

Research Progress on the Efficacy and Safety of Spironolactone in Reversing Left Ventricular Hypertrophy in Hemodialysis Patients

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Abstract: The mineralocorticoid receptor antagonist spironolactone has been shown to improve cardiac function and reverse left ventricular hypertrophy in heart failure patients, but there are no consistent findings on the efficacy and safety in hemodialysis patients. Abnormal aldosterone secretion plays a critical role in the formation of left ventricular hypertrophy. Because of the existence of “aldosterone escape”, the routine use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers does not completely inhibit aldosterone secretion. Low-dose spironolactone (25 mg/d) has been found in small-sample clinical studies to have a significant positive impact with respect to decreasing left ventricular mass index, increasing left ventricular ejection fraction, reversing left ventricular hypertrophy, and improving cardiovascular function while still being safe. More prospective multicenter clinical trials with large sample sizes are needed, however, to provide convincing evidence.

Keywords: spironolactone, hemodialysis, left ventricular hypertrophy, LVH, mineralocorticoid receptor antagonists, MRA, hyperkalemia

Introduction

Hemodialysis is a widely used clinical renal replacement therapy for patients with end-stage renal disease (ESRD). Cardiovascular disease morbidity and mortality are particularly high in hemodialysis patients, with a 5-year survival rate of 45% on average.¹ Sudden cardiac death (SCD) accounts for 25% of all-cause mortality in ESRD patients.² Left ventricular hypertrophy (LVH) is a common complication in patients with chronic kidney disease (CKD), and its prevalence rises to 75% at the onset of ESRD.³ A unique feature of cardiac morphology in ESRD patients is a marked increase in left ventricular mass (LVM). ESRD patients usually have increased blood pressure due to volume expansion, renin-angiotensin-aldosterone system (RAAS) activation, and heightened sympathetic activity. Furthermore, these patients can suffer from arterial calcification caused by abnormalities in bone mineral metabolism and collagen crosslinking, which results in a loss of large vessel compliance. Long-term hypertension and decreased arterial compliance cause increased afterload and LVM, resulting in a concentric pattern of LVH.^{4,5} LVM is directly correlated with the risk of SCD and all-cause mortality, and increased LVM is strongly associated with an increased risk of cardiovascular events (CV).⁶ In contrast, decreased LVM was closely associated with improved outcomes in ESRD patients.⁷ As a result, LVM has been shown to be an independent predictor of all-cause and cardiovascular mortality in the hemodialysis population.⁸

Serum aldosterone levels are increased in hemodialysis patients and are independently related to LVH.^{9,10} A recent study by Matsumoto et al confirmed that LVH could act as a surrogate endpoint for predicting better survival with spironolactone in dialysis patients, a result confirmed in a subsequent study.¹¹ They also noted that in addition to promoting the reversal of LVH, spironolactone can reduce the risk of cardiovascular morbidity and mortality in

hemodialysis patients. However, life-threatening hyperkalemia is the main risk of administering aldosterone antagonists in hemodialysis patients, which restricts their usage by clinicians. Systematic reviews and meta-analyses of multiple studies evaluating the safety and cardiovascular effects of spironolactone in the routine treatment of patients on hemodialysis showed that the additional use of low-dose spironolactone in combination with routine treatment in hemodialysis patients is safe and does not significantly increase serum potassium levels but improves LVH by reducing left ventricular mass index (LVMI) and increasing left ventricular ejection fraction (LVEF), which has a protective effect on the cardiovascular system.^{12–14} Jiang et al noted that the use of low-dose spironolactone (25 mg/d) in hemodialysis patients is safe and that it does not significantly alter the serum potassium level in their evaluation of the impact of mineralocorticoid receptor antagonists (MRAs) on the cardiovascular system of hemodialysis patients.¹⁵

The impact of spironolactone on cardiac function in hemodialysis patients remains controversial and requires confirmation by a large number of clinical studies. This article reviewed the literature in PubMed and EMBASE using mineralocorticoid antagonists, aldosterone antagonists or spironolactone combined with dialysis, renal disease, or kidney failure. We focused on trials using spironolactone intervention and including LVM, LVMI and LVEF as evaluation indicators of LVH and left ventricular systolic function. Our search yielded nine studies which we used to explore the efficacy and safety of spironolactone in hemodialysis patients.

