Finerenone: A New Era for Mineralocorticoid Receptor Antagonism and Cardiorenal Protection.

Dominic Parfianowicz DO
Lehigh Valley Health Network, dominic.parfianowicz@lvhn.org

Swara Shah DO
Lehigh Valley Health Network, swara.shah@lvhn.org

Catherine Nguyen
Lehigh Valley Health Network, catherine.nguyen@lvhn.org

Theresa Maitz DO
Lehigh Valley Health Network, theresa.maitz@lvhn.org

Adrija Hajra
Jacobi Medical Center

See next page for additional authors

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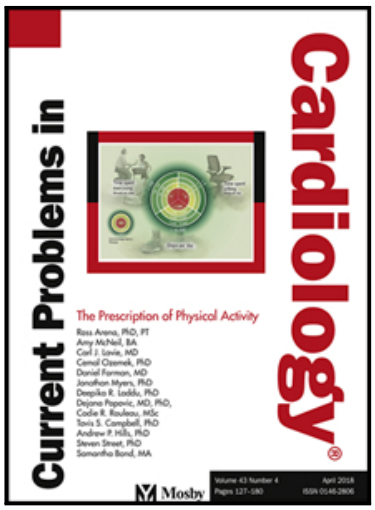
Authors

Dominic Parfianowicz DO, Swara Shah DO, Catherine Nguyen, Theresa Maitz DO, Adrija Hajra, Akshay Goel, Jayakumar Sreenivasan, Wilbert S Aronow, Apurva Vyas MD, and Rahul Gupta MD



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Finerenone: A New Era for Mineralocorticoid Receptor Antagonism and Cardiorenal Protection

Dominic Parfianowicz DO[1], Swara Shah DO[1], Catherine Nguyen DO[1], Theresa N. Maitz DO[1], Adrija Hajra MD[2], Akshay Goel MD[3], Jayakumar Sreenivasan MD MSc[4], Wilbert S. Aronow MD FACC[3], Apurva Vyas MD FACC[5], Rahul Gupta MD[5]

[1]Department of Medicine, Lehigh Valley Health Network, Allentown, PA, USA

[2]Department of Medicine, Jacobi Medical Center, Bronx, NY, USA

[3]Department of Cardiology, Westchester Medical Center and New York Medical College, Valhalla, NY, USA

[4]Department of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT

[5]Lehigh Valley Heart Institute, Lehigh Valley Health Network, Allentown, PA

Address for correspondence:
Rahul Gupta, MD
Lehigh Valley Heart Institute,
Lehigh Valley Health Network, Allentown, PA
E-mail: rgupta8687@gmail.com
T: 484-560-8402

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Abstract

The renin-angiotensin-aldosterone system is a neurohormonal system responsible for maintaining homeostasis of fluid regulation, sodium balance, and blood pressure. The complexity of this pathway enables it to be a common target for blood pressure and volume-regulating medications. The mineralocorticoid receptor is one of these targets, and is found not only in the kidney, but also tissues making up the heart, blood vessels, and adipose. Mineralocorticoid receptor antagonists have been shown to slow progression of chronic kidney disease, treat refractory hypertension and primary aldosteronism, and improve morbidity and mortality in management of heart failure with reduced ejection fraction. The more well-studied medications were derived from steroid-based compounds, and thus come with a distinct side-effect profile. To avoid these adverse effects, developing a mineralocorticoid receptor antagonist (MRA) from a non-steroidal base compound has gained much interest. This review will focus on the novel non-steroidal MRA, Finerenone, to describe its unique mechanism of action while summarizing the available clinical trials supporting its use in patients with various etiologies of cardiorenal disease.

Key Words

Finerenone, mineralocorticoid, renin-angiotensin-aldosterone system, RAAS

Introduction

The mineralocorticoid receptor (MR) plays a considerable role in the renin-angiotensin-aldosterone system (RAAS) and is expressed in a multitude of different tissues and cells, particularly those of the heart and kidney. Mainly activated by aldosterone, the MR has major effects on fluid and electrolyte regulation, blood pressure, inflammation, and fibrosis (1). Hence, it is implicated in the development and progression of cardiorenal disease (2). Targeted blockade

of the MR has been extensively studied and found to have significant clinical benefit in the management of disease entities such as heart failure, chronic kidney disease (CKD), hypertension, and primary hyperaldosteronism (3-5).

