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Cardiorenal Benefits of Finerenone in Different Races and Kidney Function in Patients with Chronic Kidney Disease

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Keywords
Mineralocorticoid receptor antagonist · Finerenone · Chronic kidney disease · Diabetic kidney disease

Abstract

Background: The mineralocorticoid receptor plays an important pathophysiological role in cardiorenal diseases by causing inflammation and fibrosis. Mineralocorticoid receptor antagonists (MRAs) are well known in treating cardiovascular disease and diverse nephropathies. However, the first-generation MRA (spironolactone) and the second-generation MRA (eplerenone) remain underutilized because of the risk of inducing severe adverse events. As a selective nonsteroidal MRA, finerenone is safer and more effective and improves cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM). However, the effect of finerenone on cardiorenal outcomes in patients of different races and kidney function (estimated glomerular filtration rate) is unclear. ***Summary:*** In this review, we summarized the impact of finerenone on patients with CKD and T2DM from randomized controlled trials. The synthesis of published data aims to address the questions pertaining to the cardiorenal benefits of finerenone among various racial groups and different levels of kidney function. ***Key Message:*** Finerenone presents racial differences and effects associated with kidney function in CKD and T2DM patients. Due to the limited data for subgroups, it is prudent to approach the conclusion with caution.

Introduction

Chronic kidney disease (CKD) is a major global health issue with economic and medical burden, and World Health Organization data shows that it has become an important impact on the health of older adults [1]. Diabetic kidney disease (DKD), the most common microvascular complication of diabetes, has become the leading cause of CKD [2]. Multiple reasons are involved in the development of CKD, such as parenchymal cell loss, chronic inflammation, and fibrosis [3]. Although

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angiotensin-converting enzyme inhibiter and angiotensin II receptor blocker have great performance, the progression of CKD keeps ongoing [4]. Accumulated evidence suggests that aldosterone, the downstream target of the renin angiotensin system, plays an important role in renal and cardiovascular (CV) disease via mineralocorticoid receptor overactivation [5, 6]. Then, pro-inflammatory and profibrotic factors cause direct kidney and CV dysfunction [7, 8]. Mineralocorticoid receptor antagonists (MRA) spironolactone (the first-generation MRA) and eplerenone (the second-generation MRA) have been widely used for many years. However, due to their multiple adverse effects such as hyperkalemia and sex hormone-related changes [9, 10], their administrations in patients with CKD is limited.

However, the nonsteroidal MRA has received much attention due to its cardiorenal benefits [10–12]. As a novel selective nonsteroidal MRA, finerenone (BAY 94-8862) has shown greater inhibition of inflammation and fibrosis as well as offers cardiac and renal end-organ protection [13, 14]. It was approved by the US Food Drug Administration (FDA) in July 2021 and the European Medicine Agency (EMA) in February 2022. Previous studies have shown that finerenone could inhibit aldosterone-regulated genes more effectively than spironolactone and has a better effect on myocardial hypertrophy and improves cardiac perfusion in animal models [14–17]. Several randomized controlled trials (RCTs) indicated the efficacy and safety of finerenone treatment on CKD and DKD patients [14, 15, 18]. However, its cardiorenal outcomes in patients of different races and kidney function are unclear. In this review, we summarized the impact of finerenone treatment on patients with CKD and type 2 diabetes mellitus (T2DM) from RCTs. The published data have been synthesized to answer the research questions addressed in this review. For this purpose, PubMed, Cochrane Library, and Embase were searched for the original documents from inception to August 1, 2023, without language restriction. References from relevant articles containing "finerenone" or "BAY 94-8862" were included. Subgroup analysis was performed based on the findings of the data synthesis. Review Manager (RevMan) software was used for data analyses (RevMan Version5.3 Cochrane, London, UK), and the forestploter package (Version 1.1.1) of R (Version 4.3.1) was used for data visualization.