“Aldosterone Escape” Mechanism, and the Role of Spironolactone in Hemodialysis Patients

In epithelial tissues, aldosterone maintains electrolyte homeostasis and intravascular volume balance. On the other hand, in nonepithelial tissues, aldosterone has direct effects on the vasculature and is linked to endothelial dysfunction, cardiac hypertrophy, myocardial fibrosis, left ventricular remodeling, and renal vascular damage. In patients with congestive heart failure (CHF), plasma aldosterone concentrations may reach 20 times normal levels, causing interstitial fibrosis and promoting left ventricular remodeling.¹⁶ In hemodialysis patients, the RAAS is activated at any time when hemodynamic instability and a reduction in the effective circulating blood volume threaten the extracellular volume, thereby increasing the production of aldosterone.

In the classical RAAS pathway, renin secreted by periglomerular cells cleaves angiotensinogen synthesized in the liver to form angiotensin I (Ang I). Ang I is converted into active angiotensin II (Ang II) under the action of angiotensin-converting enzyme (ACE) in the pulmonary circulatory system, which can constrict blood vessels and promote the secretion of aldosterone. However, even if renin cannot be generated in a tissue or organ, angiotensin can still be synthesized under the regulation of other cascade components that locally synthesize RAAS, thereby promoting aldosterone secretion.¹⁷ According to some studies, myocardial necrosis and myocardial cells are stretched, and renin expression in the heart is greatly increased, which is another pathway of local RAAS activation under pathological conditions.^{18,19} Currently, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) are the most commonly used medications to antagonize the RAAS and improve renal function in patients with CKD.²⁰ In patients with ESRD, ACEIs/ARBs can effectively lower blood pressure, improve cardiac remodeling, and play an important role in protecting cardiac and cerebrovascular functions in hemodialysis patients. These medications can also significantly reduce the mortality of hemodialysis patients.²¹ Despite the many advantages of ACEIs/ARBs, due to the phenomenon of “aldosterone escape”, even routine and sufficient use of ACEIs/ARBs cannot completely inhibit the production of aldosterone for an extended period of time, and it is difficult to maintain low blood aldosterone levels. Although aldosterone levels decrease for a short time, they gradually return to the previous or even higher concentrations.¹⁶ Bomback et al reported that 40–53% of patients are expected to experience a rebound in plasma aldosterone levels after receiving ACEI or ARB due to the phenomenon of aldosterone breakthrough.²² Abnormally high plasma aldosterone levels induce hyperfibrosis in cardiomyocytes and exacerbate ventricular remodeling.²³

For hemodialysis patients, the cardiovascular protective effects of spironolactone are many, and include its diuretic and nondiuretic antihypertensive effects (such as reducing sympathetic tone, regulating endothelial cell function, and improving vascular compliance),²⁴ antiatherosclerosis effect, reversal of LVH, and improvement of cardiac systolic function and heart rate variability.²⁵

Related Clinical Researches of Spironolactone in Hemodialysis Patients

A growing number of researchers are examining whether spironolactone can reduce mortality and improve cardiovascular function in hemodialysis patients while ensuring safety. Despite the lack of large, randomized end-point trials, useful insights can be gained from a systematic review of the short-term, small clinical studies conducted to date. The basic characteristics and results of the clinical trials included in our study are shown in Table 1.

Table 1 Characteristics and Cardiovascular Outcomes of 9 Clinical Trials in Hemodialysis Patients

