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Nonsteroidal Mineralocorticoid Receptor Antagonist Eliciting Cardiorenal Protection Is a New Option for Patients with Chronic Kidney Disease

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Abstract
Background: Mineralocorticoid receptor antagonists (MRAs) protect cardiorenal function by robust anti-inflammatory and antifibrotic functions beyond classical functions of maintaining fluid and electrolyte homeostasis. The application of traditional steroidal MRAs to chronic kidney disease (CKD) has been limited by adverse events, especially when combined with renin-angiotensin system inhibitors, guideline-recommend drugs for CKD patients. Recently, the development of nonsteroidal MRAs gives patients with CKD a promising option. ***Summary:*** The discovery of nonsteroidal MRAs is based on the molecular structure of the mineralocorticoid receptor (MR) and differs in structure from spironolactone, a progesterone derivative. The structure of nonsteroidal MRAs determines their more effective and selective inhibition of MR providing patients more benefits with fewer adverse effects than MRAs. Recently, two types of nonsteroidal MRAs, finerenone and esaxerenone, have been authorized for clinical use. We elaborate on the physiological and pathophysiological mechanisms of MR, review the history of MRAs, compare two generations of MRAs, and introduce the forward clinical trials of finerenone and esaxerenone. ***Key Messages:*** Finerenone reduces the cardiovascular and kidney composite outcomes in diabetic patients with CKD eliciting a cardiorenal protection effect. Esaxerenone can effectively reduce blood pressure in hypertensive patients and albuminuria in diabetic patients with CKD. The risk of hyperkalemia is controllable and acceptable through the serum potassium-based dose titrate. Combination therapy with sodium-glucose cotransport-2 inhibition or a new potassium binder may be a safer and more efficient approach.

Introduction

Chronic kidney disease (CKD) is defined by persistent urine abnormalities, structural abnormalities, or impaired excretory renal function [1]. It has been shown that the heart and kidney are tightly connected and should be considered as a unit in both physiological and pathological conditions, suggesting that the chronic or acute dysfunction of one organ may lead to the dysfunction of the other [2, 3]. The majority of patients with CKD also suffer from cardiovascular disease and death, classified as type 4 cardiorenal syndrome [1, 2]. As such, there is an

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urgent need to develop drugs and optimize guidance to protect cardiorenal function and so reduce the risk of end-stage events. At present, renin-angiotensin system (RAS) inhibitors and sodium-glucose cotransport-2 (SGLT2) inhibition have proven to have protective effects on both the heart and kidney [4–8]. Similarly, steroidal mineralocorticoid receptor antagonists (MRAs), a type of conventional drug, also have protective effects on the heart and kidneys [9–12]. The administration of steroidal MRAs, however, is strictly regulated due to significant side effects including male breast development, hyperkalemia, and other adverse reactions.

A new generation of MRAs, nonsteroidal MRAs, effectively and selectively block mineralocorticoid receptor (MR) and show a broad prospect in cardiorenal protection while exhibiting much fewer side effects and weaker adverse reactions compared with steroidal MRAs [13]. The phase III clinical trial data published recently showed that nonsteroidal MRAs elicit cardiorenal protection in patients with CKD and type 2 diabetes mellitus (T2DM), resulting in lower risks of CKD progression and cardiovascular events, and offering a potential new option for patients with CKD [14–17].

The purpose of this review is to introduce the advantages of nonsteroidal MRAs over steroidal MRAs and to analyze the efficacy and safety of nonsteroidal MRAs from the existing clinical trial data. Based on the existing clinical research, we put forward a potential hypothesis on the application of nonsteroidal MRAs.

Physiological and Pathophysiological Mechanism of MR

MR, a ligand-induced transcription factor, is nuclear receptor that acts as nuclear transcription factor to regulate the transcription of target genes after binding to ligands in cells (shown in Fig. 1) [18]. When aldosterone binds to MR, it promotes a receptor conformational change that allows dissociation of receptor from chaperone heterocomplexes and critical hyperphosphorylation that is associated with rapid nuclear translocation of aldosterone-MR complex. Once in the nucleus, MRs form a heterodimers by binding with hormone response elements and recruit transcriptional coregulators, allowing the transcription or repression of target genes [19]. MR distributes not only in classical epithelial tissues such as kidney, colon, and salivary glands, mediating electrolyte transportation, but also in nonclassical epithelial tissues such as blood vessels, cardiomyocytes, central nervous system, adipocytes, fibroblasts, and monocytes, suggesting that MR has a role other than regulating electrolyte transport [20–28]. MR directly promotes the expression of the subunits of ion channels and transporters, including the epithelial Na^+ channel (ENaC), high conductance calcium- and voltage-dependent potassium channel (BK), Na^+/H^+ exchanger (NHE), and the Na^+/K^+-ATPase (NKA). In addition, MR is able to regulate ion channels and transporters indirectly by controlling the expression of its regulators, including serum and glucocorticoid-induced kinase (Sgk-1), PIM3 or the kidney-specific isoform of with-no-lysine kinase 1 (KS-WNK1), the ubiquitin-specific protease 2–45 (Usp2-45), and other factors such as glucocorticoid-induced leucine zipper (also known as TSC22D3), the period circadian regulator 1 (PER1), and the scaffold protein connector enhancer of kinase suppressor of ras 3 (CNKSR3) [19]. For example, Sgk-1 cooperates with other factors and triggers a series of reactions eventually activating ENaC and leading to sodium excretion [29, 30]; the activation of Sgk-1 increased glomerular filtration rate and proteinuria and aggravates glomerular hypertrophy and fibrosis in salt-induced hypertensive mice [31, 32].

MR activation increases the expression of NADPH oxidase (Nox), reduces the expression of glucose-6-phosphate dehydrogenase in blood vessels, prevents the reduction of $NADP^+$ to NADPH, and promotes the formation of reactive oxygen species (ROS) [33, 34]. MR also produces ROS in mitochondria through mitochondrial respiratory chain complex I (MRCC I) [35]. Excess ROS stimulate ERK1/2-STAT3 signal pathway and p66Shc phosphorylation, an effector of mitochondrial dysfunction, resulting in epithelial-mesenchymal transition and mitochondria suppression [35–38]. In aldosterone-infused rats, podocytes are injured at an early stage by inducing oxidative stress and Sgk-1, resulting in the occurrence of proteinuria [39]. Through oxidative stress caused by increased ROS, MR, directly or indirectly, triggers pro-inflammatory transcription factors such as AP-1 and NF-κB [40]. In addition to triggering an inflammatory response, MR also activates both innate and acquired immune systems, stimulating leukocyte infiltration, and promoting the differentiation of macrophage into M1 type [40, 41]. This can be seen as when MR is inhibited by drugs or gene knockout, the expression of M2 anti-inflammatory markers increased and M1 pro-inflammatory markers decreased in macrophages [42–44]. MR activation stimulates the expression of profibrotic molecules, such as transforming growth factor-β1 (TGF-β1), plasminogen activator inhibitor 1 (PAI-1), endothelin 1 (ET-1), placental growth factor (PGF), connective tissue growth factor, osteopontin, and galectin-3 [45]. Inflam-

