meta-analysis

Introduction

Cardiovascular disease remains the most significant cause of death among patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1]. Increased left ventricular mass (LVM), also referred to as left ventricular hypertrophy (LVH), is an independent predictor of cardiovascular morbidity and mortality [2, 3]. Most patients with CKD eventually develop LVH, and the development, severity, and persistence of LVH are strongly associated with cardiovascular events in CKD and ESRD [4].

Spironolactone, a non-selective aldosterone antagonist, seems to have beneficial effects on cardiovascular outcomes. In patients with heart failure without severe CKD, spironolactone has been shown to reduce the number of cardiovascular events [5]. A meta-analysis by Hu et al suggested that spironolactone reduces cardiovascular mortality and the rate of rehospitalization, improves cardiac function, and simultaneously ameliorates left ventricular reverse remodeling in patients with mild-to-moderate chronic heart failure [6]. Several clinical studies regarding the effect of spironolactone on cardiovascular outcome in CKD or ESRD patients have recently been published, but the effects of spironolactone remain controversial. Mehdi et al reported no significant improvement in cardiovascular events with spironolactone treat-

ment in patients with diabetic nephropathy [7]. While in the Chronic Renal Impairment in Birmingham II (CRIB-II) study, Edwards et al demonstrated beneficial effects of spironolactone on LVM and arterial stiffness in the early stages of CKD [8]. Whether low-dose spironolactone can prevent cardiovascular events in stage 3 CKD is currently being investigated (STOP-CKD) [9]. Several small clinical trials have shown some benefits of spironolactone therapy on cardiac function in ESRD patients on hemodialysis or continuous ambulatory peritoneal dialysis [10-15]; however, the use of spironolactone is even less studied in PD patients than in hemodialysis-treated subjects [16, 17].

The risk of life-threatening hyperkalemia with spironolactone treatment in CKD and ESRD patients may severely limit the clinical usage of this drug. However, a recent clinical study showed that low-dose spironolactone is well tolerated in selected patients with early-stage CKD, and the risk of serious hyperkalemia or significant renal deterioration appears to be low [18]. Recently, safety data on the use of spironolactone in patients with regular hemodialysis have been confirmed [19-21]. Until now, no systematic review has analyzed the effect of spironolactone on cardiovascular parameters in these patient populations. The objective of this study was to systematically review data on the efficacy and safety of spironolactone in terms of cardiac morphology, function, and mortality in CKD and ESRD patients.

Methods

Search strategies

The Embase, PubMed, and Cochrane Central Register of Controlled Trials databases (up to March 2015) were searched for English-language, human-subjects clinical trials that evaluated cardiovascular outcome with spironolactone use in CKD and ESRD patients. The search terms used were “spironolactone”, “Aldactone”, “aldosterone antagonist”, “chronic kidney disease”, “end-stage renal disease”, “end-stage renal failure”, “kidney failure”, “dialysis”, and “renal replacement therapy”. The search was supplemented by reviewing reference lists, hand searching relevant journals, and corresponding with authors. Case reports, commentaries, review articles, and abstracts were excluded from this review. Case series and single-group cohort studies were also excluded. All subjects were CKD and ESRD patients, and there were no restrictions on sample size or duration of follow-up. The end points identified from the studies included the change in ejection fraction (EF), LVM, and mortality (cardiovascular and all cause), and side effects such as hyperkalemia were also reported.

Data collection

Data extraction was carried out by 2 reviewers independently (LJS and BX). The search strategy was used to obtain titles and abstracts of studies relevant to the review. The reviewers independently assessed the retrieved abstracts and full text and discarded studies that did not meet the inclusion criteria. Disagreements were resolved by consensus or by a third investigator (GRJ).

Data on the first author, year of publication, country, study design, spironolactone dosage, treatment duration, sample size, and study end point were collected. Cardiovascular and all-cause mortality and indexes of cardiac morphology and function (EF and LVM) were extracted. Moreover, data on safety and adverse events, including hyperkalemia, were also included.