Study/Year	Study Design	No. Patients	Spironolactone Usage/Duration	Outcome	Conclusion
Taheri. 2009 ²³	Random, placebo control, double blind	HD (N=8, NYHA class III–IV and LVEF<45%)	25 mg triweekly 6 months	Mean LVEF was significantly higher in the spironolactone group than in the placebo group (6.2±1.64 vs. 0.83±4.9, P=0.046); Mean LVM decreased in the spironolactone group and increased significantly in the placebo group (–8.4±4.72 vs 3±7.97, P = 0.021)	The use of spironolactone in hemodialysis patients with moderate-to-severe heart failure significantly improves cardiac function and reduces cardiovascular mortality without development of significant hyperkalemia.
McGill. 2009 ³²	Non-random, unblind	HD(N=13)	25 mg/d 9 months	No significant changes in LVMI and LVEF. LVMI(97±36 vs.101±39, P=0.22) LVEF (59±10 vs.60±10, P=0.75)	No significant changes in cardiac morphology as measured by cardiac MRI after 9 months of spironolactone treatment.
Ling. 2011 ²⁷	Non-random, unblind	HD(N=22)	25 mg triweekly 3 months	1.LVEF was significantly improved in the spironolactone group (30.49±5.01 vs. 39.70±6.87, P<0.01);Significant reduction in LVM(149.11±13.79 vs.139.15±5.03, P<0.01); 2.No significant changes in blood pressure	Spironolactone safely improves LVEF, reduces LVM, and has positive effects on the heart in hemodialysis patients with ESRD and heart failure.
Zaripova. 2012 ²⁹	Non-random, unblind	HD(N=35) (Lisinopril, Valsartan and Spironolactone)	25 mg/d 6 months	In the spironolactone group: LVMI decreased significantly from 134.9 ±12.94g/m ² to 132.2±13.41g/m ² (P<0.001); IVST decreased from 1.48±0.23 to 1.44±0.23 cm (P=0.012); LVPVT decreased from 1.43±0.26 to 1.37±0.26 cm (P=0.008); In the control group: LVMI was significantly increased (P<0.05)	Adding spironolactone to treatment with Lisinopril and Valsartan in HD patients may have a significant positive effect on left ventricular remodeling.
Feniman-De-Stefano. 2015 ²⁶	Random, placebo control, double blind	HD(N=8)	12.5 mg/d (2 weeks) and then increased to 25 mg/d 6 months	LVMI significantly decreased in the spironolactone group (77±14.6 vs 69 ±10.5g/m ^{2.7} , P=0.039); LVMI increased in the placebo group (71±14.2 vs 74±17.4g/m ^{2.7} , P>0.05); No significant change in LVEF between the two groups; Ambulatory blood pressure and 24h pulse pressure decreased in both groups.	Spironolactone was secure and effective in regression of LVH in hemodialysis patients
Lin. 2016 ³¹	Random, placebo control, double blind	HD(N=125)	25 mg/d 2 years	LVMI and LVEF significantly improved in the spironolactone group: LVMI (46.3±14.66 vs. 42.05±13.19, P=0.008) LVEF (61.7±10.33 vs 64.29±11.02, P=0.027)	Low-dose spironolactone (25 mg/d) can effectively reduce the morbidity and mortality of CCV events in non-heart failure dialysis patients with few side effects.
Charytan. 2019 ³⁰	Random, placebo control, double blind	HD (Doses of spironolactone) 12.5 mg(N=27) 25 mg(N=26) 50 mg(N=25)	12.5 mg/d, 25 mg/d, 50 mg/d 36 weeks	Indicators of cardiovascular function did not change. LVEF did not considerably improve, and LVMI exhibited a decreasing trend but not significant.	Although no beneficial indications of improved cardiovascular function were found, spironolactone was well tolerated in hemodialysis patients, with the majority of prespecified side events occurring infrequently.
Hamme. 2019 ⁸	Random, placebo control, double blind	HD(N=50)	50 mg/d 40 weeks	LVMI and LVEF did not change significantly in the spironolactone group compared with the placebo group. LVMI (–2.86±11.87 vs 0.41±10.84, P=0.337); LVEF (–0.95±7.44% vs –0.39±7.63, P=0.235); No significant differences in 24-hour ambulatory blood pressure, 6-minute walk test, and NYHA class between the two groups.	Spironolactone (50 mg/d) did not improve blood pressure, LVM and cardiac function in hemodialysis patients, but it did increase the incidence of moderate hyperkalemia (serum potassium 6.0–6.5 mmol/L) without increasing the incidence of severe hyperkalemia (serum potassium >6.5 mmol/L)

(Continued)

Table I (Continued).

Study/Year	Study Design	No. Patients	Spironolactone Usage/Duration	Outcome	Conclusion
Ziaee. 2019 ²⁸	Random, placebo control, double blind	HD(N=24)	25 mg triweekly 9 months	Significant improvement in LVMI and LVEF in the spironolactone group (P=0.04;P=0.006); No significant difference in blood pressure between the two groups.	Spironolactone can safely and effectively reverse LVH and improve LVEF in hemodialysis patients.