The first mineralocorticoid receptor antagonist (MRA) to be studied in the context of heart failure was spironolactone (6,7). Having been found to significantly reduce all-cause mortality in those patients, its success prompted further investigation into newer MRAs such as eplerenone (8,9). Eplerenone, a second generation MRA, gained popularity as compared to spironolactone due to its lower affinity for androgen, progesterone, and glucocorticoid receptors, and thus lower potential for the associated adverse side-effects (10). Both spironolactone and eplerenone are indicated for use in heart failure with reduced ejection fraction (HFrEF). However, these compounds are steroid-based and thus are similar in structure to both aldosterone and cortisol. As a direct consequence of this, there are many side effects associated with steroid MRAs that prohibit or make their use much less preferable. Due to these limitations, research into non-steroidal MRAs has gained interest (11). Finerenone is a third generation MRA dihydropyridine derivative that has shown promising results in efficacy and reduced side-effect profile in the treatment of cardiorenal disease. Thus far, it has been FDA approved for the treatment of CKD in the context of type II diabetes mellitus (T2DM). Here we aim to provide a comprehensive review of Finerenone including its biochemical and biophysical properties, the current data and research, along with future directions and implications with respect to heart failure.

Mechanism of Action and Pharmacodynamics

RAAS activation is well-described in the pathophysiology of atherosclerosis, myocardial infarction (MI), CKD, and systolic heart failure among others (12-14). The expression of angiotensinogen and angiotensin-converting enzyme (ACE) greatly increases in cardiac myocytes in the presence of atherosclerosis and after MI (15,16). Angiotensin II, formed from angiotensin I by the actions of ACE, stimulates myocyte hypertrophy along with recruitment of fibroblasts leading to scar formation at the infarcted area (17,18). Elevated concentrations and activity of ACE have also been noted in chronic systolic heart failure (19). With this setting the scene, aldosterone and the MR later help facilitate fibrosis and inflammation as well (20). As such, direct RAAS inhibition is particularly beneficial in HFrEF (14).

Finerenone is a novel third-generation non-steroidal MRA that was developed through manipulation of dihydropyridine compounds (21). It competes with aldosterone and cortisol for the MR. With its non-steroidal properties, Finerenone displays a unique affinity and binding to the MR cavity that not only plays a direct inhibitory role in the MR signaling cascade, but also prevents recruitment of cofactors involved in gene transcription for downstream hypertrophic, proinflammatory, and profibrotic effects (**Figure 1**) (22). This feature is particularly of interest as inhibition of gene transcription and subsequent protein expression has not been noted as widely in the literature with older generation MRAs. The unique binding structure of Finerenone to the MR also allows for a distinctly different side effect profile, specifically with regard to the unwanted steroidal and hormonal effects that are common with the steroidal-based MRAs. Despite the slightly altered binding schema of Finerenone, it has much higher selectivity for MR than either spironolactone or eplerenone while still being at the very least just as potent (22,23).

A series of molecular studies was conducted evaluating the mechanism of action of Finerenone (24). In these experiments, they found Finerenone to be a more potent inhibitor of the

MR than spironolactone while still having a similar affinity. Furthermore, they found that not only does Finerenone markedly impair cofactor recruitment and binding to MR as compared to spironolactone, it also inhibits basal expression of well-known MR target genes such as Sgk1. Sgk1 is mostly present in tissues of the pancreas, liver, brain, and kidney. Its overexpression has been linked to the development of hypertension, diabetes, fibrosis, and metabolic syndrome among others making it a favorable treatment target (25,26).