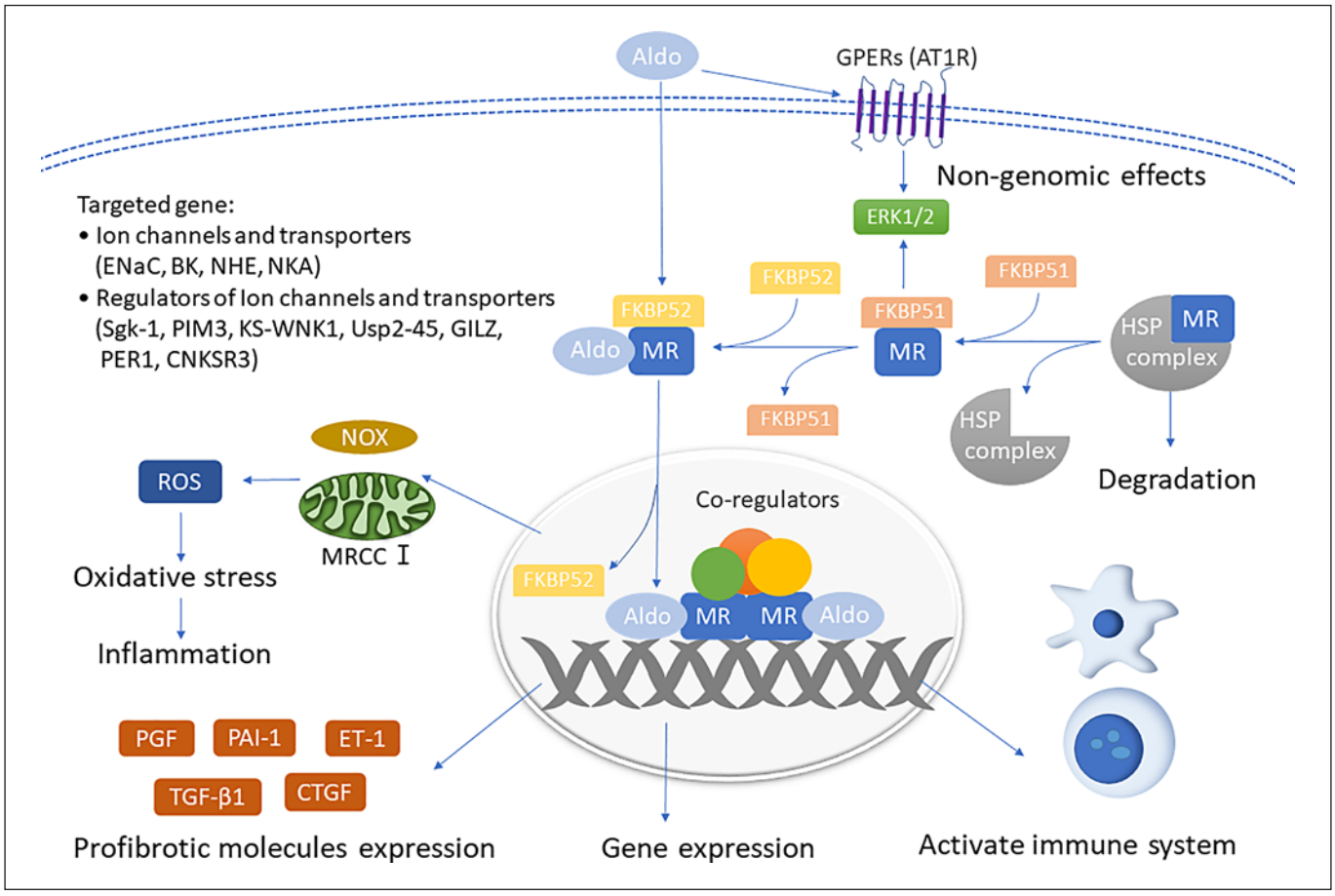

Fig. 1. Key physiological and pathophysiological action of MR. Aldo, aldosterone; GPERs, G-protein-coupled estrogen receptors; FKBP, FK506-binding protein; HSP, heat-shock protein; ENaC, epithelial Na^+ channel; BK, high conductance calcium- and voltage-dependent potassium channel; NHE, Na^+/H^+ exchanger; NKA, Na^+/K^+-ATPase; Sgk-1, serum and glucocorticoid-induced kinase; PIM3, proviral integration site of Moloney murine leukemia virus 3 kinase; KS-WNK1, kidney-specific isoform of with-no-lysine kinase 1; Usp2-45, ubiquitin-specific protease 2–45; GILZ, glucocorticoid-induced leucine zipper; PER1, period circadian regulator 1; CNKSR3, connector enhancer of kinase suppressor of ras 3; Nox, NADPH oxidase; ROS, reactive oxygen species; MRCC I, mitochondrial respiratory chain complex I; TGF-β1, transforming growth factor-β1; PAI-1, plasminogen activator inhibitor 1; ET-1, endothelin 1; PGF, placental growth factor; CTGF, connective tissue growth factor.

mation and fibrosis are important causes of CKD and cardiorenal syndrome [1, 46]. Previous clinical studies have shown that MRAs protect against acute kidney injury induced by ischemia and reperfusion, keep acute kidney injury from progressing to CKD, prevent renal fibrosis, and delay the progression of diabetic nephropathy and CKD [47].

In addition to regulating gene expression, aldosterone exerts rapid nongenomic effects that are not blocked by inhibitors of transcription; for example, aldosterone evokes rapid sodium intake through a nongenomic mechanism involving G-protein-coupled estrogen receptors in the nucleus tractus solitarius (shown in Fig. 1) [48]. In mice lacking MR DNA-binding in macrophages, inflammatory markers were equivalent to wild type mice, indicating that MR regulates a macrophage pro-inflammatory phenotype and inflammation partially via pathways that do not require DNA binding [49]. An interaction between aldosterone and angiotensin II induces early phosphorylation of ERK1/2 [27, 50]. This rapid effect cannot be blocked by spironolactone but can be blocked by epidermal growth factor receptor (eGFR) antagonist or AT1 receptor antagonist, while the late phosphorylation of ERK1/2 induced by aldosterone and angiotensin II can be blocked by spironolactone [27]. Aldosterone is able to activate ERK1/2 in an AT1 receptor-dependent

and MR-independent manner, but it needs AT1 and MR to activate c-Jun N-terminal kinase (JNK) [51]. It was also reported that MR is involved in the nongenomic effects of aldosterone, and the nongenomic effects may promote the genomic effects mediated by classical MR [52].