Assessment of risk of bias

The risk of bias in the included studies was assessed independently by 2 authors (LJS and BX). Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases were assessed using the risk of bias assessment tool, and discrepancies were resolved by discussion with a third investigator (GRJ).

Statistical analysis

Analyses were performed using Revman 5.3 (The Cochrane Collaboration, UK). For dichotomous outcomes (cardiovascular and all-cause mortality and hyperkalemia), results were expressed as relative risks (RR) with 95% confidence intervals (CI), whereas continuous variables (EF or LVM) were analyzed using the mean difference (MD) and its 95% CI. Data

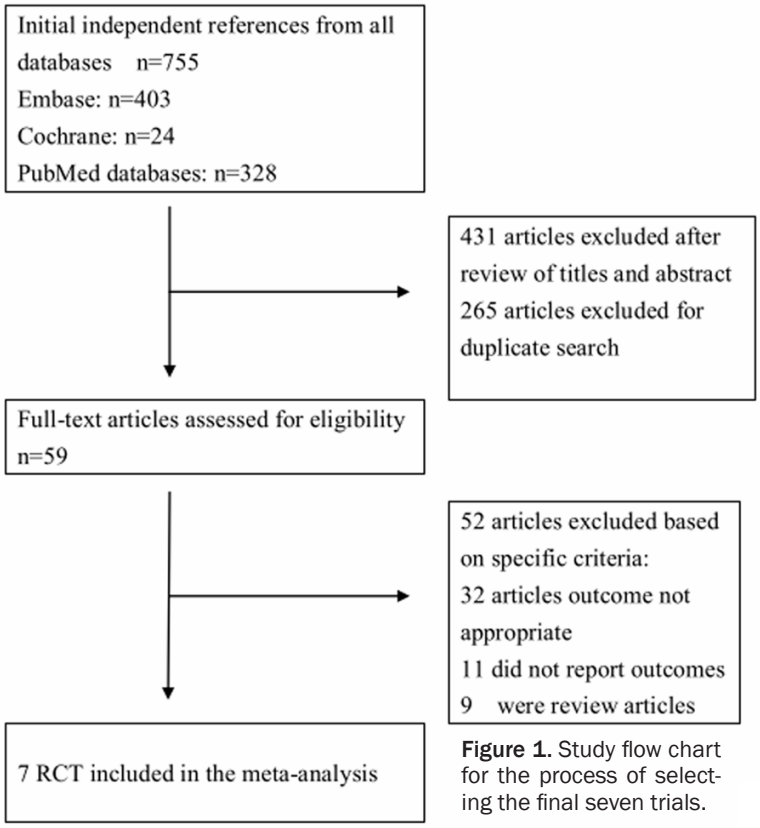

Figure 1. Study flow chart for the process of selecting the final seven trials.

were pooled using a fixed-effects model. Statistical heterogeneity was measured using the I^2 statistic and the chi-square test. Heterogeneity was not considered to be significant when $I^2 < 50\%$, whereas $I^2 > 50\%$ indicates statistically significant heterogeneity among the included studies. A P value < 0.05 for any test or model was considered to be statistically significant.

Sensitivity analyses (excluding 1 study at a time) were performed to assess the contribution of individual trials to pooled effect estimates by sequentially omitting each trial. Funnel plots were used to probe for publication bias. Forest plots were used for graphic representation of data.

Results

Search results

The combined search of Embase, PubMed, and Cochrane Central Register of Controlled Trials databases identified 755 citations, of which we excluded 431 articles after review of the title and abstract and 265 articles due to a duplicate search; 59 articles were retrieved for a detailed evaluation, and 7 studies satisfied the inclusion criteria and were finally analyzed in the meta-analysis published between 2005 and 2014. The sample size in these studies varied (14-309 patients). After entry into the formal study, patients who withdrew from the trials were counted in the total. The process used to select studies for the meta-analysis is shown in **Figure 1**. **Table 1** shows the baseline characteristics of the patients in each trial included in our study.

