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NEW THERAPIES FOR CARDIOVASCULAR DISEASE (AA BAVRY, SECTION EDITOR)

Mineralocorticoid Receptor Antagonists: a Comprehensive Review of Finerenone

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Abstract

Purpose of Review We aim to review the mechanism of action and safety profile of mineralocorticoid receptor antagonists (MRAs) and discuss the differences between selective and non-selective MRAs. More specifically, finerenone is a new medication that is currently under investigation for its promising cardiovascular and nephrological effects.

Recent Findings MRAs are well known for their utility in treating heart failure, refractory hypertension, and diverse nephropathies, namely, diabetic nephropathy. As their name denotes, MRAs inhibit the action of aldosterone at the mineralocorticoid receptor, preventing receptor activation. This prevents remodeling, decreases inflammation, and improves proteinuria. There are not significant differences in outcomes between selective and non-selective MRAs. A new selective MRA named finerenone (originally BAY 94-8862) has shown promising results in several trials (ARTS-HF and ARTS-DN) and smaller studies. Finerenone may have a dose-dependent benefit over older MRAs, decreasing rates of albuminuria and levels of BNP and NT-ProBNP without causing a significant increase in serum potassium levels. This medication is not yet approved as it is still in phase 3 clinical trials (FIGARO-DKD and FIDELIO-DKD trials).

Summary MRAs are beneficial in several disease states. Newer medications, such as finerenone, should be considered in patients with heart failure and diabetic nephropathy who may benefit from a reduction in albuminuria and BNP/NT-ProBNP. Data surrounding finerenone are limited to date. However, results from ongoing clinical trials, as well as new trials to evaluate use in other pathologies, could validate the implementation of this medication in daily practice.

Keywords Mineralocorticoid receptor antagonists · Finerenone · BAY 94-8862 · Spironolactone · Eplerenone · Aldosterone

Introduction

Diuretics are a cornerstone in the management of hypertension, heart failure, chronic kidney disease (CKD), and numerous hypervolemic disorders. Various classes of diuretics work on different channels along the nephron increasing sodium excretion through urination. The renin–angiotensin–aldosterone system (RAAS) is a neurohormonal homeostasis pathway that serves an important role in the regulation of renal sodium handling, fluid balance, osmolarity, renal blood flow, and blood pressure, and thus, is a major target for many antihypertensive and diuretic medications. The activation of the RAAS pathway leads to the production of aldosterone, a mineralocorticoid hormone produced by the adrenal cortex, which acts on receptors in the distal and collecting tubules of the nephron, causing reabsorption of sodium and secretion of potassium. Mineralocorticoid receptor antagonists (MRAs) are a group of medications that inhibit the effect of aldosterone on the mineralocorticoid receptor (MR) [1]. In this article, we

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discuss MRAs while highlighting their mechanism of action, physiological effects, adverse reactions, and literature to support their use in the management of different disease states. We will also focus on a selective MRA, finerenone, a new medication under investigation for use in heart failure and diabetic nephropathy.

The Renin–Angiotensin–Aldosterone System

The RAAS pathway starts with the secretion of renin from the granular cells of the renal juxtaglomerular apparatus (JGA). The release of renin is triggered by three main physiological stimuli: sympathetic stimulation of the β_1 receptors of the JGA, reduced sodium delivery to the distal convoluted tubule detected by the macula densa, and reduced perfusion pressure in the kidney detected by baroreceptors in afferent arterioles [2]. Renin secretion is inhibited by atrial natriuretic peptide (ANP) and brain natriuretic peptides (BNP), which are produced by cardiac tissue in response, to chamber distention as occurs with increased plasma volume. Renin enzymatically cleaves angiotensinogen, a precursor protein produced by hepatocytes, into Angiotensin I (ATI). ATI is then converted to Angiotensin II (ATII) by angiotensin converting enzyme (ACE), which is produced by endothelial cells in the lungs and to a lesser extent the endothelium and renal epithelial cells. ATII stimulates two different G protein coupled transmembrane receptors: ATI receptor and ATII receptor. ATII also serves as an autoregulator of the glomerular filtration rate (GFR) and controls sodium excretion. ATII stimulation of the ATI receptor prevails over ATII stimulation and leads to vasoconstriction of the afferent and efferent arterioles, aldosterone release from the adrenal cortex, norepinephrine release from presynaptic terminal endings, sodium reabsorption in the proximal convoluted tubule, and antidiuretic hormone (ADH) release from the hypothalamus [2–4]. These mechanisms lead to increased sodium reabsorption, potassium excretion, elevation of hydraulic pressures to maintain an appropriate GFR, water reabsorption in the collecting duct, and increased effective circulating volume [5].