Development History of MRAs

The discovery of steroidal MRAs began with successfully confirming progesterone as a MRA in 1955 [53]. Before that, scientists had found that deoxycorticosterone acetate, an MR agonist, caused sodium chloride retention and potassium diuresis and was associated with inflammation and fibrosis in multiple organs [54, 55]. After the systematic separation of steroids by chromatography, aldosterone was distinguished with the initial name of electrocortin which reflected its function of promoting potassium excretion and sodium retention [56]. When the aldosterone structure revealed that aldosterone contained a unique aldehyde group at C18 instead of the usual methyl group, the name was soon changed [57]. In 1957, the two steroidal drugs SC-5233 and SC-8108, both modified from progesterone, showed that aldosterone antagonism caused potassium retention and sodium secretion [58, 59]. However, subcutaneous administration limited its clinical application and so spironolactone made up for this limitation through oral administration, promoting its implementation in clinics [60, 61]. From 1957 to 1987, scientists discovered 17 spironolactone derivatives and confirmed their role in inhibiting aldosterone as potassium preserving diuretics [62]. Although a large number of studies on spironolactone have been carried out, research on MR did not begin to be published until 1972 [63, 64].

The discovery of nonsteroidal MRAs began with the successful cloning of the MR in 1987 [65]. Evans' research team discovered the coding DNA sequence of the MR and demonstrated that the MR has a high affinity not only for aldosterone but also for glucocorticoids [65]. The expression of MR provided a molecular basis for the invention of nonsteroidal mineralocorticoid antagonists and was a milestone in the development history of MRAs [13, 66–68]. The development of MRAs can be divided into three stages: determining steroidal spironolactone as the first MRA shortly after aldosterone purification; finding more selective steroidal mineralocorticoid antagonists such as eplerenone; and selecting more specific and effective nonsteroidal mineralocorticoid antagonists with an ultra-high-throughput screening method using a functional cell-based assay. This has been gradually researched and applied in a clinical setting [66, 68].

Pharmacological Comparison between Steroidal and Nonsteroidal MRA

Many metabolites and derivatives of spironolactone have been analyzed for drug safety and efficacy, but only spironolactone, canrenone, and eplerenone have been approved for clinical use [62]. The randomized controlled trials RALES for spironolactone, and EPHESUS and EMPHASIS-heart failure (HF) for eplerenone provided evidence for the clinical application of MRAs in the treatment of HF, based on which a clinical guideline for the dynamic monitoring of blood potassium and renal function during the application of MRAs was devised [9–11]. Although both have accumulated some evidence of cardiorenal protection, problems due to their structure have limited a wide clinical application.

The tissue distribution of these two drugs, analyzed by quantitative whole-body autoradiography showed that the accumulation of spironolactone in the kidneys is sixfold higher than that in cardiac tissue, and the accumulation of eplerenone in the kidneys is three times higher than in cardiac tissue (shown in Table 1) [69]. Due to this drug distribution, hyperkalemia was very common and frequently resulted in therapy interruption in real-world adults initiating MRA therapy, especially among participants with CKD [70]. As spironolactone is a progesterone derivative, sharing with progesterone a high degree of plasma binding but with a reduced affinity for progesterone receptors, spironolactone inhibits progesterone and androgen receptors and causes problems such as male breast development, sexual dysfunction, and female irregular menstruation [71]. Eplerenone has high selectivity, while its relatively low affinity for MR requires a higher dose of administration to obtain the MR-blocking effect similar to spironolactone, with a half-maximal inhibitory concentration (IC50) value of 990 nM and 24 nM, respectively [72].

The new generation of nonsteroidal MRAs, finerenone and esaxerenone, has a balanced distribution in kidney and cardiac tissue (shown in Table 1), which may reduce the likelihood of hyperkalemia and contribute to a potent cardiorenal protective effect [69, 73]. Finerenone and esaxerenone inhibit aldosterone-induced transcriptional activation of human MR with an IC50 value of 18 nM and 3.7 nM, respectively [13, 74]. The mean terminal half-life ($t_{1/2}$) of a 5 mg esaxerenone oral tablet in healthy humans is 16.7–18.7 h [75, 76]. The $t_{1/2}$ of finerenone in healthy humans, administered as a 1–40 mg polyethylene glycol solution formulation or as a 10–80 mg immediate-release tablet formulation (with higher bioavailability vs. polyethylene glycol solution) is 1.70–2.83 h and 1.89–4.29 h, respectively [77]. Pop-

Table 1. Comparison between steroidal and nonsteroidal MRA

	Steroidal MRAs		Nonsteroidal MRAs	
	spironolactone	eplerenone	finerenone	esaxerenone
Affinity (IC50 for MR) [13, 72, 74]	24 nM	990 nM	18 nM	3.7 nM (66 nM and 970 nM for spironolactone and eplerenone)
Selectivity (IC50 for GR, AR, PR) [13, 74]	GR = 2,600, AR = 640, PR = 180	GR = 36,000, AR = 42,000, PR = 7,400	GR, AR, PR >5,000	GR, AR, PR >10,000
$t_{1/2}$ [75–77]	16.5 h	4–6 h	1.70–4.29 h	16.7–18.7 h
Active metabolites [72]	7a-Thiomethylspironolactone, canrenone	None	None	None
Effect on mutated MR_{S810L} [81]	Agonists		Antagonist	N/A
Tissue distribution [69, 73]	Kidney > Cardiac 6-fold	Kidney > Cardiac 3-fold	Kidney = Cardiac	
Mechanism of antagonism [81]	passive		Bulky passive	
Adverse events	Hyperkalemia, decreased libido, male breast development, sexual dysfunction, abnormal menstruation	Hyponatremia, vaginal bleeding, hyperlipidemia, hyperkalemia, CYP3A enzyme inhibitor	Hyperkalemia, no other major adverse reactions	

IC50, half-maximal inhibitory concentration; $t_{1/2}$, mean terminal half-life; GR, glucocorticoid receptor; AR, androgen receptors; PR, progesterone receptors.

ulation pharmacokinetic and exposure-response analysis of finerenone based on ARTS-DN and FIDELIO-DKD trials demonstrated a pharmacokinetic half-life of 2–3 h, similar to that seen in healthy humans, and a steady state was achieved after 2 days [78, 79]. The result is similar to the pharmacokinetic assay in individuals with renal impairment, revealing that finerenone can be safely and effectually applied to CKD patients [72, 80].