Risk of bias

The risks of bias in included studies are shown in **Figures 2** and **3**. Random sequence generation was unclear in 6 studies, and allocation concealment was adequate in 2 of 7 trials (28.6%) and unclear in 5 out of 7 trials (71.4%). Participants and investigators were not blinded in 3 studies, and blinding was unclear in the remaining 4 studies. Blinding of outcome assessors was clear in 3 studies and unclear in the remaining 4 studies. Incomplete outcome was clear in 5 studies and unclear in the remaining 2 studies. Selective reporting was clear in 3 studies. Four studies were judged to be at low risk of bias due to funding, and the risk of bias was unclear in the remaining 3 studies. Publication bias was evaluated using a funnel plot, and publication bias was not evident in our study.

Study outcomes

Effects on cardiac morphology and function: There was significant reduction in LVM with spironolactone (3 studies, 156 patients; MD, -7.91 g; 95% CI, -14.94 to -0.89; P = 0.03) compared with placebo therapy [8, 11, 13]. No significant heterogeneity was observed between the trials included in this analysis (chi square = 2.79, P = 0.25, I^2 = 28%). Forest plots displaying the effect of spironolactone on LVM changes are shown in **Figure 4**. Among the 7 trials, only 4

Table 1. The basic characteristics of included studies

Author	Year	Country	Study design	Patients	Number	Treatment with ACEI/ARB	Spironolactone Intervention	Duration	EF	LVM	Cardiovascular mortality	All-cause mortality	Hyperk-alemia
Edwards [8]	2009	UK	RCT	CKD	112	R	25 mg/day	36 weeks	R	R	R	R	R
Taheri [13]	2009	Iran	RCT	HD	16	R	25 mg three times/week	6 months	R	R	R	R	R
Edwards [22]	2010	UK	RCT	CKD	110	R	25 mg/day	36 weeks	R	NR	NR	NR	NR
Taheri [15]	2012	Iran	RCT	PD	18	N	25 mg three times/week	6 months	R	NR	R	R	R
Flevari [11]	2013	Greece	Cross-over RCT	HD	14	R	25 mg thrice weekly	4 months	NR	R	NR	NR	R
Matsumoto [10]	2014	Japan	RCT	HD	309	R	25 mg/day	3 years	NR	NR	R	R	R
Ito [16]	2014	Japan	RCT	PD	158	R	Dose not known	2 years	N	N	R	R	R

Abbreviations: RCT: randomized controlled trial, HD: hemodialysis, PD: peritoneal dialysis, R: reported, NR: not-reported, N: No numeric data.