Aldosterone and Mineralocorticoid Receptor Interaction in the Heart

Aldosterone is a mineralocorticoid steroid hormone produced in the zona glomerulosa of the adrenal cortex. It is released by AGII activation. Aldosterone acts on the principal cells of the kidney at the level of the collecting ducts, increasing the concentration of epithelial sodium channels (ENaC) and stimulating the basolateral Na+/K+ ATPase pump which leads to increased sodium reabsorption, potassium secretion, and increased effective circulating volume [6]. In addition to its regulatory impact on the kidney, aldosterone also stimulates the mineralocorticoid receptors in the heart. It is hypothesized that aldosterone may directly stimulate the proliferation of cardiomyocytes and fibroblasts in response to inflammation or damage [7, 8]. Animal studies have shown that aldosterone can activate the Kirsten Ras (Ki-RasA) protein and the MAP kinase (MAPK1/2) signaling cascade by active phosphorylation, leading to remodeling and fibrosis [9]. In fact, heart failure patients have been found to have higher circulating aldosterone levels in blood by up to 20%, providing an opportunity for RAAS inhibitors to decrease the deleterious effects of aldosterone [10].

Mineralocorticoid Receptor Antagonists in Cardiovascular Disease

MRAs directly bind to and block MR, disabling aldosterone or 11-deoxycorticosterone from activating it, thereby reducing the degree of inflammation and remodeling in the heart. MRAs are classified as specific or non-specific based on the chemical class. Specific MRAs are non-steroidal, while non-specific MRAs are steroidal in nature. Non-specific MRAs were discovered first and were widely used due to their metabolic regulatory effects as strong anti-mineralocorticoid, moderate anti-androgen, and weak anti-steroidogenesis agents. These drugs inhibit the effects of androgens by blocking the receptors stimulated by testosterone and dihydrotestosterone. The anti-steroidogenesis function could potentially lead to inhibition of 17 and 18 alpha-hydroxylase, 17, 20-lyase, 5 alpha-reductase, 11 beta-hydroxylase, 21-hydroxylase, 3 beta-hydroxysteroid dehydrogenase, and the cholesterol side-chain cleavage enzyme [11]. Common side effects from the medication include gynecomastia, breast tenderness, and feminization [12]. This anti-androgenic side effect makes spironolactone a therapy for polycystic ovary syndrome and acne [13, 14]. For polycystic ovary syndrome, there is evidence recommending high-dose spironolactone for improved outcomes, while showing a safety profile from a metabolic standpoint. Zulian et al. evaluated spironolactone 100 mg once daily given for a 12-month therapy with and without dietary-induced weight loss and found a significant decrease pf triglycerides in the overweight subjects, increased high-density lipoprotein (HDL)–cholesterol levels in non-overweight population, and decreased insulin levels at 60 min after an oral glucose tolerance test in overweight female after the 12-month follow-up [13]. For acne, it has been recommended as an alternative treatment for moderate and severe acne vulgaris in females [14].

Non-specific Mineralocorticoid Receptor Antagonist in Cardiovascular Disease

Non-specific MRAs include spironolactone and drospirenone. Extensive studies on spironolactone have demonstrated

significant benefits for heart failure with reduced ejection fraction (HFrEF), refractory hypertension, hyperaldosteronism, hypokalemia, ascites secondary to cirrhosis, alopecia, hypertrichosis, and acne. The cardiovascular benefits and affordable cost have made this medication widely used in the management of HFrEF. The use of spironolactone was further supported by the RALES trial published in 1999 [15]. This prospective study sought to determine mortality benefit from spironolactone in patients with HFrEF with a left ventricle ejection fraction (LVEF) < 35% and a New York Heart Association (NYHA) III/IV by randomizing 1663 patients to either spironolactone or placebo groups. Most randomized patients were already on a combination of Angiotensin Converting Enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs), a loop diuretic, or digoxin based on guideline-directed management for severe heart failure at the time of the study. The study showed an improvement in mortality (relative risk (RR) of death 0.70; 95% CI 0.60–0.82, $P < 0.001$) and reduced frequency of hospitalization (RR of hospitalization 0.65; 95% CI 0.54–0.77, $P < 0.001$) in the spironolactone group when compared with the control arm. Side effects included gynecomastia in 10% of men enrolled in the study. Studies have also advocated for the use of spironolactone in heart failure with preserved ejection fraction (HFpEF) suggesting a possible benefit. The TOPCAT trial, published in 2014 [16], included 3445 patients with symptomatic heart failure and a LVEF > 45% who were assigned to receive 15 to 45 mg of daily spironolactone. The study did not find a significant reduction in the incidence of the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure [16]. Nevertheless, TOPCAT trial has been criticized after publication secondary to geographic inconsistencies in patient population, as the majority of the subjects (49%) were enrolled by eastern European countries (Russia and the Republic of Georgia), which did not have BNP level availability prior to patient recruitment, and it was only available later in the study. The trial concluded no significant benefit from spironolactone treatment effect overall for the primary endpoint (hazard ratio (HR) 0.89; 95% CI 0.77–1.04, $P = 0.14$), but these findings were likely pulled by the eastern cohort (HR 1.10; 95% CI 0.79–1.51, $P = 0.12$), compared with the north and south American cohorts which found significant improvement (HR 0.82; 95% CI 0.69–0.98, $P = 0.026$), raising the question if spironolactone truly benefits mortality in heart failure, in spite of the LVEF [17]. Most recently, spironolactone was also studied as an additional treatment for acute heart failure (ATHENA-HF trial) at high doses (25–100 mg daily) for 96 h after diagnosis. It was found to be well-tolerated but did not improve 30-day mortality or heart failure hospitalization rates [18].