Binding studies revealed that finerenone has a higher antagonistic potency for MR than spironolactone, and quantification of MR subcellular localization under hormonal treatment showed that finerenone alters nuclear translocation of the receptor more efficiently than spironolactone [81]. Finerenone stably binds to Asn-770 and Ser-810 residues of the MR ligand-binding domain, a structure unique to MR and absent from other steroidal hormone receptors, which enables finerenone to have high selectivity [81]. In addition, unlike spironolactone and eplerenone, finerenone does not display any agonistic activity when acting through the MR_{S810L} and inactivates this mutant receptor [81–83]. The co-crystal structure of MR ligand-binding domain/esaxerenone revealed that its high affinity to MR resulted from its intrusive binding pattern into the large and secluded binding pocket of MR formed by the rearrangement of side chains, again a feature only exhibited in MR. This binding pattern is unique to esaxerenone and completely different from that seen in steroidal MR antagonists or previously published nonsteroidal antagonists [84]. As an inverse agonist, finerenone inhibits the recruitment of MR, steroidal receptor coactivator-1, and RNA pol II to the promoter of the sodium channel nonvoltage-gated 1 α (SCNN1A) gene, a common MR target gene, and even reduces recruitment in the basal state, where aldosterone stimulation does not exist. For spironolactone, partial aldosterone-like activity promotes MR and SRC-1 binding to the promoter of the SCNN1A gene without promoting that of the RNA Pol II [85]. These characteristics of nonsteroidal MRAs show their potential for the treatment of cardiovascular and kidney diseases with high efficacy and fewer side effects.

Clinical Study of Nonsteroidal MRAs

Phase II and III clinical trials of nonsteroidal MRAs have been completed. In January 2019, Japan PMDA approved the indication of esaxerenone for the treatment of hypertension [86]. In July 2021, the US Food and Drug Administration (FDA) approved the indication of finerenone to reduce the risk of sustained eGFR decline, end-stage renal disease, cardiovascular death, nonfatal myocardial infarction (MI), and hospitalization for HF in adults with CKD associated with T2DM [87]. The chemical structure determined the therapeutic differ-

ences between these two MRAs. Esaxerenone can be classified as pyrroles and sulfones [86]. Finerenone can be classified as amides, naphthyridines, and nitriles [87]. In preclinical studies, esaxerenone and finerenone both alleviated oxidative stress, fibrosis, and inflammation, and exhibited cardiorenal protective effects in hypertensive rats and rodent kidney injuring models, respectively [43, 88–90]. Esaxerenone increased the urinary sodium/potassium concentration ratio in healthy humans in a dose-dependent manner, and had an antihypertension effect in hypertensive rats [88, 91]. The longer elimination half-life of esaxerenone may coordinate with sodium excretion to decrease blood pressure (BP). In addition, esaxerenone and finerenone may modulate transcription differently which could lead to their different effects on BP.

Therapeutic Effects of Esaxerenone

Clinical trials of esaxerenone are mainly being carried out in Japan. Currently, the published phase III trials focus primarily on essential hypertension and T2DM with nephropathy (shown in Table 2). ESAX-HTN reported that the sitting BP and 24-h BP-lowering effect of the esaxerenone 5.0 mg/day group was significantly better than that of the eplerenone and esaxerenone 2.5 mg/day group, while the esaxerenone 2.5 mg/day group showed a reduced nighttime BP and 24-h systolic BP (SBP) to a greater extent than eplerenone [14, 88]. As such, esaxerenone may be an effective treatment option for nocturnal hypertension, especially in older patients and those with a non-dipper pattern of nocturnal BP [88]. The more evident antihypertension effects of esaxerenone throughout a 24 h period are derived from its strong MR-blocking effects with a long $t_{1/2}$, partly owing to its nonsteroidal structure. A phase III trial exploring the antihypertension effects of esaxerenone as mono or in combination with calcium channel blockers (CCB) or RAS inhibitors found that changes in sitting and 24-h BP was similar among all groups and that the proportion of patients who had achieved targeted sitting BP (SBP/DBP <140/90 mm Hg) at the end of treatment was 67.6%, 62.5%, and 57.1%, respectively [89]. The treatment period of these two studies was the same (52 weeks), but the proportion of patients reaching targeted BP in ESAX-HTN (5 mg/day) is less than that in the esaxerenone 2.5–5 mg/day mono group. This may have been due to the different baseline of patients, as well as the addition of one other drug (CCB, RAS inhibitor, or thiazide diuretic) which was allowed to patients whose BP was not sufficiently controlled after week 12 by esaxerenone alone. For patients with HF and moderate kidney dysfunction, esaxerenone is also effective and well-tolerated [90, 91]. In general, the clinical trials showed that dose escalation of esaxerenone from 2.5 to 5 mg/day was possible and that the majority of patients did not require additional antihypertensive therapy to achieve target BP, but that a combination therapy benefited patients with uncontrolled BP.

In the ESAX-DN study, the addition of esaxerenone to existing RAS inhibitor therapy significantly reduced urinary albumin-to-creatinine ratio (UACR) and, in some patients, led to UACR remission and reduced the risk of albuminuria progression in patients with T2DM and UACR of 45–300 mg/g creatinine. Consistent with results seen with finerenone, UACR mainly decreased within 4 months and remained low thereafter [15, 16]. During the first 24 weeks of treatment with esaxerenone, eGFR gradually declined and held steady for the remainder of the study. At the end of treatment, the eGFR reduction rate was about 10% on average and the percentage of patients with a ≥30% reduction in eGFR on two consecutive occasions was 5% in the esaxerenone group and 2% in the placebo group [15]. These results are consistent with the findings that esaxerenone was administered to patients with T2DM and UACR ≥300 mg/g creatinine [92]. Remarkably, in phase III studies of finerenone, eGFR also decreased faster in the finerenone group than in placebo group until month 24, after which the finerenone group with higher eGFR exhibited a renal protective effect [16, 17]. The follow-up time in esaxerenone trials to date might be too short to observe this effect.

Safety of Esaxerenone

The proportion of patients with adverse events was similar in esaxerenone, eplerenone, and placebo groups. The most notable adverse events were increased serum potassium and decreased eGFR. The EXSA-HTN study found that the proportion of patients with two consecutive serum potassium levels ≥5.5 mM or ≥6.0 mM once during the treatment period was 0.9% in the esaxerenone 2.5 mg/day group, 0.6% in the esaxerenone 5 mg/day, and no patient in the eplerenone group had serum potassium levels meeting these criteria. Compared with the eplerenone group, the maximal serum potassium level in the esaxerenone 2.5 and 5 mg/day groups was slightly higher (4.48 and 4.56 mM compared to 4.40 mM in eplerenone) [14]. In patients with T2DM and nephropathy, the proportion of patients with two consecutive serum potassium levels ≥5.5 or one ≥6.0 mM was 9% in EXSA-DN, which is consistent with subgroup analysis that showed that rates of hyperkalemia in the esaxerenone group were

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Table 2. Main clinical trials of esaxerenone