Abbreviations: ESRD, end-stage renal disease; HD, hemodialysis; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; IVST, interventricular septum thickness; LVPVT, left ventricular posterior wall thickness; CCV, cardiocerebrovascular; NYHA, the New York Heart Association; MRI, magnetic resonance imaging.

Feniman-De-Stefano D et al performed a controlled, randomized, double blind study to verify the safety and efficacy of spironolactone in the treatment of LVH in hemodialysis patients without heart failure, 17 patients were included with spironolactone (maximum dose 25 mg/d).²⁶ After 6 months, LVMI in the treatment group decreased from $(77 \pm 14.6) \text{ g/m}^{2.7}$ to $(69 \pm 10.5) \text{ g/m}^{2.7}$; however, the placebo group increased from $(71 \pm 14.2) \text{ g/m}^{2.7}$ to $(74 \pm 14.7) \text{ g/m}^{2.7}$. They concluded that LVH is the major risk factor for cardiovascular events in hemodialysis population. And spironolactone is safe and effective in the treating LVH in hemodialysis patients.

Taheri et al enrolled 16 patients with $\text{LVEF} \leq 45\%$ and moderate-to-severe heart failure in a study evaluating whether low-dose spironolactone could be administered in hemodialysis patients with moderate-to-severe heart failure.²³ Eight patients in the treatment group received spironolactone 25 mg after each dialysis session, and the rest received a placebo. After 6 months of treatment, the mean LVEF increased significantly more in the treatment group than in the placebo group (6.2 ± 1.64 vs 0.83 ± 4.9 , $P=0.046$). The mean LVM decreased in the treatment group, but increased significantly in the placebo group during the study period (-8.4 ± 4.72 vs 3 ± 7.97 , $P=0.021$). This study found that spironolactone improved considerably cardiac function and decreased LVM in continuous hemodialysis patients with moderate to severe heart failure without developing significant hyperkalemia.

Likewise, the effectiveness and safety of spironolactone in hemodialysis patients with ESRD and heart failure were also evaluated by liang et al.²⁷ The study included 44 patients with heart failure (the New York Heart Association (NYHA) class 3 and 4 and $\text{LVEF} \leq 45\%$), the patients received spironolactone (25 mg three times/week) for 3 months. The results reveal that, when compared to the control group, there were significant differences in LVEF and LVM before and after the test, and that improvement in LVEF and LVM increased with treatment duration. Spironolactone was found to safely improve LVEF and lower LVM in hemodialysis patients with ESRD and heart failure. Furthermore, spironolactone may have an independent beneficial effect on LVM reduction. Ziaee et al used the same dose and frequency of spironolactone for hemodialysis patients.²⁸ After 9 months, the LVMI and LVEF of the treatment group were significantly improved compared with the control group ($P=0.04$, $P=0.006$), however there was no difference in blood pressure between the two groups. Spironolactone was also proven to be safe and effective in reversing LVH and improving LVEF.

Because ACEIs or/and ARBs are often used by hemodialysis patients with heart failure, researchers are more concerned about the occurrence of hyperkalemia once spironolactone is added. Zaripova et al conducted a study evaluating the additional effect of spironolactone on LVH in anuric hemodialysis patients already receiving ACEI and ARB.²⁹ The treatment group ($n=36$) in addition to Lisinopril and Valsartan received Spironolactone 25 mg daily, the control group ($n=35$) received Lisinopril and Valsartan. After 6 months, echocardiography in the treatment group showed that LVMI significantly decreased from 134.9 ± 12.94 to $132.2 \pm 13.41 \text{ g/m}^2$ ($P < 0.001$), interventricular septum thickness (IVST) decreased from $1.48 \pm 0.23 \text{ cm}$ to $1.44 \pm 0.23 \text{ cm}$ ($P=0.012$). And throughout the whole course of treatment, there were no cases of severe hyperkalemia in either group. They came to the conclusion that spironolactone may significantly improve left ventricular remodeling in hemodialysis patients receiving treatment with Lisinopril and Valsartan.