CV and Renal Benefits of Finerenone

Three phase 2 randomized double-blind and placebo-controlled clinical trials of finerenone (NCT01346565, NCT1874431, NCT01968668), two phase 3 randomized double-blind and placebo-controlled clinical trials of finerenone (NCT02540993, NCT02545049), and a pooled analysis of these two clinical trials analyzed the cardiorenal outcomes with finerenone compared to placebo (Table 1). The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS, NCT01346565) [19] consisted of two parts. In part A, finerenone was compared with the placebo to evaluate the safety tolerability and renal effects of oral finerenone in 65 patients with heart failure with reduced ejection fraction (HErEF) and mild CKD. In part B, finerenone was compared to both placebo and open-label spironolactone in 392 patients with HErEF and moderate CKD. The results of ARTS have shown that finerenone significantly increase the serum potassium compared to placebo with a dose of 10 mg per day but reduced the risk of hyperkalemia compared to spironolactone (5.3 vs. 12.7%; $p = 0.048$). But, reduced B-type natriuretic peptide (BNP) and albuminuria levels were similar to spironolactone.

In the ARTS-Diabetic Nephropathy study (ARTS-DN, NCT1874431) [20], 823 patients with T2DM and albuminuria (UACR >30 mg/g) were under treatment with a renin-angiotensin blocker. The results showed that the UACR was reduced with finerenone (7.5-, 10-, 15-, and 20-mg/day groups) compared with placebo (7.5 mg/day, HR: 0.79, 90% CI: 0.68–0.91; $p = 0.004$; 10 mg/day, HR: 0.76, 90% CI: 0.65–0.88; $p = 0.001$; 15 mg/day, HR: 0.67, 90% CI: 0.58–0.77; $p < 0.001$; 20 mg/day, HR: 0.62, 90% CI: 0.54–0.72; $p < 0.001$).

ARTS-DN Japan (NCT01968668) [21] was a phase 2 RCT that compared the safety and efficiency of finerenone and placebo in 96 Japanese patients with T2DM and DKD. The results showed that the UACR was significantly reduced at 90 days compared with placebo and without serious adverse events or deaths.

Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD, NCT02540993) [22] was a phase 3 clinical trial which evaluated the long-term effects on cardiorenal outcomes in 5,743 patients with T2DM and CKD. The primary outcomes were a composite of kidney failure (end-stage kidney disease or estimated glomerular filtration rate [eGFR] ≤15 mL/min/17.3 m^2), a sustained decrease of at least 40% in the eGFR from baseline, or death from renal disease. The key secondary outcomes were composite of CV death, nonfatal stroke, nonfatal myocardial infarction (MI), or hospitalization for heart failure (HHF). After a median of 2.6 years, the finerenone significantly reduced the primary composite of kidney outcomes by 18% (HR: 0.82; 95% CI: 0.73–0.93; $p = 0.001$) and reduced the key secondary composite of CV outcomes (CV death, MI, and

Table 1. Results from placebo-controlled clinical trials of finerenone

Study	Phase	Comparator arms	Patients number	Primary outcome	Results from the primary outcome
ARTS (NCT01346565) [19]	2	Part A: Finerenone versus placebo Part B: Finerenone versus open-label spironolactone	Part A: 65 Part B: 392	Change in serum potassium	Significantly increased the serum potassium compared to placebo with a dose of 10 mg per day but reduced the risk of hyperkalemia compared to spironolactone
ARTS-DN (NCT1874431) [20]	2	Finerenone versus placebo	823	Change in the ratio of UACR	UACR was reduced in finerenone compared with placebo
ARTS-DN Japan (NCT01968668) [21]	2	Finerenone versus placebo	96	Change in the ratio of UACR	UACR was significantly reduced at 90 days compared with placebo
FIDELIO-DKD (NCT02540993) [22]	3	Finerenone versus placebo	5,743	Composite of kidney failure (end-stage kidney disease or eGFR ≤15 mL/min/17.3 m^2), a sustained decrease of at least 40% in the eGFR from baseline, or death from renal disease	Significantly reduced the primary composite of kidney outcomes by 18%
FIGARO-DKD (NCT0254509) [23]	3	Finerenone versus placebo	7,437	Composite of CV disease (CV death, nonfatal MI, nonfatal stroke, or HHF)	Reduced the relative risk in primary outcomes by 13% compared with the placebo
FIDELITY [24]	Pooled analysis of FIDELIO-DKD and FIGARO-DKD	Finerenone versus placebo	13,026	Composite of CV endpoints (CV death, nonfatal MI, nonfatal stroke, or HHF) and renal endpoints (first onset of kidney failure, sustained ≥57% decreased in eGFR from baseline or renal death)	Significant reduction in composite of CV endpoints by 14% and 22% reduction in HHF; reduced the relative risk in renal endpoints by 23% compared with placebo

HHF) by 14% (HR: 0.86; 95% CI: 0.75–0.99; $p = 0.03$) compared with placebo groups.

Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD; NCT0254509) [23] was another phase 3 RCT that assessed the cardiorenal effects in 7,437 patients with CKD and T2DM. Patients received the maximum dose on manufacturer's label of RASB, and serum potassium was ≤4.8 mmol. In this trial, the primary outcomes were composite of CV disease (CV death, nonfatal MI, nonfatal stroke, or HHF) and the key secondary outcomes were kidney disease (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal disease). According to the results of the median follow-up of 3.4 years, finerenone reduced the relative risk in primary outcomes (CV death, MI, stroke, or HHF) by 13% (HR: 0.87; 95% CI: 0.76–0.98; $p = 0.03$) compared with the placebo group. However, the events of key secondary outcomes were not significant in the finerenone group and in the placebo group (HR: 0.87; 95% CI: 0.76–1.01). From the safety outcomes, the attack rate of hyperkalemia was higher in the finerenone group than in the placebo group, but there were no fatal incidents of hyperkalemia.

FIDELITY [24] was a prespecified pooled analysis to gather more information of finerenone efficacy and safety in patients with CKD and T2DM. It was composed of the FIGARO-DKD and FIDELIO-DKD studies. This analysis included a total of 13,026 patients (mean age, 64.8±9.5 years; mean eGFR, 57.6±21.7 mL/min/17.3 m^2) with T2DM and CKD treated with maximum tolerated dose of angiotensin-converting enzyme inhibiter or angiotensin II

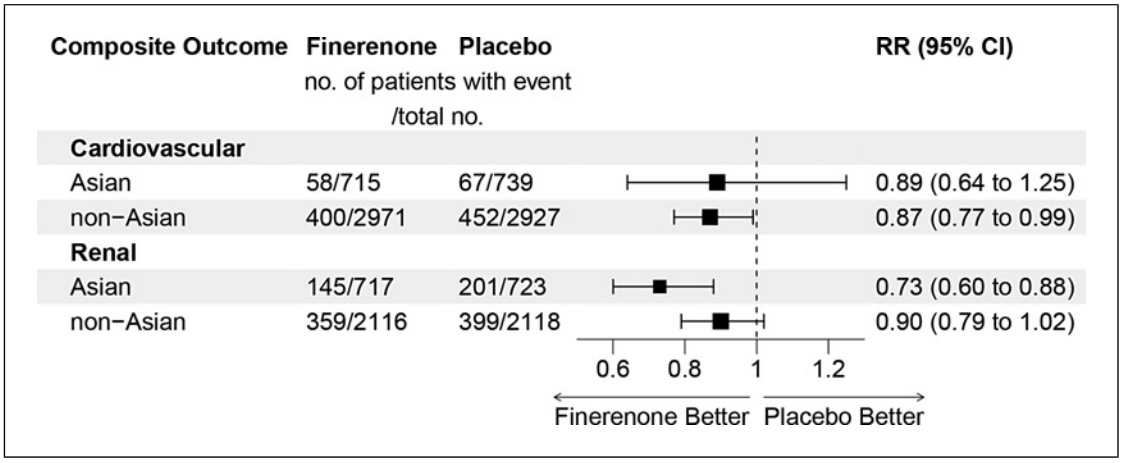

Fig. 1. Forest plot of relative risk of the composite outcome in difference races.

receptor blocker. In this pooled analysis, the interest efficacy outcomes were composite of CV endpoints (CV death, nonfatal MI, nonfatal stroke, or HHF) and renal endpoints (first onset of kidney failure, sustained ≥ 57% decreased in eGFR from baseline, or renal death). After a median follow-up of 3.0 years, the analysis results showed a significant reduction in composite of CV endpoints (CV death, nonfatal MI, nonfatal stroke) in finerenone groups, with a relative risk reduction of 14% (HR: 0.86; 95% CI: 0.78–0.95; p = 0.002) and 22% reduction in HHF (HR: 0.78; 95% CI: 0.66–0.92). Similarly, finerenone reduced the relative risk in renal endpoints (first onset of kidney failure, sustained ≥57% decreased in eGFR from baseline, or renal death) by 23% (HR: 0.77; 95% CI: 0.67–0.88; p = 0.0002) compared with the placebo group.