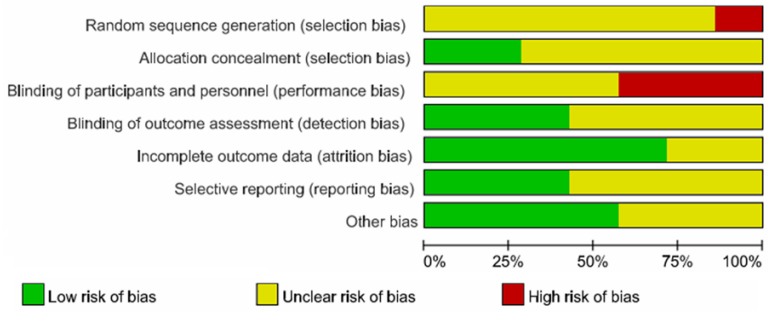

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

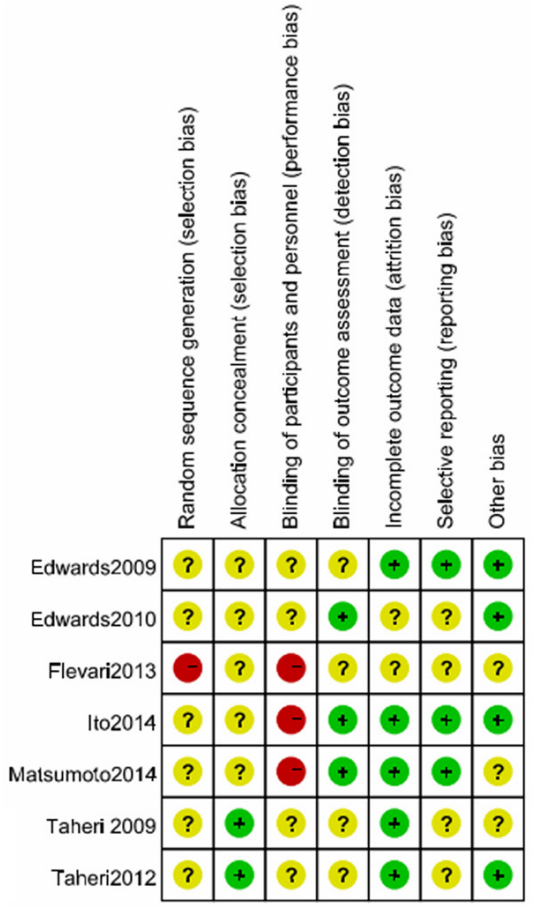

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

recorded EF from baseline to the end of the study [8, 13, 15, 22]. The results showed that spironolactone therapy, compared with placebo treatment, did not significantly improve EF (MD, 0.26%; 95% CI, -1.61 to 2.14, P = 0.78) (**Figure 5**). We found no heterogeneity in this analysis (chi square = 1.99, P = 0.57, I^2 = 0%).

Cardiovascular and all-cause mortality: Among the 7 trials included, only 5 recorded cardiovascular mortality. 5 cases died of cardiovascular causes with spironolactone therapy, while 15 cases reported with placebo. Compared with placebo treatment, spironolactone therapy tended to reduce cardiovascular mortality (RR, 0.37; 95% CI, 0.15 to 0.93, P = 0.03), with no evidence of heterogeneity (chi square = 0.88, P = 0.83, I^2 = 0%) [8, 10, 13, 15, 16] (**Figure 6**). All-cause mortality was recorded as 15 in 308 patients with spironolactone therapy and 40 in 305 patients with placebo treatment. A significant improvement in all-cause mortality was also found with spironolactone therapy when compared with placebo (RR, 0.38; 95% CI, 0.22 to 0.65, P = 0.0005), and no heterogeneity was found in this analysis (chi square = 3.94, P = 0.27, I^2 = 24%) (**Figure 7**).

Hyperkalemia: As shown in **Figure 8**, the incidence of hyperkalemia with spironolactone treatment was similar to placebo, and there was no superior significant in hyperkalemia with spironolactone compared with placebo alone (6 studies [641 patients]) (RR, 2.0; 95% CI, 0.76 to 5.23; P = 0.16). No significant heterogeneity was observed among the trials included in this analysis (chi square = 2.90, P = 0.71, I^2 = 0%).

Discussion

Our findings show that spironolactone therapy, compared with placebo, significantly improved LVM in CKD and ESRD patients. We also found a significant reduction in the risk of cardiovascular and all-cause mortality in these patients population. However, spironolactone does not seem to improve EF, which is an important index of cardiac function. There was no significant difference in the incidence of hyperkalemia between spironolactone- and placebo-treated patients, and the results of this analysis showed no statistical heterogeneity.