A mouse model was used for isoproterenol-induced cardiac fibrosis to evaluate the effects of Finerenone and eplerenone (27). Finerenone displayed potent inhibition of cardiac fibrosis and decreased cardiac strain patterns as compared to eplerenone, which was found to have little effect on either. These antifibrotic effects occurred by inhibiting gene expression of profibrotic tenascin (TN) through Finerenone -mediated prevention of MR cofactor binding. TN is an extracellular matrix protein that is implicated in myocardial fibrosis and cardiac remodeling (28). Overexpression of this protein results in increased inflammation with recruitment of macrophages and profibrotic cytokines (29). The study noted a greatly truncated expression of TN along with lower concentrations of macrophages in mice treated with Finerenone as compared to eplerenone (27).

Steroidal MRAs have been shown to be beneficial in CKD through the reduction of endothelial dysfunction and oxidative stress which in turn improved the degree of albuminuria (30). Unfortunately, these agents must be used carefully due to the potential of worsening renal function and hyperkalemia (31). Finerenone was found to have a similar effect on nephropathy resulting in a reduction of albuminuria and improved estimated glomerular filtration rate (eGFR) through higher concentrations of nitric oxide and decreased levels of oxidative stress (32-34).

However, with finerenone, there was a slightly decreased risk of hyperkalemia which will be discussed later.

Pharmacokinetics

Finerenone is an oral medication with studies using dosages ranging from 1.25mg to 20mg daily. It undergoes first-pass metabolism by cytochrome P450 (CYP) enzymes in the gut wall and liver, predominantly by CYP3A4 and CYP2C8 (35). It was found to have no significant clinical drug-drug interactions with substrates of CYP enzymes (36). This, however, is still being widely examined. Furthermore, mild to moderate hepatic impairment, as defined by Child-Pugh A and B respectively, had little effect on systemic concentration and distribution of Finerenone supporting a predominantly gut-mediated metabolism (37).

Pharmacokinetic studies involving Finerenone have described it to be linearly dosed (38,39). Its chemical structure has greater polarity and lower lipophilicity, which contributes to its wide distribution throughout the body (40). In contrast to steroidal MRAs which accumulate in greater concentrations in the kidney, Finerenone was found to be equally distributed between the heart and kidney. This may help to explain the superiority of Finerenone compared to steroidal MRAs with regard to cardio-protection and prevention of myocardial fibrosis (41). Finerenone is cleared mainly by oxidative transformation into biologically inactive naphthyridine metabolites which are later excreted renally (42). Renal excretion of Finerenone, however, is minimal. Patients with moderate to severe renal impairment, as defined by creatinine clearance (CrCl) of 30-50 mL/min and <30 mL/min respectively, had increased exposure of Finerenone in the bloodstream however maximum drug concentration remained unaffected (43). Plasma half-life is about 2 hours, and yet twice-daily dosing has not shown much clinical difference (44).

Interestingly, twice-daily dosing was actually found to produce higher rates of hyperkalemia compared to once-daily dosing (44). This suggests that the comparatively short half-life of Finerenone is able to produce long-lasting protective downstream effects while the more frequent dosing creates a steady state with greater potential to increase serum potassium levels.

Clinical Uses

MRAs, particularly the first- and second-generation agents, are well recognized for their use in heart failure, hypertension, and chronic kidney disease (glomerulosclerosis, nephropathies, etc). Mineralocorticoid antagonism has also gained interest in the post-renal transplant patient and in primary open-angle glaucoma (45,46). MRAs are of benefit in many systemic diseases and in time, the newer generation non-steroidal MRAs will likely be viewed in a similar light.

In 2021, Finerenone was FDA-approved for use in patients with CKD in the setting of T2DM. This approval was based on the results of the "Finerenone in reducing kidney failure and disease progression in diabetic kidney disease" (FIDELIO-DKD) trial. A secondary analysis of the FIDELIO-DKD trial showed that the administration of Finerenone reduced the risk for development of new-onset atrial fibrillation/flutter by 1.3% (95% confidence interval: 0.53-0.94; p= 0.016) (47). This was thought to be due to Finerenone's effect of blunting cardiac fibrosis and subsequent atrial remodeling. It is important to note that the Finerenone-associated cardiorenal benefits were present irrespective of baseline rhythm. The analysis showed a relatively low but significant risk reduction of new-onset atrial fibrillation/flutter and will require further study for more data collection and support for confirmation. However, it contributes to the mounting support for Finerenone in the treatment and prevention of progressive cardiorenal disease.