Cardiorenal Benefits of Finerenone in Different Races

The FIDELIO-DKD study reported the primary composite renal outcome in different races. In Asian patients, finerenone significantly reduced the incidence of composite renal outcomes by 27% (risk ratio [RR]: 0.73; 95% CI: 0.60–0.88), while in non-Asian patients, the RR was 0.90 (95% CI: 0.79–1.02), indicating no difference compared with placebo. As the FIGARO-DKD study showed, the primary composite CV outcome between Asian and non-Asian groups was RR: 0.89, 95% CI: 0.64–1.25, versus RR: 0.87, 95% CI: 0.77–0.99, respectively (Fig 1). And the Latin America subgroup [23] (HR: 0.65; 95% CI: 0.44–0.96) was the region where finerenone benefited the most.

Cardiorenal Benefits of Finerenone in Different Kidney Functions

According to the FIDELIO-DKD and FIGARO-DKD reported data, we used the baseline eGFR to represent different levels of kidney function. Finerenone decreased the occurrence of the primary composite renal outcome by 15% in the eGFR <60 mL/min/1.73 m^2 group (RR: 0.85; 95% CI: 0.76–0.95). In the eGFR ≥60 mL/min/1.73 m^2 group (RR: 0.80; 95% CI: 0.58–1.11), it seemed useless. As for the primary composite CV outcome, finerenone favored neither the eGFR <60 mL/min/1.73 m^2 group (RR: 0.88; 95% CI: 0.74–1.05) nor the eGFR ≥60 mL/min/1.73 m^2 group (RR: 0.88; 95% CI: 0.75–1.03) (Fig. 2). But according to a previous report [25], in patients with a baseline eGFR ≥60 mL/min/1.73 m^2, the event rates for first HHF and CV were lower (HR: 0.74; 95% CI: 0.61–0.90).

Discussion

As a selective nonsteroidal MRA, finerenone has been shown to be more effective and beneficial in cardiac and renal diseases. Numerous phase 2 and phase 3 clinical trials provided substantial evidence for the efficacy and safety of finerenone for patients with CKD. The overall results have shown that the renal and CV events were decreased significantly in the finerenone group than in the placebo group.

According to our results, finerenone is better for Asian in renal benefits, while it is better for non-Asian in CV benefits. Previous studies showed that different races

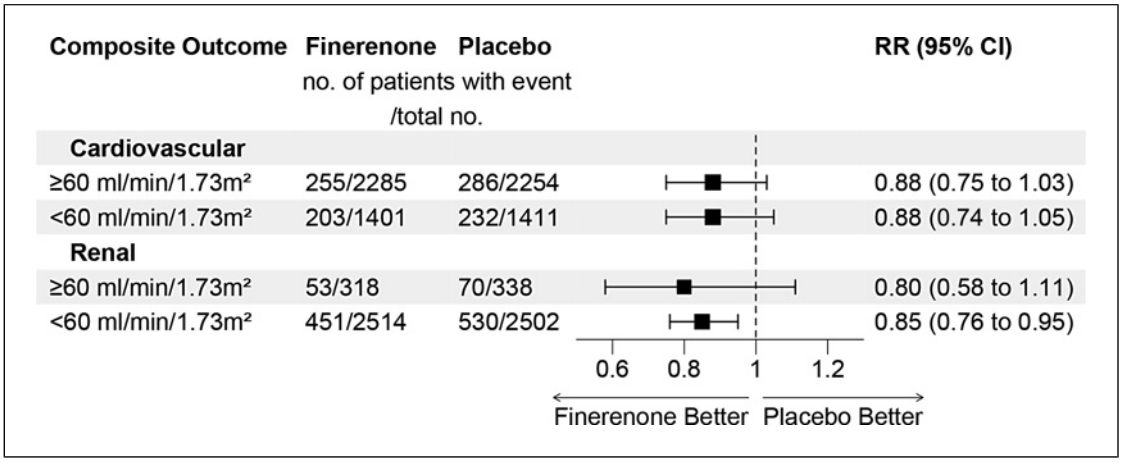

Fig. 2. Forest plot of relative risk of the composite outcome in kidney functions.

could influence the safety and effect of spironolactone and eplerenone [26, 27]; finerenone may exhibit similar effects. Mineralocorticoid receptor (also known as *NR3C2*, nuclear receptor superfamily 3, group C, member 2) polymorphism could lead to racial differences in MRA response. A previous study reported that spironolactone-induced potassium elevation is more pronounced among *NR3C2 215G* allele carriers [28]. Whether *NR3C2* polymorphism also affects the cardiorenal benefits of finerenone and contributes to racial differences in finerenone effects is unknown. However, as genetic samples are not available, this cannot be evaluated.