Other benefits from spironolactone include decreased proteinuria in chronic kidney disease (CKD), and therefore, prevention of CKD progression. Chrysostomou and Becker found that adjunctive use of spironolactone with an ACEi or ARB significantly decreased proteinuria in 54% of patients with proteinuria greater than 1 g/day [19]. The antiproteinuric effect of spironolactone has been validated in several studies as a second line therapy, in addition to ACEi or ARB, especially in cases of overt proteinuria (> 1 g/day) [20]. Similarly, evidence has also supported a significant antiproteinuric effect of aldosterone blockers, particularly spironolactone and eplerenone, in patients with diabetic nephropathy [21, 22].

Another non-specific MRA is drospirenone which has been used mostly as a contraception strategy and as hormonal therapy for menopausal symptoms. Evidence supporting the use of drospirenone in cardiovascular or renal conditions is inconclusive [23].

Specific Mineralocorticoid Antagonists in Cardiovascular Disease

Given the side effect profile of non-specific MRAs, specific MRAs were designed to ideally provide the same antimineralocorticoid benefits while minimizing adverse effects. Specific MRAs include eplerenone, canrenone, mexrenone, and finerenone. Eplerenone is the most commonly used and best studied selective MRA. This medication has been supported by multiple clinical trials, including the EPHESUS and EMPHASIS-HF trials [24, 25]. The EPHESUS trial was the pivotal trial supporting eplerenone and was designed to assess its efficacy in patients with heart failure post myocardial infarction. It showed a benefit in morbidity and overall mortality (RR 0.85, 95% CI 0.75–0.96, $P = 0.008$) after giving eplerenone to post-myocardial infarction patients who developed left ventricular dysfunction and heart failure [24]. In addition to heart failure benefit, there was a lower risk of sudden cardiac death from cardiac causes (RR 0.79, 95% CI 0.64–0.97%, $P = 0.03$). Eplerenone demonstrated beneficial effects as early as 7 days after initiation showing a comparative improvement in systolic and diastolic blood pressure changes compared with placebo, but it showed a mildly higher risk of hyperkalemia (5.5% in the eplerenone group vs. 3.9% in the placebo group, $P = 0.002$). Afterwards, The EMPHASIS-HF trial was published, which assess the effects of eplerenone in patients with systolic heart failure and mild symptoms. This study randomized 2737 patients with HFrEF < 35% and NYHA class II into an eplerenone group vs. a placebo group, both of which were on optimal medical therapy with either ACEi or ARB and a beta blocker. After an approximate 1.8-year follow-up, patients with moderate systolic dysfunction and NYHA class II symptoms in the eplerenone group had a reduced risk of composite cardiovascular death or heart failure hospitalization (18.3% vs. 25.9%, respectively, HR 0.63; 95% CI 0.55–0.76, $P < 0.001$) [25].

Canrenone was supported for the management of congestive heart failure by the COFFEE-IT trial, which found an

improvement in mortality with the use of canrenone plus conventional therapy compared with the conventional therapy group [26]. Investigators found that patients on canrenone had decreased HgbA1C levels, uric acid, and systolic and diastolic blood pressures. After a 10-year follow-up, they also found decreased left ventricular mass compared with the control group, as well as decreased mortality in patients within the 68–83-year age range [26]. Despite these positive findings, canrenone is not widely used. Mexrenone has not been extensively studied in cardiovascular medicine. Finally, finerenone is the most recent selective MRA, with most evidence suggesting a benefit in heart failure and diabetic nephropathy.

Effect of MRA on Albuminuria

Mineralocorticoid receptor antagonists have been proposed as a therapeutic agent in patients with albuminuria, particularly in those with proteinuria > 1 g/day [19]. Different MRAs are proposed to have various levels of impact on proteinuria. Spironolactone was amongst the first MRAs evaluated as an adjunctive therapy to ACEi to reduce proteinuria in patients with CKD. Several randomized controlled trials (RCTs) have supported these findings. Bianchi et al. found that CKD patients treated with spironolactone for 1 year had a significant decrease in proteinuria compared with controls (2.1 ± 0.08 to 0.89 ± 0.06 g/g creatinine, $P < 0.001$) [27]. These findings suggestive of reduction in proteinuria and CKD progression have been further supported by several RCTs and metanalysis [28]. A large metanalysis including seven RCTs in patients receiving ACEi/ARB and spironolactone (25 mg) vs placebo showed a significant reduction in proteinuria, with an average of 800 mg/day (95% CI 330–1270 mg/day) [29]. Of note, these studies did not maximize the dose of ACEi/ARB, which could have potentially changed the outcomes, as there is available evidence supporting the dose-dependent effect of ACEi/ARB in proteinuria [30, 31].