CKD is a major cause of increased mortality and morbidity through the increased incidence

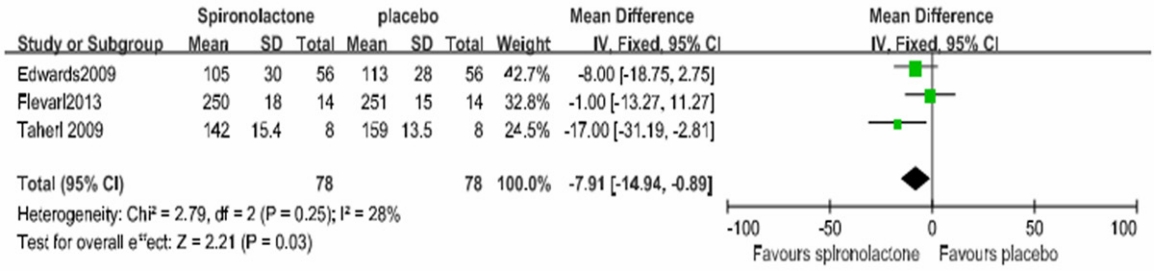

Figure 4. Forest plot of therapeutic effect on LVM in CKD and ESRD patients, pooled mean difference and 95% confidence interval for spironolactone versus placebo. LVM: left ventricular mass.

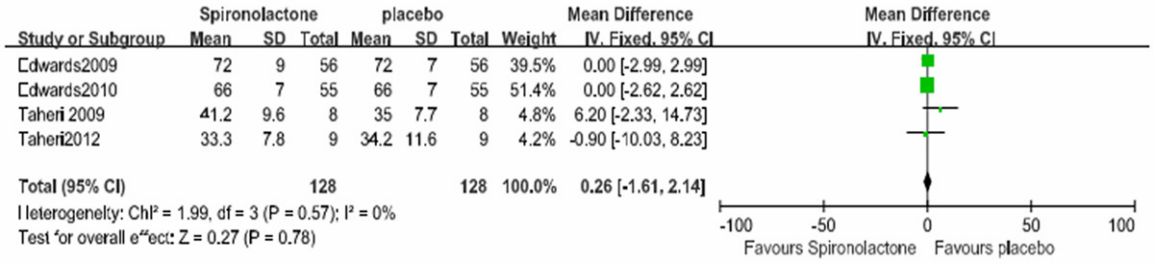

Figure 5. Forest plot of therapeutic effect on EF in CKD and ESRD patients, pooled mean difference and 95% confidence interval for spironolactone versus placebo. EF: ejection fraction.

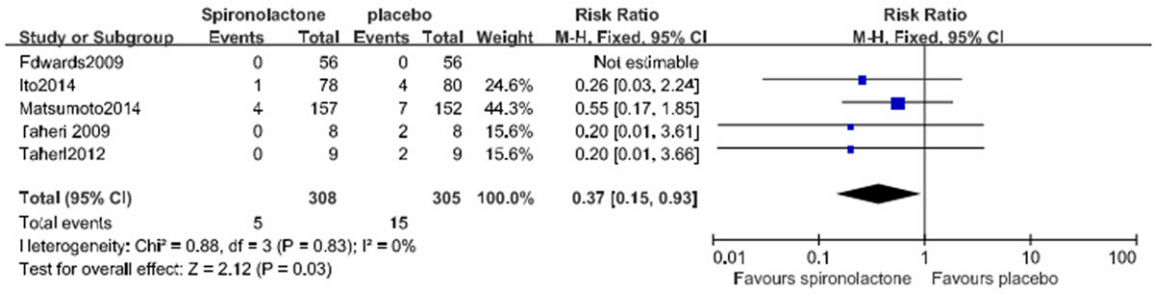

Figure 6. Forest plot of therapeutic effect on cardiovascular mortality in CKD and ESRD patients, pooled risk ratio and 95% confidence interval for spironolactone versus placebo.

of vascular events and progression to ESRD [23]. There are accumulating data suggesting that spironolactone offers cardioprotection in non-CKD patients [24, 25], but the use of spironolactone to reduce the risk of cardiovascular outcomes in CKD and ESRD patients remains controversial. Several studies have reported the different effects of spironolactone therapy on cardiovascular outcomes in CKD and dialysis patients [7, 10, 13, 15, 26]. Meta-analysis of all available study data confirms that the effects of spironolactone treatment on major cardiovascular events in CKD patients are still unknown [27].