Previous studies demonstrated that cardiorenal risk could be decreased by reducing the albuminuria level [29]. According to the data from the population pharmacokinetics and pharmacodynamics analysis of finerenone, doses of 10–20 mg once daily appear safe and efficacious at reducing albuminuria [30]. The data from the animal models showed that the kidney protective effects of finerenone were mediated through anti-inflammatory and antifibrotic and regression of tubulointerstitial fibrosis via inhibition of the MR overactivation [14, 31, 32]. Currently, sodium-glucose cotransporter 2 (SGLT2i) has become the new standard therapy. It can be combined with finerenone and may achieve the superposition of cardiorenal benefits effect via mechanism complementarity. The mechanism of action of SGL2i may be related to the hemodynamic effects and the decrease of albuminuria, and the kidney single-cell transcriptome data showed that SGLT2i affected mitochondrial function in proximal tubular cells [33, 34]. Furthermore, SGLT2i has been shown to normalize systolic blood pressure and mitigate the development of tubular fibrosis in mice [35]. On the other hand, finerenone slows the progression of kidney disease by inhibiting the excessive activation of MR. Results from a network meta-analysis suggest that finerenone is comparable to SGLT2i in terms of reducing CV risks. It is recommended to prescribe finerenone and SGLT2i in patients with prominent CV risks, while SGLT2i alone is recommended for patients with heightened renal events [36]. The ongoing CONFIDENCE (NCT05254002) trial [37] is the first RCT that aims to evaluate the additive efficacy, safety, and tolerability of combining finerenone with SGLT2i. This trial will provide answers to some of the questions surrounding the use of dual therapy comprising finerenone and SGLT2i in patients with CKD in the near future.

Hyperkalemia is a major concern for the use of finerenone. According to the results of two phase 3 RCTs (FIDELIO-DKD, FIGARO-DKD) and a pooled analysis (FIDELITY), finerenone led to an increased risk of hyperkalemia in patients with CKD compared with the placebo [22, 23]. It may be related to the MRA increase in sodium excretion and decrease in potassium excretion in the kidney, thus increasing in serum potassium levels [38]. In spite of that, according to previous RCTs and mate-analysis results, the incidence of hyperkalemia was a lower risk in the finerenone than in the class steroidal MRAs [4, 39].

In addition, CV calcifications are common in patients with CKD, and they are considered as independent risk factors for CV disease [40]. CV calcification is a cell-mediated process, involving the deposition of calcium phosphate and driven by vascular smooth muscle cells [41, 42]. It is noteworthy that vascular smooth muscle

cells express mineralocorticoid receptors, which are sensitive to aldosterone and can be blocked by spironolactone [43]. A previous RCT (MiREnDa, NCT01691053) [44] evaluated the CV effectiveness and safety of spironolactone in hemodialysis patients. The results demonstrated that spironolactone reduced markers of vascular calcification and exerted a beneficial effect on vascular calcification in CKD patients. Maybe finerenone has a similar effect; however, no data are available regarding the positive influence on CV calcifications in patients.

The limitation of this review should be concerned. First, this review utilized only publicly available and published data. However, few data were available in the subgroup of patients with CKD and DKD in these RCTs. Second, data for subgroups were from FIDELIO-DKD and FIGARO-DKD. More data are required to affirm the cardiorenal benefits in different races and kidney functions.

Conclusion

Finerenone is a potent and safe MRA for patients with CKD and DKD and has different efficacy in different races and kidney functions. Due to the limited data for subgroups, it is prudent to approach the conclusion with caution. Finerenone demonstrates greater efficacy in reducing the risk of composite renal outcomes among Asian patients while better in reducing the risk of composite CV outcomes among non-Asian patients. In different kidney function subgroups, finerenone decreased the occurrence of the primary composite renal outcome in the eGFR <60 mL/min/1.73 m^2 group. However, it appears to be ineffective in the eGFR ≥60 mL/min/1.73 m^2 group for composite renal outcomes and for primary composite CV outcomes in any different kidney function.

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Conflict of Interest Statement

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Pingjiang Li: conceptualization, methodology, and writing – original draft; Yuying Cui: writing – review and editing; Xiaoming Xu: formal analysis and data curation; Jianjun Dong: supervision; Lin Liao: project administration and funding acquisition.

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