Charytan et al conducted a double-blind, placebo-controlled, multiple dosage spironolactone dialysis trial (SPin-D) involving 129 patients with hemodialysis. They were randomized to placebo ($n=51$) or spironolactone 12.5 mg ($n=27$), 25 mg ($n=26$), or 50 mg ($n=25$) daily.³⁰ After 36 weeks of observation, compared to the placebo group, the multi-dose spironolactone group was well tolerated and safe in hemodialysis patients, however there were no significant changes in

LVMI and LVEF, and no convincing improvements in cardiac structure or function. SPin-D differs from previous trials in that it evaluated the efficacy of various doses of spironolactone. According to this study, spironolactone 25 mg/d is safer for hemodialysis patients under proper monitoring than 50 mg/d, and 25 mg/d would be the best option if a single fixed dose is used.

Some small pilot studies have validated the potential advantages of spironolactone, however outcomes from several recently published research have not been as anticipated. The Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease (MiREnDa) trial was a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of spironolactone in hemodialysis patients.⁸ The primary efficacy endpoint of this study was the change of LVMI as measured by cardiac magnetic resonance (CMR) scans. And the safety endpoints were development of hyperkalemia and change in residual renal function. 97 hemodialysis patients were randomized to the spironolactone group (n=50) was given spironolactone 50 mg/d, and the placebo group (n=47). After 40 weeks of treatment, the LVMI of the spironolactone group was not significantly changed compared with the placebo group (-2.86 ± 11.87 vs 0.41 ± 10.84 g/m², $P=0.337$). In this study, treatment with spironolactone 50 mg/d did not change LVMI, cardiac function, or blood pressure in hemodialysis patients.

A 2-year multicentric, randomized, placebo-controlled study by Lin et al was to evaluate the long-term effects and adverse effects of spironolactone on hemodialysis patients.³¹ 253 non-heart failure dialysis patients with ESRD were randomly assigned to the spironolactone group (25 mg/d, n=125) or the placebo group (n=128). During the 2-year follow-up, in the spironolactone group, LVMI decreased by 8.7 g/m^{2.7}, LVEF increased by 5.1%, and the incidence of death due to cardiocerebrovascular (CCV) events or any cause in dialysis patients with ESRD was significantly reduced. Their study demonstrated that low-dose spironolactone is effective in reducing the risk of CCV morbidity and mortality in non-heart failure dialysis patients with few side effects. In the article of MiREnDa trial, authors discuss the differences from the study by Lin et al and the reasons for the different results.⁸ One explanation for these inconsistent results could be the pattern of renal replacement therapy: hemodialysis was used in MiREnDa, however, a mix of 60% hemodialysis and 40% continuous ambulatory peritoneal dialysis in the study by Lin et al. The important cause of LVH are recurrent volume expansions and the presence of an arteriovenous fistula in hemodialysis patients, both of which are absent on continuous ambulatory peritoneal dialysis. Another distinction is the measurement mode of LVM. CMR used in the MiREnDa trial, whereas echocardiography was used in the study of Lin et al. Furthermore, the difference in study duration (9 months vs 2 years) and the shorter observation period may not have been sufficient to observe changes in cardiac structure and function.

McGill et al treated 13 hemodialysis patients with spironolactone 25 mg/d for 9 months, but did not find any changes in LVM by CMR.³² In contrast, Taheri et al reported that spironolactone (25 mg, three times/week) was administered to 16 hemodialysis patients with moderate-to-severe heart failure, after 6 months of treatment, LVM (8.4 ± 4.72 vs 3.0 ± 7.97) and LVEF (6.2 ± 1.64 vs 0.83 ± 4.9) were significantly reduced by echocardiography, and the difference was statistically significant.²³ Due to the small sample sizes and inconsistent measuring techniques, as well as the fact that many criteria are not unified, the results of the aforementioned studies different.

In a meta-analysis to evaluate the safety and cardiovascular effects of low-dose spironolactone on end-stage renal failure patients undergoing hemodialysis and conventional treatment, nine trials with a total sample size of 765 patients were included in the study, among them, there were 138 patients in the spironolactone group.¹² The results showed that the LVMI of the spironolactone group was significantly lower than that of the control group [SMD=-0.58, 95% CI (-0.82, -0.34), $P<0.00001$]; the LVEF of the spironolactone group was significantly higher than that of the control group [MD=4.91, 95% CI (2.58, 7.24), $P<0.00001$], and significantly reduced all-cause mortality [OR=0.4, 95% CI (0.42, 0.66), $P=0.0003$] and CCV mortality [OR=0.4, 95% CI (0.22, 0.72), $P=0.002$]. This study indicated that on the basis of conventional treatment, the addition of low-dose spironolactone can significantly improve LVMI and LVEF in hemodialysis patients, and have a protective effect on their cardiovascular system without significantly increasing serum potassium levels.