Eplerenone has limited evidence regarding reduction of proteinuria. Tsuboi et al. studied non-diabetic patients with urinary protein excretion > 1 g/gCr taking renin–angiotensin system inhibitors [32, 33]. The study found a 38% reduction in urinary protein excretion after a 1-year period. Of note, patients with decreased GFR benefited more as compared with those with preserved GFR [34]. Currently, there is an on-going double-blind RCT, the EVALUATE study, analyzing the antialbuminuric effect of low-dose eplerenone [34]. Other studies assessing the effect of eplerenone in proteinuria include studies done by Ando et al. and Epstein et al. which compare eplerenone to placebo and evaluate the urine albumin creatinine ratio. However, these two studies did not include patients that were on gold standard therapy for proteinuria in CKD [35]. Boesby et al. (eplerenone vs. ACEi/ARB) and Tylicki et al. (eplerenone vs. ACEi/Aliskiren) evaluated the impact of eplerenone in the urine albumin creatinine ratio, but both studies had significant limitations, including a small sample size and short treatment period (8 weeks) [36].

There is substantial evidence regarding Finerenone on proteinuria, particularly in those with diabetic nephropathy. This will be further discussed in the section below "Finerenone Use in Diabetic Nephropathy and Proteinuria."

Finerenone, a Novel MRA with Evidence in Heart Disease and Nephropathy

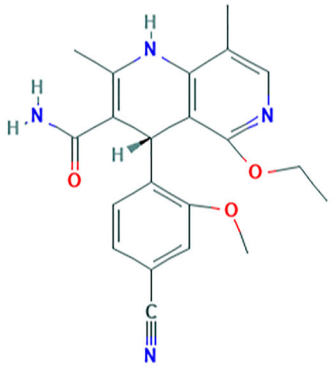
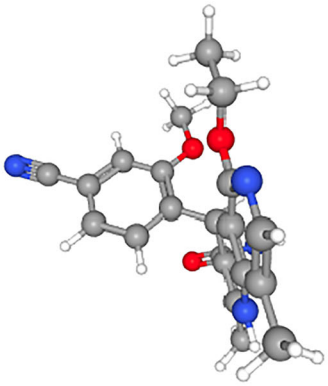
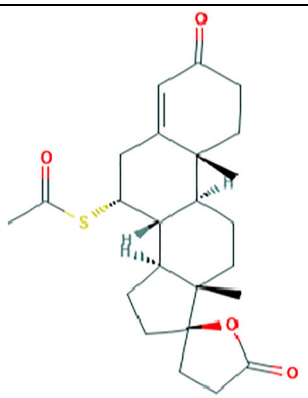
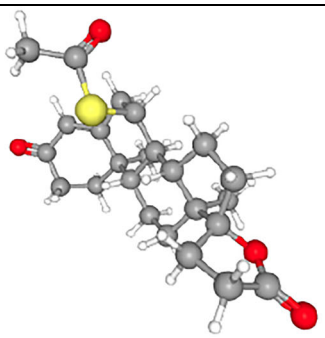
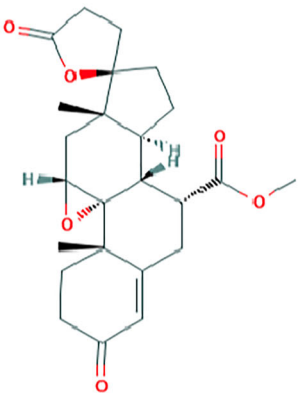
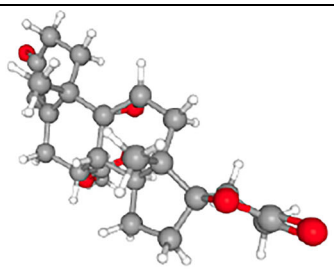
Finerenone, originally called BAY 94-8862, is a novel potent selective MRA with stronger mineralocorticoid receptor-binding potential compared with eplerenone and spironolactone. The medication was developed by Bayer AG pharmaceuticals from a precursor drug called Bayer BR-4628, a compound found to be a potent and selective MRA. From a chemical standpoint, the molecular formula is $C_{21}H_{22}N_4O_3$; its IUPAC name is (4*S*)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide [37]. Different to its counterpart MRAs, this drug leads to the protrusion of MR helix 12, which disables MR activation upon ligand binding [38] (see Table 1, illustrating the chemical structures in 2D and 3D of the MRA extensively discussed in this manuscript).