Trial/phase	Primary end point	Patient involved	Intervention	Sample size/ duration	Results	Findings
ESAX-HTN III [14]	Change in sitting SBP/DBP	•Age ≥20 years •4 weeks washout period •Mean sitting SBP/DBP 140–179/90–109 mm Hg • Mean 24-h BPs ≥130/80 mm Hg at week 3 of the washout period	•Esaxerenone: 2.5 mg/day 5 mg/day •Eplerenone: 50 mg/day	•1,001 people •12 weeks	•Change difference in BP: point estimates (95% CI) •eplerenone and esaxerenone 2.5 mg/day groups −1.6 (−3.3 to 0.1) mm Hg for SBP −0.7 (−1.8 to 0.3) mm Hg for DBP •eplerenone and esaxerenone 5 mg/day groups −4.8 (−6.4 to −3.1) mm Hg for SBP −2.3 (−3.3 to −1.3) mm Hg for DBP (both $p <$ 0.001) •Proportion of patients achieving target sitting BP: esaxerenone 5 mg and 2.5 mg/day: 41.2% and 31.5% eplerenone 50 mg/day: 27.5% (BP <140/90 mm Hg) •Hyperkalemia (K^+ levels ≥5.5 or 6.0 mM): esaxerenone 2.5 mg and 5 mg/day: 0.9% and 0.6% no patient in the eplerenone group •eGFR remained stable in eplerenone group but decreased slightly at weeks 4 and 12 in both esaxerenone groups	•Antihypertensive effects •Esaxerenone 2.5 mg/day reduced 24-h SBP to a greater extent than eplerenone •Esaxerenone 5 mg/day significantly reduced both 24-h BP and sitting BP compared with esaxerenone 2.5 mg/day and eplerenone •The rate of increased serum K^+ levels was slightly higher in the esaxerenone groups
ESAX-DN III [15]	Proportion of patients with UACR remission (UACR<30 mg/g, ≥30% reduction from baseline)	•Age ≥20 years •Hypertension and type 2 diabetes •Received RAS inhibitor treatment for ≥12 weeks •UACR of 45–300 mg/g • eGFR ≥30 mL/min/1.73 m^2 (first morning urine)	•Esaxerenone: 1.25 mg/day up titrated to 2.5 mg/day on basis of serum K^+ levels •Placebo	•455 people •52 weeks	•Proportion of remission: esaxerenone versus placebo: 22% versus 4% difference 18%; 95% CI: 12–25%; $p < 0.001$ •Proportion of >30% reduction in UACR: esaxerenone: 69%; 95% CI: 63–75% placebo: 20%; 95% CI: 15–26% •Hyperkalemia(K^+ levels ≥5.5 or 6.0 mM): esaxerenone versus placebo: 9% versus 2%, $p = 0.002$ •Percent change in eGFR: esaxerenone versus placebo: −11% versus −1%; geometric least-square mean ratio to placebo 0.9; 95% CI: 0.88–0.93	•Adding esaxerenone to existing RASi therapy significantly reduce UACR and in some patients lead to UACR remission and reduce the risk of albuminuria progression •Serum K^+ elevates in esaxerenone group but is reversible •eGFR decreases during first 24 weeks patients with ≥30% eGFR reduction is 5% and 2% in esaxerenone and placebo group, respectively
ESAX in T2D and macro-albuminuria III [89]	Changes in UCRA	•Age ≥20 years •Hypertension and type 2 diabetes •Received RAS inhibitor treatment for 12 weeks •UACR >300 mg/g • eGFR ≥30 mL/min/1.73 m^2 (first morning urine)	•Esaxerenone: 1.25 mg/day up titrated to 2.5 mg/day on basis of serum K^+ levels •Single-arm study	•56 people •28 weeks	•UACR decreased from baseline by 54.6% (95% CI: 46.9%–61.3%; from 544.1 mg/g to 246.8 mg/g) •Proportion of UACR <300 mg/g, ≥30% reduction 51.8% (95% CI: 38.0%–65.3%) •Hyperkalemia(K+ levels ≥5.5 or 6.0 mM): 5.4% •eGFR change at week 24: −8.3 mL/min/1.73 m^2	•Adding esaxerenone to existing RAS inhibitor reduces UACR in patients with T2DM and UACR ≥300 mg/g •Esaxerenone increased serum K^+ levels and decreased eGFR levels, but is reversible
ESAX as mono or combination in hypertension III [88]	Change in sitting SBP/DBP	•Age ≥20 years •Essential hypertension SBP 140–180 mm Hg DBP 90–110 mm Hg 24-h BP ≥130/80 mm Hg •eGFR ≥60 mL/min/1.73 m^2 •Untreated or received only RAS inhibitor or CCB	•Monotherapy •1–12 weeks: esax 2.5 mg/day up titrated to 5 mg/day on basis of serum K^+ and BP •<52 weeks: add CCB, RASi or thiazide diuretic if not controlled •Combination therapy •1–12 weeks: esax (idem) add CCB or RAS inhibitor •<52 weeks: add dose (not esax) or drug (idem) if not controlled	•368 people •52 weeks	•Overall changes in sitting SBP/DBP (95% CI): mm Hg week 12: −16.1 (−17.3, −14.9)/−7.7 (−8.4, −6.9) week 28: −18.9 (−20.2, −17.7)/−9.9 (−10.7, −9.2) week 52: −23.1 (−25.0, −21.1)/−12.5 (−13.6, −11.3) (all $p < 0.0001$ vs. baseline) •Proportion of patients (SBP/DBP <140/90 mm Hg): esax 67.6%, esax + CCB 62.5%, esax + RASi 57.1% •Proportion of patients (serum K^+ increased): esax 7.3%, esax + CCB 1.7%, esax + RASi 9.4% •Hyperkalemia (K^+ ≥5.5 or 6.0 mM): esax 1.6%, esax + CCB 0%, esax + RASi 0%	•Changes in BP in mono or combination therapy is similar •Up titrated of esax from 2.5 to 5 mg/day is feasible and majority of patients can achieve target BP •Serum K^+ and adverse event are similar in mono and combination therapy group

RASi, RAS inhibitor; esax, esaxerenone; CCB, calcium channel blocker; CI, confidence interval; UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

higher in patients with baseline eGFR <60 mL/min/1.73 m^2 and baseline serum potassium level >4.5 mM [15]. Interestingly, all studies revealed that serum potassium level generally increased during the first 2 weeks of the trials and reached a maximum at 2–6 weeks [14, 15, 92]. Thus, monitoring serum potassium levels in early stages, especially for specific patients, and adjusting dosage accordingly is important. If serum potassium levels stayed within safe limits during this time, esaxerenone could be safely administered.