LVM is considered to be an independent predictor of cardiovascular events and an important cardiac morphology index of left ventricular [28]. Increased LVM or LVMI is a known modifiable cardiovascular risk factor, especially in patients with ESRD, and a reduction in LVM has been shown to have a favorable effect on cardiovascular outcomes. Our pooled analysis of these studies demonstrated a significant improvement in LVM with spironolactone therapy when compared to placebo. We did not analyze LVMI, because some trials did not provide specific LVMI values or did not provide information on body surface area. Therefore, our analysis

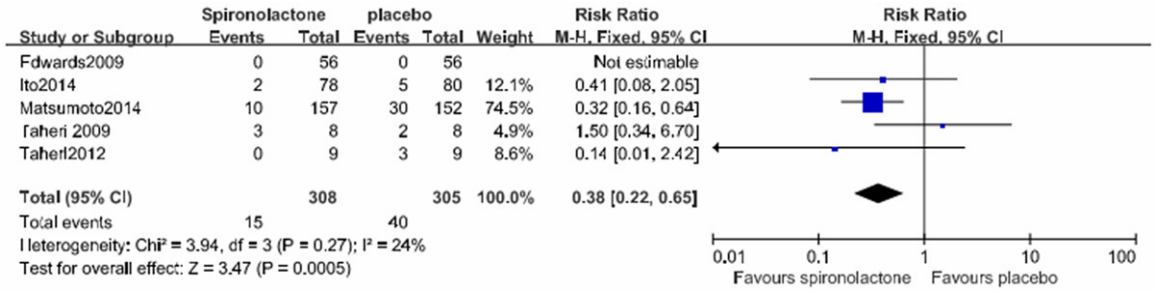

Figure 7. Forest plot of therapeutic effect on all-cause mortality in CKD and ESRD patients, pooled risk ratio and 95% confidence interval for spironolactone versus placebo.

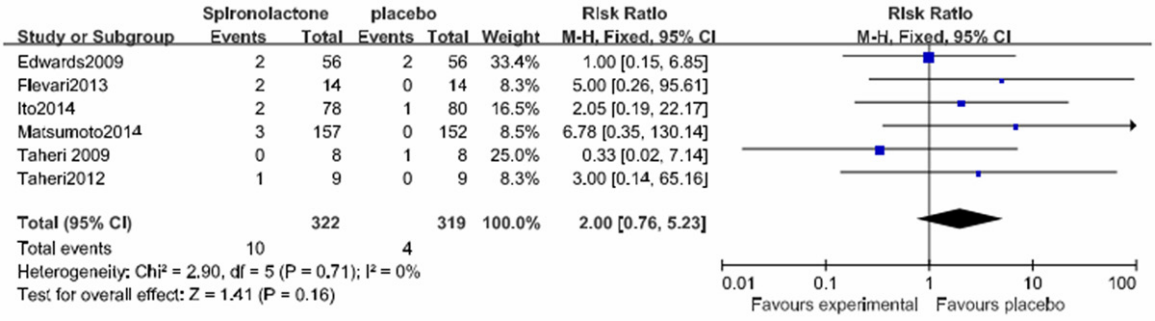

Figure 8. Forest plot of therapeutic effect on adverse events of hyperkalemia and CKD or ESRD patients, pooled risk ratio and 95% confidence interval for spironolactone versus placebo.