Since finerenone's discovery, the drug has shown promising potential for the management of cardiorenal diseases, particularly in patients with heart failure and mild renal dysfunction [39•]. While optimal dosing has yet to be determined, the medication is taken orally once a day. Various doses have been tested, including 2.5 mg, 5 mg, 10 mg, 15, mg, and 20 mg, with dose-finding trials currently being performed. Finerenone seems to have lower rates of hyperkalemia than spironolactone but similar effects on NT-ProBNP and albuminuria [40••, 41••, 42]. The drug is currently undergoing phase 3 trials, particularly for use in diabetic nephropathy (FIGARO-DKD and FIDELIO-DKD trials) (see Table 2) [39•, 43••].

Metabolism, Pharmacokinetics, and Pharmacodynamics of Finerenone

Finerenone is metabolized by CYP3A4 (90%) and CYP2C8 (10%). However, renal dysfunction alters clearance of the medication. Patients with different creatinine clearances (CrCl) had the same maximum serum concentration, but elimination half-life was prolonged in those with worse kidney function: < 30 ml/min/m^2 (3.0 h), 30–50 ml/min/m^2 (2.88 h), 50–80 ml/min/m^2 (2.34 h), and > 80 ml/min/m^2 (2.23 h). Given its significant protein binding capacity, finerenone is also impacted by serum albumin levels; thus, hypoalbuminemia (e.g., nephrotic syndrome, malnutrition) may result in increased blood levels of the drug [44].

Table 1 Chemical structure comparison of finerenone, spironolactone, and eplerenone

Medication (MRA)	Chemical structure, 2D*	Chemical structure, 3D*	Molecular formula
Finerenone (37)			$C_{21}H_{22}N_4O_3$
Spironolactone (52)			$C_{24}H_{32}O_4S$
Eplerenone (53)			$C_{24}H_{30}O_6$

Finerenone is a high potency MRA, with a half maximal inhibitory concentration (IC_{50}) of 18 nM, compared with other steroidal hormone receptors [45]. Lentini et al. developed one of the first bioavailability RCTs, in which the pharmacokinetics and absorption of finerenone during fasting and postprandial states were assessed. Investigators found that finerenone was rapidly absorbed during fasting states, with a median time to maximum plasma concentration (t_{max}) of 0.5–1 h, exhibiting dose-linear pharmacokinetics and rapid elimination from plasma (geometric mean terminal half-life ($t_{½}$) of 1.7–2.83 h). In the postprandial state, the elimination rate from plasma was affected, but not the absorption. They also concluded that finerenone did not influence laboratory parameters such as urinary electrolytes, serum aldosterone, and AGII. Finerenone was found to be tolerable with favorable pharmacokinetics despite the prandial state [46].

Table 2 Pivotal trials on finerenone

Randomized controlled trial (NCT)	Drugs compared/Dose protocol	Randomized sample (*n*)	Primary endpoints	Findings
ARTS-HF (NCT01807221) [40••]	Finerenone vs. eplerenone Dose protocol: ○ Finerenone: 2.5, 5, 7.5, 10, or 15 mg orally once daily, up titrated to 5, 10, 15, 20, or 20 mg orally once daily, respectively, on day 30 ○ Eplerenone: 25 mg orally every other day, increased to 25 mg orally once daily on day 30, and to 50 mg orally once daily on day 60, for 90 days	1066 total	Percentage of patients with a > 30% decrease in NT-ProBNP from baseline to day 90	A) NT-proBNP reduction >30%: ○ Finerenone: - 30.9, 32.5, 37.3, 38.8, and 34.2% NT-proBNP reduction in the 2.5 to 5 mg, 5 to 10 mg, 7.5 to 15 mg, 10 to 20 mg, and 15 to 20 mg orally once daily, respectively ($P = 0.42$–0.88). - In the 10 to 20 mg orally once daily, there was a nominal benefit (HR: 0.56; 95% CI, 0.35–0.90; $P = 0.02$). ○ Eplerenone: 37.2%. B) Hyperkalemia (> 5.6%): 4.3% in finerenone group
ARTS-DN (NCT1874431) [41••]	Finerenone vs. matching placebo Dose protocol: ○ Finerenone: 1.25, 2.5, 5, 7.5, 10, 15, or 25 mg orally once daily for 90 days ○ Matching placebo: orally once daily for 90 days	823 total	Urine albumin creatinine ratio at day 90 vs at baseline.	A. Urine albumin creatinine ratio reduction: ○ Finerenone: 7.5 mg/day, (0.79; 90% CI 0.68–0.91; $P = .004$); for 10 mg/day (0.76; 90% CI 0.65–0.88; $P = .001$); for 15 mg/day, (0.67; 90% CI 0.58–0.77; $P < .001$); for 20 mg/day (0.62; 90% CI 0.54–0.72; $P < .001$) B. Hyperkalemia: incidences in the finerenone 7.5, 15, and 20-mg/day groups were 2.1%, 3.2%, and 1.7%, respectively. C. eGFR reduction > 30%: No difference between finerenone and placebo
FIGARO-DKD (NCT02545049) [39•]	Finerenone vs. matching placebo Dose protocol: ○ Finerenone: 10 mg or 20 mg finerenone tablet to be given orally, once daily. ○ Matching placebo: orally once daily	7437 total	Time to occurrence of composite endpoint of cardiovascular death and non-fatal cardiovascular events (MI, stroke, hospitalization for HF)	Ongoing phase 3 trial
FIDELIO-DKD (NCT02540993) [43••]	Finerenone vs. matching placebo Dose protocol: ○ Finerenone: 10 mg or 20 mg finerenone tablet to be given orally, once daily. ○ Matching placebo: orally once daily	5734 total	Time to occurrence of composite endpoint of onset of kidney failure, sustained decrease of eGFR ≥ 40%, during at least a 4-week period or until renal death.	Ongoing phase 3 trial