Safety of Spironolactone in Hemodialysis Patients

Is it safe for hemodialysis patients to take MRAs? This is an issue that treating physicians are rightfully concerned about and cannot ignore while considering using this class of therapies. For the examination of safety, researchers tend to focus on the incidence of hyperkalemia. Several studies have demonstrated that spironolactone can greatly improve the prognosis of patients with heart failure and myocardial infarction without renal insufficiency.^{4,33} Because of its “sodium excretion and potassium retention” effect, there are still some risks associated with the use of ESRD in hemodialysis. However, some researchers suggest that hyperkalemia may not be a problem in hemodialysis patients because the factors affecting serum potassium in dialysis patients are mostly controlled by dialysis rather than renal tubular function.^{31,34} In a meta-analysis evaluating the benefits and side effects of mineralocorticoid receptor antagonists in renal failure patients undergoing dialysis, 14 eligible randomized controlled trials from 2005 to 2020 were included, with a total of 1309 participants.³⁵ The study showed that mineralocorticoid receptor antagonists may improve clinical outcomes in patients with renal failure without significantly increasing the risk of hyperkalemia. The safety of taking spironolactone in hemodialysis patients benefits from a steady potassium level in the body, and it must be emphasized that these patients undergo strict drug treatment monitoring throughout the process.²⁶ An overview of the effects of spironolactone on serum potassium and adverse reactions in HD patients in 9 clinical trials is shown in Table 2.

Lin et al discovered that after 2 years of follow-up, the serum potassium level in the spironolactone group (25 mg/d) increased, although there was no significant difference compared to the control group ($P>0.05$).³¹ In addition, adverse events caused discontinuation of medication in the spironolactone group (five due to nonphysiologic gynecomastia, one due

Table 2 Effects of Spironolactone on Serum Potassium and Adverse Reactions in HD Patients

Study/Year	Study Design	No. Patients	Spironolactone Usage/Duration	Effects on Serum Potassium and Adverse Reactions
Taheri. 2009 ²³	Random, placebo control, double blind	HD (N=8, NYHA class III–IV and LVEF<45%)	25 mg triweekly 6 months	No significant increase in the incidence of hyperkalemia.
McGill. 2009 ³²	Non-random, unblind	HD(N=13)	25 mg/d 9 months	The mean minimum and maximum serum potassium levels in the spironolactone group were 3.7 ± 0.3 mmol/L and 5.3 ± 0.4 mmol/L, respectively
Ling. 2011 ²⁷	Non-random, unblind	HD(N=22)	25 mg triweekly 3 months	There was no significant hyperkalemia during the study that would have required stopping the experiment.
Zaripova. 2012 ²⁹	Non-random, unblind	HD(N=35) (Lisinopril, Valsartan and Spironolactone)	25 mg/d 6 months	No hyperkalemia occurred in either group during the entire treatment period.
Feniman-De-Stefano. 2015 ²⁶	Random, placebo control, double blind	HD(N=8)	12.5 mg/d (2 weeks) and then increased to 25 mg/d 6 months	No significant difference in serum potassium between the two groups
Lin. 2016 ³¹	Random, placebo control, double blind	HD(N=125)	25 mg/d 2 years	The serum potassium level in the spironolactone group increased, but there was no significant difference compared to the control group ($P>0.05$). Adverse events caused discontinuation of medication in the spironolactone group (five due to nonphysiologic gynecomastia, one due to breast soreness, and two due to nausea)
Charytan. 2019 ³⁰	Random, placebo control, double blind	HD (Doses of spironolactone) 12.5 mg(N=27) 25 mg(N=26) 50 mg(N=25)	12.5mg/d, 25 mg/d, 50 mg/d 36 weeks	The frequency of hyperkalemia increased in the 50 mg group, exhibiting a linear trend; rash, nausea, and constipation were more common with spironolactone, but were not dose-limited, and no individuals discontinued due to adverse effects such as breast enlargement or tenderness.
Hamme. 2019 ⁸	Random, placebo control, double blind	HD(N=50)	50 mg/d 40 weeks	The incidence of moderate hyperkalemia was significantly higher in the spironolactone group than in the placebo group (155 vs 80 events, $P<0.034$); No significant difference in the incidence of severe hyperkalemia between the two groups (14 vs 24 events, $P<0.225$); Four patients in the spironolactone group discontinued medication due to hyperkalemia, breast pain, gynecomastia, and diarrhea, and there was no difference in serious adverse events between the two groups (81 vs 85 events, $P=0.725$)
Ziaee. 2019 ²⁸	Random, placebo control, double blind	HD(N=24)	25 mg triweekly 9 months	No significant difference in serum potassium levels between the two groups