In patients with hypertension, the eGFR in the esaxerenone groups decreased by about 5–8 mL/min/1.73 m^2 by the end of the study, with decreases generally seen in the first 12 weeks with levels remaining steady after this initial decrease; the eGFR in the eplerenone groups remained stable [14, 89]. A phase I study showed that esaxerenone dose-dependently increased plasma renin activity and plasma aldosterone concentration via MR blockade [93]. These effects were verified in the EXSA-HTN study where they were greater than those seen with eplerenone, indicating that esaxerenone may act more strongly on renal tubules and inhibit MR in other tissues more strongly than eplerenone [14]. Although the eGFR slightly decreased in both studies, a post hoc analysis of the SPRINT and ACCORD-BP trials supported that an eGFR decrease of up to 20% after BP lowering can be accepted and suggested that the limit can be extended up to 46% depending on the achieved BP reduction [94]. In EXSA-DN, the percent change in eGFR from baseline to the end of treatment in the esaxerenone group was significantly higher than that in the placebo group (−11% vs. −1%) and the eGFR continued to decrease until week 24, after which it remained stable and returned to a level similar to that of the placebo group at the post-treatment follow-up [15]. In patients with T2DM and macroalbuminuria, eGFR decreased by 8.3 mL/min/1.73 m^2 in the esaxerenone group which is similar to decrease seen in patients with hypertension.

All in all, increased potassium levels and reduced eGFR appear to be reversible, suggesting that esaxerenone can be safely used in patients with hypertension. Its use in patients with nephropathy needs further study.

Therapeutic Effects of Finerenone

After the phase II studies identified the most effective and robust dosage of finerenone [95–97], the phase III clinical trials FIDELIO-DKD and FIGARO-DKD (shown in Table 3), carried out worldwide, both draw a conclusion that finerenone improved cardiovascular composite outcomes (death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for HF) in patients with T2DM and CKD compared with a placebo [16, 17]. However, analysis of individual cardiovascular outcomes showed that finerenone only reduced the risk of hospitalization for HF in FIGARO-DKD [16, 17]. The EPHESUS trial, which explored the effect of eplerenone on patients with left HF after acute MI (left ventricular ejection fraction LVEF ≤40%), and the EMPHASIS-HF trial, which looked at patients with systolic HF with mild symptoms (NYHA grade II and above, LVEF ≤40%), have both shown that eplerenone can significantly reduce the risk of hospitalization or death due to cardiovascular events [10, 11]. The RALES trial also showed that spironolactone significantly reduced the risk of hospitalization or death due to cardiovascular events in patients with severe HF (NYHA grade III and above) [9]. When compared to results seen in other trials those found in the finerenone trials show its efficacy as questionable. The TOPCAT trial showed that spironolactone did not reduce the risk of death from cardiovascular events or hospitalization for HF in patients with preserved ejection fraction HF (LVEF ≥45%), which suggests that the reason why finerenone did not reduce the risk of cardiovascular death may be excluding patients with symptomatic HF (NYHA grade II and above), reducing the cardiovascular risk of patients and making it hard to get positive results [12]. This also indicates the potential of finerenone in both diabetic and nondiabetic patients with HF, but its clinical application needs further clinical trials.

Only in the FIDELIO-DKD trial was kidney composite outcomes (kidney failure, a sustained decrease from baseline of at least 40% in eGFR for a period of at least 4 weeks, or death from renal causes) improved possibly due to the different baseline of enrolled patients. FIDELIO-DKD included patients with UACR 300–5,000 mg/g and eGFR 25–60 mL/min/1.73 m^2, while patients with UACR 30–300 mg/g, eGFR ≥60 mL/min/1.73 m^2, and patients with UACR 300–5,000 mg/g, eGFR ≥75 mL/min/1.73 m^2 were included in FIGARO-DKD but not FIDELIO-DKD, which made the average eGFR of FIGARO-DKD higher than that in FIDELIO-DKD (68 and 44 mL/min/1.73 m^2, respectively) [16, 17]. It is worth noting that kidney composite outcomes with a ≥57% decrease in eGFR were improved in both trials, but only in FIGARO-DKD was the incidence of end-stage kidney disease lower in the finerenone group than in the placebo [16, 17]. This finding suggests that finerenone reduces the risk of clinical cardiovascular outcomes and kidney disease progression in a broad range of patients with T2DM and CKD, especially early in treatment before CKD has progressed. As more

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Table 3. Main clinical trials of finerenone