Finerenone in Cardiovascular Disease

Finerenone has improved selectivity for mineralocorticoid receptors over non-selective MRAs, in addition to lower rates of hyperkalemia. Three randomized control trials have been conducted for finerenone and heart failure which are published by Pitt et al. [42], Filippatos et al. [40••], and Sato et al. [47]. Pitt et al. assessed the safety and tolerability of finerenone in heart failure and mild to moderate CKD. Filippatos et al. described the impact of finerenone in patients with worsening chronic heart failure with diabetes and/or chronic kidney disease (ARTS-HF trial) (see Table 2) [47]. Sato et al. performed a study very similar to the ARTS-HF trial in a smaller Japanese cohort. These three RCTs are discussed in greater detail below.

Pitt et al. evaluated the safety and tolerability of finerenone in patients with heart failure and mild to moderate CKD in a large, randomized, double-blind clinical trial. The trial consisted of two phases in which they first assessed the safety and tolerability of finerenone (2.5, 5, or 10 mg once daily) in 65 patients with HFrEF and mild CKD. This was followed by a second phase in which they compared finerenone to placebo and open-label spironolactone (25 or 50 mg once daily) in 392 patients with HFrEF and moderate CKD. The results showed that finerenone was safer in terms of displaying lower potassium serum levels compared with spironolactone (0.04–0.30 vs. 0.45 mmol/L, respectively, $P < 0.01$), and lower incidence of hyperkalemia (5.3% vs. 12.7%, respectively, $P = 0.048$). They also found that the finerenone group had a more significant decrease in NT-ProBNP during subsequent visits compared with spironolactone, as well as a dose-dependent decrease (median decrease of − 193.65, IQR (− 630; 102) in those receiving finerenone 10 mg once daily, compared with − 170.30, IQR (− 585; 70) in those on receiving spironolactone 25-50 mg once daily). Similar trends were observed with the BNP (median decrease of − 31, IQR (− 122; 5) in those receiving 10 mg of finerenone once daily, compared with − 47, IQR (− 150; 16) in those on spironolactone 25-50 mg once daily). The geometric mean ratio vs. baseline used to assess changes in urine albumin creatinine ratio also showed a beneficial outcome in the finerenone 10 mg once daily group compared with spironolactone 25–50 mg once daily group (geometric mean ratio of 0.72 (geometric SD of 2.34) vs. a geometric mean ratio of 0.61 (geometric SD of 2.62), respectively). In conclusion, BNP, NT-ProBNP and urine albumin creatinine ratio showed significant improvement in patients on finerenone with similar or better results compared with spironolactone [31].

The ARTS-HF trial (NCT01807221) published by Filippatos et al. aimed to evaluate oral doses of finerenone given for a 90-day period in patients with worsening heart failure/left ventricular ejection fraction, chronic kidney disease, and/or diabetes mellitus. This randomized, double-blind, phase 2b multicenter study enrolled a total of 1066 patients to receive either finerenone or eplerenone. The finerenone group received a once daily dose of either 2.5, 5, 7.5, 10, or 15 mg which was then up titrated to a dose of 5, 10, 15, 20, or 20 mg, respectively, on day 30. The eplerenone group received 25 mg every other day which was subsequently increased to 25 mg once daily at day 30 and to 50 mg once daily at day 60. Both groups were followed and re-evaluated at day 90. The primary outcome was > 30% reduction in NT-ProBNP from baseline at day 90. They also evaluated additional composite clinical endpoints including all-cause mortality, cardiovascular hospitalizations or emergency room presentation for worsening heart failure. A decrease in NT-ProBNP > 30% occurred in 37.2% of patients in the eplerenone group and 30.9, 32.5, 37.3, 38.8, and 34.2% decrease in the finerenone group based on the incremental doses protocol, without a statistically significant difference between the two medications ($P = 0.42$–0.88). Of note, the 2.5 mg finerenone group increased to 5 mg at day 30 was the only dose that did not achieve the desired outcome. The remaining sub-groups showed a significant decrease in NT-ProBNP. Remarkably, the finerenone 10 mg daily sub-group increased to 20 mg once daily reached nominal statistically significant improvement (HR 0.56; 95% CI 0.35–0.90, $P = 0.02$). Of note, this phase 2b trial was not designed to detect statistically significant differences. In terms of safety, 4.3% of the patients receiving finerenone experienced hyperkalemia ≥ 5.6 mmol/L [40••].