was restricted due to insufficient data on parameters of cardiac morphology and function in the 7 trials included in this study. The number of the trials included was too small, and more randomized controlled trials (RCTs) are necessary to investigate the validity of our conclusions. EF is an important index used to evaluate cardiac function. However, among the 7 trials analyzed, only 4 recorded EF data, including 2 heavily weighted studies showing that spironolactone had no effect on EF in early-stage CKD patients and 2 small trials reporting that spironolactone therapy improved EF in dialysis patients. Our pooled analysis of these studies demonstrated no significant improvement in EF with spironolactone therapy compared to placebo, and the overall findings are somewhat inconsistent with previous studies. Bias may have been introduced by combining the results of 2 heavily weighted studies with those of smaller studies. I^2 statistical analysis showed that these studies were homogeneous. In 2014, Ito et al reported that spironolactone prevented cardiac hypertrophy and decreased EF in patients undergoing peritoneal dialysis, without significant adverse effects [15]; however, we did not include this RCT in our LVMI and EF analysis due to the lack of detailed data and the authors, who reported these data using only figures, did not respond to our attempts to obtain more information.

We further observed that treatment with spironolactone can significantly reduce cardiovascular mortality in CKD and ESRD patients. In our analysis, the incidence of cardiovascular mortality was not reported in some of the reviewed trials. Some trials reported mortality due to cardiac causes not described in detail, which may have influenced the results. No significant heterogeneity was found between the trials included in our study. Among the 7 trials included, 5 recorded all-cause mortality, and we found a significant improvement in all-cause mortality with spironolactone therapy. The sensitivity analyses suggested this beneficial effect on all-cause mortality disappeared when the study by Matsumoto et al was omitted (RR, 1.61%; P = 0.02), which was a heavily weighted study [10]. When discussing the mortality findings, we should make it clear that this was only seen in the ESRD population and has not been

extensively studied in the CKD population. It seems plausible that spironolactone has a beneficial effect on cardiovascular and all-cause mortality in these patient populations.

As the evidence for spironolactone use in kidney disease grows, the question of safety arises, particularly given the pre-existing risk of hyperkalemia in advanced CKD and ESRD. Shavit recently analyzed the effects of spironolactone in patients with CKD and ESRD in a narrative review [29]. Their review, which included both observational trials and RCTs, confirmed that the risk of hyperkalemia in both CKD and ESRD patients was significantly lower than previously thought and that, with the appropriate laboratory surveillance, instituting spironolactone therapy in these patients may be a reasonable treatment option. We conducted an analysis of the development of hyperkalemia, and although each trial defined hyperkalemia differently, we found no significant difference between spironolactone and placebo, which is consistent with previous studies. Overall, spironolactone therapy was well tolerated in CKD and ESRD patients.

Our study has several limitations. First, the short study durations with designs to assess surrogate end points may affect the result, also, the limitations include the relatively small sample size and sparse or absent long-term follow up data on the effects of spironolactone therapy on end points. We could not explore differences among other indexes of cardiac morphology and function, as relevant data were not available. More detailed information is needed to clarify the cardiovascular response to spironolactone. Second, although our statistical analyses suggested a low probability of publication bias, publication bias is always a concern. Selection bias cannot be completely ruled out, as we only retrieved articles from English-language journals and published trials. Third, although most studies were RCTs, there was a crossover-design study, and some trials did not report their study methods in enough detail to determine the methods used and the trial quality. Last, although no heterogeneity was found in our study, an individual heavily weighted study may confuse meta-analysis outcomes.

In conclusion, the use of spironolactone in CKD and ESRD patients seems to have a beneficial effect on LVM and reduce the risk of cardiovascular and all-cause mortality, but it does not seem to improve EF. Spironolactone therapy did not result in a higher incidence of hyperkalemia, suggesting spironolactone was well tolerated in these patients.

The potential effects of spironolactone remain unclear and await clarification. The results of our study indicate that further large-scale, multicenter, randomized, double-blind, placebo-controlled trials are needed to confirm the effects of spironolactone as a therapeutic agent on cardiovascular outcomes in patients with CKD and ESRD. Fortunately, several large clinical studies, such as Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease trial (BARACK D) [30] and Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease Study (MiREnDa) [31], will provide new insights into the effects of spironolactone therapy on cardiovascular outcomes and mortality in CKD and ESRD patients.

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Disclosure of conflict of interest

None.

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