Abbreviations: HD, hemodialysis; LVEF, left ventricular ejection fraction; NYHA, the New York Heart Association.

to breast soreness, and two due to nausea). The authors also pointed out that the use of spironolactone is safer in dialysis patients than in non dialysis patients because potassium is metabolized very little through the kidneys and is excreted through dialysis, which can be a great advantage. In the MiREnDa trial, spironolactone increased the frequency of moderate hyperkalemia (potassium levels of 6.0–6.5 mmol/L) compared with the control group but did not increase severe hyperkalemia (≥ 6.5 mmol/L).⁸ In addition, 4 patients in the spironolactone group discontinued medication due to hyperkalemia, breast pain, gynecomastia, and diarrhea. Charytan et al evaluated the safety and efficacy of multiple spironolactone doses (12.5 mg/d, 25 mg/d, 50 mg/d) in a randomized placebo-controlled, double-blind experiment (Spin-D).³⁰ After 36 weeks of follow-up in 129 hemodialysis patients, the incidence of hyperkalemia was similar between the spironolactone and placebo groups; however, a significant linear trend, with an increase in the incidence of hyperkalemia at the 50 mg/day dose was reported. In terms of other adverse reactions, spironolactone was well tolerated by patients across the different doses of spironolactone examined compared with the placebo group. There were no patients who discontinued use owing to the adverse events of breast enlargement or tenderness, and although the incidence of constipation and rash increased, the increases were minor and generally not dose-limiting.

In several of the studies included in this article, patients were treated with spironolactone after hemodialysis to avoid transient potassium elevations, and some of these studies followed hemodialysis patients on spironolactone 25 mg daily for 6 months to 12 months.^{23,27,28} Although variables such as dietary potassium consumption, dialysate potassium concentration, spironolactone dose, and use of ACEIs/ARBs differed between studies, the incidence of hyperkalemia in patients treated with spironolactone did not increase. This outcome is thought to be connected to the promptness and sufficiency of dialysis as well as the adjustability of the dialysate potassium concentration. Therefore, even if spironolactone is administered in combination with ACEIs and/or ARBs, the risk of serious hyperkalemia is very minimal, provided that serum potassium is closely monitored and that dialysate composition is promptly adjusted.

Spironolactone is safe in the short-term treatment of hemodialysis patients, according to reviews of six prospective trials by Chua et al and ten studies by Baker et al, however more large controlled trials are required before definitive treatment recommendations can be given.^{34,36} A recent meta-analysis of nine trials, including a total of 1128 chronic dialysis patients, examined the effectiveness and safety of low-dose MRAs in dialysis patients who received low-dose MRA (25 mg/day spironolactone or 50 mg spironolactone 3 times/week).³⁷ The authors concluded that low-dose MRAs increase the incidence of mild hyperkalemia (serum potassium level 5.5 mmol/L) but not moderate or severe hyperkalemia (serum potassium level 6.0 mmol/L and 6.5 mmol/L). The fact that low-dose MRAs do not raise the risk of moderate-to-severe hyperkalemia and necessitate close monitoring of serum potassium levels supports the idea that low-dose MRA use may be safe. Similarly, in a review evaluating the benefits and harms of aldosterone receptor antagonists in ESRD patients receiving hemodialysis and peritoneal dialysis, Hasegawa et al found that aldosterone antagonists have little or no effect on the risk of developing hyperkalemia and may lower the risk of cardiovascular and cerebrovascular diseases.³⁸ Furthermore, studies have shown that the SPin-D and MiREnDa trials are reliable in terms of spironolactone dose and safety; as long as the patient is properly monitored and the relevant factors affecting serum potassium (eg, diet, dialysate potassium concentration, and drugs that affect potassium metabolism) are taken into account, spironolactone up to 25 mg/d is quite safe.^{13,39}