Sato et al. performed a study with the same design as ARTS-HF but in a Japanese cohort; however, this RCT only included a total of 72 patients. When outcomes were analyzed, all of them demonstrated non-statistically significant findings most likely secondary to a lack of power and limited sample size. The authors stated that even though conclusions could not be obtained, finerenone was very well tolerated by the selected cohort [20]. These findings lack statistical significance and external validity.

After the publication of these three RCTs, a large meta-analysis compared the efficacy and safety of finerenone to spironolactone or eplerenone, in patients with chronic heart failure by including some of the aforementioned RCTs in a total of 1520 heart failure patients. This analysis suggested that finerenone 10 mg once daily was equivalent to spironolactone 25 mg once daily and eplerenone 50 mg once daily ($P < 0.05$). Also noted was a trend towards dose-dependent efficacy (non-statistically significant) in reducing NT-ProBNP, particularly with finerenone 10 mg once daily compared with steroidal MRAs such as spironolactone or eplerenone (RR 1.18, 95% CI 0.88–1.57, $P > 0.05$). The incidence of side effects was significantly lower with finerenone 10 mg once daily compared with spironolactone 25-50 mg once daily (RR 0.81, 95% CI 0.66–0.99, $P = 0.04$). A trend towards lower serum potassium levels (non-statistically significant) was noted in the finerenone 10 mg once daily

group compared with spironolactone 25-50 mg once daily group, but without a statistical significance (mean difference − 0.14, 95% CI, − 0.30–0.02, $P = 0.9$). Finally, the investigators concluded that the estimated glomerular filtration rate (eGFR) was higher in the finerenone 10 mg once daily group compared with the steroidal MRAs group (spironolactone 25 once daily/eplerenone 50 mg once daily) (mean difference 2.07, 95% CI − 0.04–4.17, $P = 0.05$) [48].

Finerenone Impact on Vascular Function

It has been shown in vitro that finerenone reduced aldosterone-induced smooth muscle cell proliferation in a dose-dependent fashion. It has also prevented aldosterone-induced endothelial cell apoptosis. In vivo, oral use of finerenone has shown an accelerated re-endothelialization 3 days after an electric injury in the carotid artery in a murine model. Dutzmann, et al. also described that finerenone inhibited both intimal and medial cell proliferation of the femoral artery of a murine model 10 days after induced injury, as well as attenuated neointimal lesion formation 21 days following the same injury. These findings suggest a positive endovascular effect through rebuilding vascular integrity and preventing development of vascular remodeling [49]. Gonzáléz-Blásquez et al. hypothesized that finerenone could reverse both endothelial dysfunction and microalbuminuria, since both were associated with an increase in oxidative stress [50]. They proved their hypothesis by treating rat models with pre-defined CKD, endothelial dysfunction, and low nitric oxide availability. A decrease in albuminuria > 40% and reduced systolic blood pressure were noted in the finerenone 10 mg once daily group. They also noticed decreased contraction of the aortic rings in rats receiving finerenone, likely from an upregulation in phosphorylated protein kinase B and endothelial nitric oxide (NO) synthase, as well as an increase in NO availability. A significant increase of manganese-dependent superoxide dismutase (SOD) and copper zinc SOD levels in the aortic rings, as well as increased total SOD activity, was observed in rats in the finerenone 10 mg once daily group. The authors concluded that finerenone improved endothelial dysfunction by enhancing NO bioavailability and decreasing superoxide anion levels due to an upregulation in SOD activity, resulting in reduced albuminuria [50].

Finerenone Use in Diabetic Nephropathy and Proteinuria

There is strong evidence supporting the use of finerenone in CKD, particularly in diabetic nephropathy. Finerenone is thought to provide all of the benefits of classic anti-proteinuric medications such as steroidal MRAs, but with fewer side effects, namely, hyperkalemia. Translational studies have found promising results, particularly Kolkhof et al., who demonstrated improved survival and nephroprotection in hypertensive rats receiving finerenone [51]. Based on available literature, finerenone seems to be an adequate alternative when considering eGFR, albuminuria, and hyperkalemia rates. These findings were supported by main RCTs including the ARTS-DN, FIGARO-DKD, and FIDELIO-DKD trials (see Table 2) [39•, 41••, 43••]. The last two are ongoing phase 3 trials.