Adverse Effects and Contraindications

MRAs have been shown to have benefit in patients with HFrEF, however their side effect profile is not negligible. The adverse effects of hyperkalemia, progressive renal dysfunction, and gynecomastia among others have strongly limited use of the first and second generation MRAs. Hyperkalemia and increased creatinine are two of the most common adverse effects associated with Finerenone compared to a placebo (48). Finerenone should be withheld in patients whose potassium level is greater than 5.5 mmol/L. The initial Mineralocorticoid Receptor Antagonist Tolerability Study-Heart Failure (ARTS-HF) trial which was done to evaluate the efficacy of Finerenone compared to spironolactone showed that Finerenone had a lower risk of hyperkalemia compared to spironolactone (44). The ARTS-HF trial data demonstrated that 4.3% of patients receiving Finerenone experienced hyperkalemia (>5.6mmol/L). Finerenone is also a substrate metabolized by the CYP system, specifically by CYP3A4 in the gut wall and liver and later cleared renally (35). Relative contraindications for Finerenone would be concomitant administration of CYP3A4 inhibitors such as erythromycin, diltiazem, and verapamil. The degree of clinically significant CYP inhibition owed to Finerenone is still being evaluated. The elimination half-life is more prolonged with worsening kidney function which may require dose adjustment (43). Additionally, given that it has a significant protein binding capacity, its concentration in the blood may be elevated in patients with hypoalbuminemia.

Clinical Trials

To date, there have been two similar clinical trials which have evaluated the effect of Finerenone on cardiovascular outcomes. Both trials tested a specific population subset: those with CKD in the setting of T2DM.

The FIDELIO-DKD trial was a double-blinded, parallel group trial which randomized 5674 patients with T2DM and CKD to receive either Finerenone or placebo (49). Finerenone was given at a dosage of 10mg or 20mg depending on the degree of renal dysfunction and potassium levels. The primary outcome was renal failure (end stage renal disease or eGRF<15mL/min), decrease in baseline eGFR by greater than 40%, or renal mortality. Patients receiving Finerenone were found to be at lower risk for CKD progression (kidney failure with a decrease of greater than 40% from baseline GFR or death from renal causes; 95% confidence interval 0.73-0.93; P=0.001). About 46% of patients had baseline cardiovascular disease. The secondary outcome event was a composite cardiovascular outcome of time to cardiovascular death, myocardial infarction, stroke, or heart failure hospitalization. Patients receiving Finerenone similarly had decreased rates of cardiovascular events (95% CI 0.75-0.99, P=0.03) compared to placebo (49).

The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial was a phase III, double-blind randomized trial which looked at the primary outcome of composite of death from cardiovascular causes, nonfatal myocardial infarctions, or hospitalization for heart failure (50). There was a total of 7437 patients with CKD and T2DM who were maximally optimized on RAAS inhibitor therapy and divided to receive either Finerenone or placebo. The primary outcome event occurred in 12.5% of patients in the Finerenone group and 14.2% in the placebo group, while a secondary outcome event (kidney failure, worsening eGFR, or death from renal causes) occurred in 9.5% in the Finerenone group and 10.8% in the placebo group. The analysis revealed a lower incidence of heart failure hospitalization being primarily responsible for the improved cardiovascular outcomes in the Finerenone group.

Given the similarity in design and assessment of these two trials, a pooled analysis was conducted called “Combined FIDELIO-DKD and FIGARO-DKD trial programme analysis” (FIDELITY). This analysis supported the robustness and safety of Finerenone across a wide spectrum of patients with T2DM and CKD. It revealed that Finerenone does have a cardioprotective and reno-protective effect; the relative risk reduction was 14% for the composite cardiovascular outcome and 23% for the composite kidney outcome (51).