Trial/phase	Primary end point	Patient involved	Intervention	Sample size/ duration	Results	Findings
FIDELIO-DKD III [16]	Time-to-event analysis: a composite of kidney failure, eGFR decrease ≥40% over 4 weeks, or death from renal causes	•Age ≥18 years •T2DM and CKD •UACR 30–300 mg/g, eGFR 25–60 mL/min/1.73 m^2 or UACR 300–5,000 mg/g eGFR 25–75 mL/min/1.73 m^2 •diabetic retinopathy •Maximal RAS inhibitor •Serum K^+ ≤4.8 mM	•Finerenone •eGFR 25–60 10 mg/day (1 month later up titrated to 20 mg based on K^+ and eGFR) •eGFR ≥60 mL/min/m^2 20 mg/day •Placebo	•5,734 people •2.6 years	•The primary composite outcome: finerenone versus placebo group: 504 (17.8%) and 600 (21.1%) patients (hazard ratio, 0.82; 95% CI: 0.73–0.93; $p = 0.001$) •Key secondary outcome (hospitalization for heart failure, death from cardiovascular causes, nonfatal MI, or nonfatal stroke) finerenone versus placebo group: 367 (13.0%) and 420 (14.8%) patients (hazard ratio: 0.86; 95% CI: 0.75–0.99; $p = 0.03$) •Hyperkalemia related adverse events: finerenone versus placebo group: 18.3% and 9.0% •Hyperkalemia leading to discontinuation of trial finerenone versus placebo group: 2.3% and 0.9% •Serum K^+ levels ≥5.5 and 6.0 mM: finerenone: 21.7%, 4.5%; placebo: 9.8%, 1.4%	•Finerenone improved cardiovascular and renal outcomes in patients with T2DM who had stage 3–4 CKD with moderately elevated albuminuria or stage 2–4 CKD with severely elevated albuminuria •Finerenone is associated with a higher risk of hyperkalemia than placebo discontinuation of the trial regimen due to hyperkalemia was infrequent
FIGARO-DKD III [17]	Time-to-event analysis: a composite of death from cardiovascular causes, hospitalization for heart failure, nonfatal stroke, or nonfatal MI	•Age ≥18 years •T2DM and CKD •UACR 30–300 mg/g, eGFR 25–90 mL/min/1.73 m^2 or UACR 300–5,000 mg/g eGFR ≥60 mL/min/1.73 m^2 •Maximal RAS inhibitor •Serum K^+ ≤4.8 mM	•Finerenone •eGFR 25–60 10 mg/day (1 month later up titrated to 20 mg based on K^+ and eGFR) •eGFR ≥60 mL/min/m^2 20 mg/day •Placebo	•7,437 people •3.4 years	•The primary composite outcome: finerenone versus placebo group: 458 (12.4%) and 519 (14.2%) patients (hazard ratio, 0.87; 95% CI: 0.76–0.98; $p = 0.03$) •Key secondary outcome (kidney failure, eGFR decrease ≥40%, death from renal causes) finerenone versus placebo group: 350 (9.5%) and 395 (10.8%) patients (hazard ratio,0.87; 95% CI: 0.76–1.01) •Hyperkalemia: finerenone versus placebo group: 10.8% and 5.3% •Hyperkalemia leading to discontinuation of trial: finerenone versus placebo group: 1.2% and 0.4%	•Finerenone improved cardiovascular outcomes in patients with T2DM who had stage 2–4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria •Finerenone is associated with a higher risk of hyperkalemia than placebo discontinuation of the trial regimen due to hyperkalemia was infrequent
ARTS-DN II [94]	Changes in UCRA	•CKD and T2DM •UACR 30 mg/g, eGFR >30 mL/min/1.73 m^2 •RAS inhibitor •Serum K^+ ≤4.8 mM	•Finerenone: 1.25, 2.5, 5 7.5, 10, 15, 20 mg/day •Placebo	•823 people •90 days	•Mean ratios of UACR at 90 days versus baseline 7.5 mg/day: 0.79 (90% CI, 0.68–0.91; $p = 0.004$) 10 mg/day: 0.76 (90% CI, 0.65–0.88; $p = 0.001$) 15 mg/day: 0.67 (90% CI, 0.58–0.77; $p < 0.001$) 20 mg/day: 0.62 (90% CI, 0.54–0.72; $p < 0.001$) •Hyperkalemia: 1.5 mg/day: 2.1%; 2.5 mg/day: 1.1% 5 mg/day: 1.0%; 7.5 mg/day: 2.1%; 10 mg/day: 0% 15 mg/day: 3.2%; 20 mg/day: 1.7%	•Finerenone exhibits dose-dependent UACR reduction at the four highest doses group versus placebo in patients with T2DM and CKD •Discontinuation of hyperkalemia occurred in 1.8% of patients receiving finerenone 7.5–20 mg/day, compared with no cases in the placebo group
ARTS-HF II [95]	Proportion of patients with >30% decline in NT-proBNP	•HFrEF, T2DM and/or CKD •eGFR >30 mL/min/1.73 m^2 in patients with T2DM or 30–60 mL/min/1.73 m^2 in those without T2DM •Therapy for HF for at least 3 months •Left ventricular ejection fraction of 40% or less	•Finerenone 2.5, 5, 7.5, 10, or 15 mg/day, titrated to 5, 10, 15, 20 or 20 mg/day, respectively, on day 30 •Eplerenone 25 mg every other day, increased to 25 mg/day on day 30, and to 50 mg/day on day 60	•1,066 people •90 days	•Proportion of patients with >30% decline in NT-proBNP: similar with finerenone versus eplerenone •Composite clinical endpoint of all-cause death, cardiovascular hospitalizations, or emergency presentation for worsening HF the incidence was lower in finerenone compared with eplerenone, except for finerenone 2.5→5 mg/ day group •Hyperkalemia: finerenone: 3.6, 3.8, 3.7, 3.6, 6.3% (from low to high dose); eplerenone 4.7% •Serum K^+ level at day 90 was greater in eplerenone group (+0.262 mM) than in each of the finerenone dose groups (+0.119–0.202 mM)	•The 10 mg/day finerenone titrated to 20 mg/day after 30 days would provide the best balance of safety and efficacy for further investigation in larger clinical trials •Compared with eplerenone, finerenone decreased composite clinical endpoint •Serum K^+ is dose dependent in finerenone groups and similar to eplerenone group
ARTS II [96]	Change in serum potassium	•HFrEF and CKD •NYHA class II–III •left ventricular ejection fraction ≤40% •eGFR 60–90 (part A) or 30–60 mL/min/1.73 m^2 (B) •Therapy for HFrEF •Serum K^+ ≤4.8 mM	•Part A •finerenone: 2.5, 5.10 mg/day •placebo •Part B •finerenone: 2.5, 5.10 mg/day or 5 mg twice daily (bid) •open label spironolactone 25 or 50 mg/day •placebo	•Part A 65 people 28 days •Part B 393 people 28 days	•Part A: Finerenone of all doses is safe and tolerable •Part B •Finerenone 10 mg/day and 5 mg b.i.d. show greater increase in serum K^+ level from baseline $p = 0.0243$ and 0.0003, respectively •Serum K^+ level increase in finerenone is smaller than in spironolactone ($p < 0.0001$ for 2.5, 5, 10 mg/day and $p = 0.0107$ for 5 mg b.i.d.)	•For a significantly smaller increase in serum potassium, finerenone was equi-efficient in lowering albuminuria and cardiac biomarkers compared with spironolactone

CI, confidence interval; UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; HF, heart failure; HFrEF, left ventricular ejection fraction.

than 60% of the patients had albuminuric CKD with an eGFR of at least 60 mL/min/1.73 m^2 at baseline in FIGARO-DKD, UACR screening is useful for early CKD diagnosis and for treatment to improve outcomes [17]. A pooled analysis of FIDELIO-DKD and FIGARO-DKD further validates these results [98].

A series of prespecified or post hoc analyses have been carried out and more details about finerenone have been specified. A result from FIGARO-DKD analysis demonstrated that finerenone reduces new-onset HF and improves HF outcomes (risk of cardiovascular death, first hospitalization for HF, or total hospitalization for HF) in patients with CKD and T2DM, with no evidence of differences in a history of HF [99]. Analyses of FIDELIO-DKD reported that among patients with CKD and T2DM, finerenone reduced the incidence of the composite cardiovascular and kidney outcome, and new-onset atrial fibrillation or flutter, irrespective of treatment effect based on preexisting atherosclerotic cardiovascular disease status and history of atrial fibrillation at baseline [100, 101]. Hemoglobin A1c (HbA1c) levels have been reported to be an independent risk factor for mortality in both diabetic and nondiabetic patients with chronic HF and previous studies have shown that compared with spironolactone, eplerenone had a superior metabolic effect, especially on HbA1c in chronic HF patients [102, 103]. As such, addressing the question of whether finerenone affects or is affected by HbA1c level is necessary. A subgroup analysis of FIDELIO-DKD showed that neither HbA1c levels nor insulin use has an influence on the cardiorenal protective effect of finerenone in patients with CKD and T2D, and there is no metabolic effect of finerenone on HbA1c according to both FIDELIO-DKD and FIGARO-DKD [104].