The ARTS-DN trial (NCT1874431), published by Kabris et al., provides strong evidence for the use of finerenone as an alternative to non-selective MRAs in diabetic nephropathy [41••]. This was a randomized double-blind, multicenter, placebo-controlled, parallel-group study, that included 821 patients receiving finerenone. The authors evaluated the safety and efficacy of different doses of finerenone and administered the drug for a 90-day period to patients with diabetic nephropathy with high or very high albuminuria who were pre-treated with ACEi/ARB. The study subjects received doses ranging from 1.25 up to 25 mg once daily or a matching placebo for 90 days. The primary outcome was urine albumin creatinine ratio day 90 compared with baseline. The safety endpoints included changes in serum potassium and eGFR. Investigators found that the mean placebo-corrected ratios of urine albumin creatinine ratio at day 90 vs. baseline was reduced in the finerenone group, at doses of 7.5 mg (0.79; 90% CI 0.68–0.91, $P = 0.004$), 10 mg (0.76; 90% CI 0.65–0.88, $P = 0.001$), 15 mg (0.67; 90% CI 0.58–0.77, $P < 0.001$), and 20 mg once daily (0.62; 90% CI 0.54–0.72, $P < 0.001$). The safety endpoint (hyperkalemia rate) was not dose-dependent, with rates of 2.1%, 3.2%, and 1.7% for the finerenone groups receiving 7.5 mg, 15 mg, and 20 mg once daily, respectively. There were no significant changes in the eGFR (defined as > 30%) across sub-groups [41••]. In conclusion, they found that finerenone had a dose-dependent reduction in urine albumin creatinine ratio [41••].

The FIGARO-DKD (NCT02545049) trial is an active phase 3 randomized double-blind, placebo-controlled, parallel-group, multicenter, event-driven clinical trial. The aim of this trial is to assess the safety and effectiveness of finerenone vs. placebo in patients with diabetic nephropathy from type 2 diabetes mellitus who are on standard medical therapy [43••]. The trial includes 7437 participants and compares finerenone 10 mg and 20 mg once daily with placebo. The primary outcomes are cardiovascular death and non-fatal cardiovascular events, including myocardial infarction, stroke, and hospitalization for heart failure. Secondary outcomes include a decrease in eGFR, all-cause mortality, change in the urine albumin creatinine ratio, and onset of kidney failure. The composite endpoint includes the onset of kidney failure, a sustained decrease in eGFR, all-cause mortality, all-cause hospitalization, and change in urine albumin creatinine ratio. The study includes patients pretreated with ACEi/ARB without hyperkalemia (serum potassium < 4.8 mmol/L) [43••]. This study is still on-going, and final results are pending.

The FIDELIO-DKD (NCT02540993) trial is an active phase 3 randomized, double-blind, placebo-controlled, parallel group, multicenter, event-driven clinical trial. The inclusion criteria and drug administration protocol are nearly identical to those used in the FIGARO_DKD trial. The trial includes 5734 patients with GFR of 25–75 mL/min/1.73 m^2 and urine albumin creatinine ratio ranging from 30 to 5000 mg/g. The study set a 90% statistical power in order to detect a 20% reduction in the occurrence of the primary outcome (alpha error = 0.05), time to first occurrence of the composite endpoint (onset of kidney failure, sustained decrease of GFR ≥ 40%), and with a minimum 4-week follow-up period or renal death. As in the FIGARO-DKD trial, this trial also includes patients pretreated with ACEi/ARB without hyperkalemia (serum potassium < 4.8 mmol/L) [39•]. The results of this trial are also pending, and it is expected to have a total duration of 5.5 years.

Future Considerations

MRAs are a cornerstone in the management of various cardiovascular and renal diseases. Multiple studies have shown the utility of MRAs in improving urine albumin creatinine ratio, refractory hypertension, heart failure-induced remodeling, and vascular injury. MRAs are well-tolerated by patients, and physicians are familiar with the mechanism of action and drug interactions. Non-selective MRAs like spironolactone are widely prescribed due to the ease of access for patients and well-studied benefits. However, selective MRAs are a great alternative, especially when considering adverse effects. While eplerenone is the safest alternative to spironolactone, newer medications like finerenone may be a promising alternative with a lower risk of hyperkalemia and comparable cardiovascular and renal benefits to other selective and non-selective MRAs. Finerenone appears to be well-tolerated, has a safe pharmacologic profile, and predictable dose-dependent effect. Results from the FIGARO-DKD and FIDELIO-DKD trial may provide more data to support the use of finerenone [39•, 43••]. As of now, the biggest limitations to using finerenone are the lack of appropriately powered randomized clinical trial to support its use, the novelty of the medication, and the lack of FDA approval given the ongoing phase 3 trials.

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Compliance with Ethical Standards

Conflict of Interest Dr. Rico-Mesa, White, and Ahmadian-Tehrani have nothing to disclose.

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Human and Animal Rights and Informed Consent This manuscript does not contain any studies with human or animal subjects.

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