Another randomized controlled trial referred to as the Mineralocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF) was a double-blind, phase 2b trial that evaluated dosing and safety of Finerenone in patients with HFrEF and CKD (52). This was the first trial to compare the efficacy of Finerenone to eplerenone by measuring the number of patients who had a greater than 30% reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP). The safety profile of Finerenone was similar to that of eplerenone. In this study, it was also determined that the best dosage adjustment of Finerenone for greatest reduction in composite outcome is 10mg to 20mg. The adverse event rate of potassium increases to greater than 5.6 mmol/L was similar in both eplerenone and Finerenone groups (4.3% in both groups).

Two trials of similar design evaluating efficacy and safety of Finerenone in patients with diabetic nephropathy were conducted. The Mineralocorticoid Receptor Antagonist Tolerability Study - Diabetic Nephropathy (ARTS-DN) was a randomized, double-blind, phase 2b multicenter study that was the first of these two studies (34). A total of 823 patients were randomized to different daily doses of Finerenone (1.25, 2.5, 5, 7.25, 10, 15, 20mg) and compared to placebo. The primary outcome was a change in baseline urine albumin-creatinine ratio (UACR) over 90 days. Secondary outcomes were changes in potassium and eGFR. This study found a dose dependent UACR reduction in the Finerenone groups compared to placebo

with the greatest reduction observed in the 20mg Finerenone group (HR 0.62; 90% CI, 0.54-0.72; p<0.001). There were slight increases in serum potassium in the 7.5, 15, and 20mg Finerenone groups that lead to discontinuation. There was no significant difference in eGFR decrease in the Finerenone groups as compared to placebo.

A similar trial replicating ARTS-DN was conducted in Japan named as ARTS-DN Japan (53). The key difference between the two trials was sample size as ARTS-DN Japan only randomized 96 patients. Similar to ARTS-DN, there was a dose-dependent reduction in UACR in the Finerenone groups as compared to placebo. There was no major difference in elevation of serum potassium, however. This may have been owed to the smaller sample size. The major results are summarized in **Table 1**.

Future Areas of Research

The FIGARO-DKD study showed promise that Finerenone improves cardiovascular outcomes in patients with T2DM and stage 2-4 CKD with moderate albuminuria or stage 1-2 CKD with severely elevated albuminuria. This benefit was largely driven by a lower incidence of heart failure hospitalization with Finerenone. Of note, the study excluded patients with symptomatic HFrEF. A pooled analysis of FIGARO-DKD noted a significant reduction in new-onset heart failure and an improvement in overall heart failure outcomes in that specific patient population (54). This was observed regardless of heart failure history. Future clinical trials are needed to address whether the addition of Finerenone to the treatment regimen for HFrEF has similar benefits.

Through the duration of the FIGARO-DKD trial, SGLT2 inhibitors (SGLT2i) became a standard of care in medical management in patients with T2DM and CKD (55). This raised a

question of whether the benefit of Finerenone would still be seen in the context of an SGLT2i. Subgroup analysis of the FIGARO-DKD trial showed that Finerenone was significantly cardioprotective with or without the concomitant use of SGLT2i (56). Furthermore, the use of preclinical mouse models demonstrated cardiorenal and survival benefits with administration of both SGLT2i and Finerenone together (57). There is currently a three-arm trial known as "COmbinatioN effect of Finerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study" (CONFIDENCE study) that will compare patients randomized to Finerenone and Empagliflozin, Finerenone and placebo, and Empagliflozin and placebo over a period of 6 months. Its goal is to assess if dual therapy with Finerenone and Empagliflozin is of more benefit compared to each agent alone. The primary outcome is reduction in UACR with secondary outcomes being the safety outcomes of changes in serum potassium and eGFR. This study is essentially building off the ARTS trials to involve an SGLT-2 inhibitor. As with the subgroup analyses done for the FIGARO and FIDELIO trials, it will be interesting to see if the combination of both Finerenone and SGLT2i is able to provide a survival benefit in patients with heart failure as well.