Safety of Finerenone

In terms of safety analysis, FIDELIO-DKD and FIGARO-DKD showed that the incidence of adverse events in the finerenone group was similar to that of the placebo group, and that finerenone had no effect on body weight. Finerenone treatment had modest effects on BP: the mean difference between finerenone and placebo in the change from baseline in the systolic BP was −3.5 mm Hg at month 4 and −2.6 mm Hg at month 24 in FIGARO-DKD. Due to the difference in patients at baseline, the incidence of hyperkalemia in FIDELIO-DKD is higher than that of FIGARO-DKD, which is 18.3% versus 9.0% and 10.8% versus 5.3% in finerenone versus placebo group, respectively [16, 17]. The serum potassium level mainly increased within month 1 and remains largely stable thereafter. Independent risk factors for at least mild hyperkalemia are higher serum potassium, lower eGFR, increased urine albumin-creatinine ratio, younger age, female sex, β-blocker use, and finerenone assignment, while diuretic or SGLT2 inhibitor use reduced risk according to an analysis of FIDELIO-DKD [105]. Irrespective of treatment (finerenone or placebo), short-term increases in serum potassium levels and decreases in eGFR were associated with subsequent hyperkalemia. At month 4, the magnitude of increased hyperkalemia risk for any change of serum potassium and eGFR from baseline was smaller with finerenone than with placebo [105]. Monitoring serum potassium at months 1 and 4 after finerenone treatment initiation and at 4-month intervals thereafter, and dose titration based on those results (threshold serum potassium from ≤4.8 to ≤5.0 mmol/L), minimized the impact of hyperkalemia and provided a basis for clinical use of finerenone [105, 106].

The attributes that short half-life, absence of active metabolites, balanced kidney-heart distribution, a novel mechanism of distinct MR blockade, and different effects on subsequent gene expression make finerenone more likely to have a low rate of hyperkalemia than spironolactone and eplerenone. In the ARTS study with spironolactone as control, finerenone showed a significantly smaller increase in serum potassium and equal efficiency in lowering albuminuria and cardiac biomarkers in patients with HF and reduced left ventricular ejection fraction (HFrEF) and CKD [97]. However, the maximal dosage of finerenone in this study was 10 mg/day, less than the recommended 20 mg/day, which is needed for the effects on kidney outcomes to approach saturation [79]. It is worth mentioning that the rise in serum potassium with finerenone 5 mg twice daily was larger in comparison with finerenone 10 mg/day, whereas the therapeutic effects for albuminuria and cardiac biomarkers were similar [97]. In the ARTS-HF study with eplerenone as the control, finerenone did not reduce the incidence of hyperkalemia compared with eplerenone and the incidence of hyperkalemia in finerenone 15–20 mg/day group was slightly higher than in the eplerenone group (6.3% and 4.7%, respectively), but the average change of blood potassium concentration measured at end of the study compared with baseline showed that each concentration of finerenone group was lower than that of the eplerenone group (+0.119–0.202 mM and +0.262 mM, respectively) [96]. As previous studies on spironolactone and eplerenone mainly focus on HF having a different renal function at baseline compared with FIDELIO-DKD and FIGARO-DKD, the incidence of hyperkalemia cannot be compared. Therefore, no study to date can systematically explain whether finerenone reduces the risk of hyperkalemia compared with spironolactone and eplerenone.

Conclusion

The new nonsteroidal MRAs contain the robust anti-inflammatory and antifibrotic actions of conventional MRAs in a more selective and efficacious way. These outstanding effects result from their unique molecular structures, allowing for the absence of active metabolites, balanced kidney-heart distribution, novel mechanisms of distinct MR blockade, and different effects on subsequent gene expression. Clinical studies of these drugs have validated their various indications. Esaxerenone is effective and well-tolerated in patients with hypertension, exhibiting an albuminuria-lowering effect in patients with T2MD and CKD. Monotherapy of esaxerenone has the same antihypertensive effect as use of esaxerenone in combination with CCB or RAS inhibitor therapy, and its long $t_{1/2}$ further reveals its powerful antihypertensive potency [89]. Spironolactone has been approved to be the most effective add-on drug for the treatment of resistant hypertension defined as uncontrolled hypertension despite treatment with maximally tolerated doses of three drugs [107]. It shows promise to control resistant hypertension more effectively with the administration of nonsteroidal MRAs.

Different from esaxerenone, finerenone shows improved cardiovascular and kidney outcomes in patients with T2MD and CKD with little change to BP. The current studies of finerenone are confined to diabetic patients. Despite unfolding protective effects on HF and CKD, the application of finerenone on these diseases like SGLT2 and RAS inhibitors remains to be verified. Among patients with HFrEF, the aggregate treatment effects of the combined use of an angiotensin receptor-neprilysin inhibitor (ARNI), β blocker, MRA, and SGLT2 inhibitor are substantial [108]. Early comprehensive disease-modifying pharmacological therapy is prospective and may become a new therapy standard. Concomitant use of SGLT2 inhibitor with finerenone decreased CKD progression risk, and with esaxerenone decreased hyperkalemia risk in patients with CKD and T2DM [79, 109]. The effects of finerenone on kidney and cardiovascular outcomes were consistent irrespective of the use of glucagon-like peptide-1 receptor agonist (GLP-1RA) [110]. More details about combination therapy with nonsteroidal MRAs remain to be verified.

When nonsteroidal MRAs are used in the clinic, hyperkalemia remains the main concern for physicians, but by dynamically monitoring serum potassium as described above and the use of combination therapy may help alleviate this concern. AMETHYST-DN, a phase II study of patiromer, a nonabsorbed, orally administered potassium binding polymer, demonstrated that in the case of RAS inhibitor therapy patiromer statistically significantly decreases serum potassium level after 4 weeks of treatment in patients with hyperkalemia and diabetic kidney disease [111]. Another phase II study AMBER probing into the value of patiromer for allowing more persistent use of spironolactone in patients with CKD, HF, and resistant hypertension showed that patiromer achieved this goal by reducing the risk of hyperkalemia [112, 113]. A phase III study aiming at improving RAS inhibitor use in patients with HFrEF with hyperkalemia or a history of hyperkalemia leading to RAS inhibitor therapy compromise is being conducted [114]. An SGLT2 inhibitor might be another option; research has approved the concurrent use of an SGLT2 inhibitor to reduce the magnitude of serum potassium elevation without any change to the antihypertensive and albuminuria-suppressing effects in Japanese patients with T2DM and albuminuria treated with esaxerenone [109].

In conclusion, nonsteroidal MRAs bind to MRs more efficiently and selectively than conventional steroidal MRAs, thus protecting cardiorenal function by inhibiting MR-mediated inflammation and fibrosis and lowering BP by maintaining fluid and electrolyte homeostasis. Esaxerenone is able to effectively reduce BP, and finerenone has a protective effect on cardiovascular and kidney function in patients with T2DM and CKD. Therefore, nonsteroidal MRAs may be a novel and optimal option of guideline-compliant therapy for these patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Wenyu Liu drafted the manuscript. Shengqiang Yu revised and approved the final manuscript.

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