In terms of side effects, the second-generation steroid MRA eplerenone has higher mineralocorticoid receptor (MR) selectivity than spironolactone and therefore is less likely to cause anti-androgenic and progestational side effects due to unspecific binding to androgen and progesterone receptors.^{40,41} However, eplerenone lacks the potency of spironolactone because its affinity for MR is 40 times lower than that of spironolactone.⁴² Walsh et al conducted a placebo-controlled, multicenter randomized controlled trial to investigate the safety and tolerability of eplerenone in hemodialysis patients.⁴³ The participants were randomly assigned to receive eplerenone 50 mg daily ($n = 77$) or a placebo ($n = 77$) for 13 weeks. The results showed that 9 patients (11.7%) in the eplerenone group developed hyperkalemia (potassium level > 6.5 mEq/L) compared with 2 patients (2.6%) in the placebo group. They concluded that eplerenone increased the risk of hyperkalemia but did not result in an excess need to permanently discontinue the drug. It is also worth noting that none of the sex hormone-related side effects, including gynecomastia, breast pain, erectile dysfunction, etc., were observed in this trial using eplerenone. Additionally, finerenone is a novel nonsteroidal MRA with high affinity and a higher selectivity for MR than spironolactone or eplerenone (over 500-fold more

selective for MR than for any other steroid receptor), and thereby effectively avoids the adverse effects of traditional steroidal MRAs.^{40,42} Finerenone is distributed almost equally between cardiac and renal tissues, reducing accumulation in the kidney.⁴⁴ Studies have suggested that finerenone has better safety and tolerability than other MRAs in patients with renal impairment.^{45,46} Despite the fact that eplerenone and finerenone appear superior to spironolactone in terms of adverse effects, multicenter, large-sample randomized controlled trials in patients with MHD are necessary to confirm this relative advantage.

Currently, there are two ongoing large, multicenter, major-outcome clinical trials, both of which are using spironolactone up to 25 mg/d: ACHIEVE (Aldosterone blockade for Health Improvement Evaluation in End stage renal disease trial; NCT03020303) and ALCHEMIST (Aldosterone antagonist Chronic Hemodialysis Interventional Survival Trial; NCT01848639). ALCHEMIST aims to recruit 825 high-risk chronic hemodialysis patients, and ACHIEVE aims to recruit 2750 chronic hemodialysis or peritoneal dialysis patients. We look forward to more convincing results from these two large multicenter clinical studies.

Conclusion

According to the current small pilot trials, adding low-dose spironolactone (25 mg/d) to the treatment protocol of hemodialysis patients is safe and effective at reversing LVH and improving cardiovascular function. In addition, we acknowledge that this conclusion is subject to publication bias, presumably as a result of the multiple positive small center series. Whether 25 mg/d is the ideal dose in terms of safety and efficacy remains a crucial question; results from additional prospective, large-scale, multicenter clinical trials are required to establish the optimal dose and confirm clinical efficacy. We anticipate more persuasive data from the two large multicenter clinical trials that are presently underway.

Abbreviations

CKD, Chronic kidney disease; ESRD, End-stage renal disease; SCD, Sudden cardiac death; LVH, Left ventricular hypertrophy; LVM, Left ventricular mass; LVMI, Left ventricular mass index; LVEF, left ventricular ejection fraction; RAAS, Renin-angiotensin-aldosterone system; MRAs, Mineralocorticoid Receptor Antagonists; ACEIs/ARBs, Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers; CV, Cardiovascular; CCV, Cardiocerebrovascular; CHF, Congestive heart failure; NYHA, the New York Heart Association; IVST, Interventricular septum thickness; CMR, Cardiac magnetic resonance; MR, the mineralocorticoid receptor.

Acknowledgments

We would like to appreciate all members participated in this work and the Department of Family Medicine of the University of Hong Kong-Shenzhen Hospital for their support.

Funding

This review was funded by Shenzhen Key Medical Discipline Construction Fund (NO.SP2018-C0071).

Disclosure

The authors declare no potential conflicts of interest in this work.

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