Conclusion

Mineralocorticoids have long been used to decrease progression of CKD, hypertension, and HFrEF. Finerenone is a selective non-steroidal mineralocorticoid which decreases both renal and myocardial fibrosis while having lower rates of hyperkalemia compared to other mineralocorticoids. Based on the ART-HF, FIGARO-DKD, and FIDELIO-DKD, Finerenone reduces cardiovascular death and progression of renal failure in patients with CKD associated

with T2DM. Future clinical trials will address if Finerenone alone and in conjunction with goal directed medical therapy can decrease morbidity and mortality in patients with HFrEF.

Conflict of Interest

1) All authors have participated in the work and have reviewed and agree with the content of the article; 2) None of the article contents are under consideration for publication in any other journal or have been published in any journal; 3) No portion of the text has been copied from other material in the literature; 4) I am aware that it is the authors responsibility to obtain permission for any figures or tables reproduced from any prior publications, and to cover fully any costs involved.

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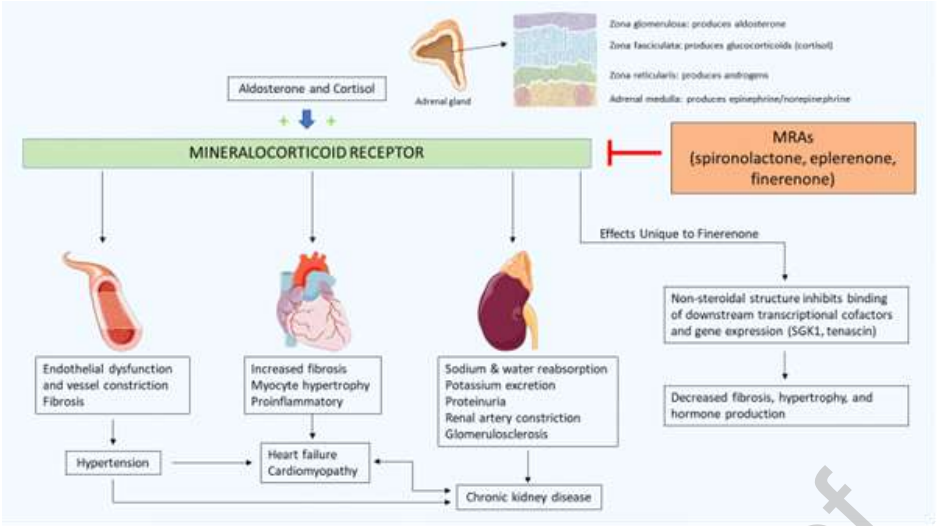
Figure 1: The mechanism of action of MRAs including unique effects of Finerenone



MRA= Mineralocorticoid Receptor Antagonist

Table 1: Summary of trials evaluating the efficacy and safety of Finerenone

Clinical Trial	Methods	Outcomes	Findings
ARTS-HF	Randomized, double-blind, phase 2b multicenter study Finerenone uptitrated from 2.5, 5, 7.5, 10, or 15mg which was uptitrated to 5, 10, 15, 20, or 20mg respectively on day 30. Alternative group received eplerenone 25mg every other day and was increased to 25mg daily on day 30 to 50mg on day 6 N= 1066	Primary endpoint: % of individuals with decrease in >30% of NT pro-BNP until day 90. Composite endpoint: death from any cause, cardiovascular hospitalizations, or heart failure exacerbation presenting to the ED till day 90.	Finerenone induced a 30% or greater decrease in NT pro-BNP similarly to the eplerenone. Finerenone group treated with 10->20mg had a statistically significant less frequency of the composite clinical endpoint compared to eplerenone treated.
FIGARO-DKD	Randomized, double-blind, placebo-controlled phase 3 multicenter study Patients with T2DM and CKD were randomized to receive either Finerenone or placebo. N = 7437	To assess the safety and effectiveness of Finerenone vs. placebo. Primary outcomes are cardiovascular death and non-fatal cardiovascular events (ie. MI, stroke, hospitalization for heart failure). Secondary outcomes are decrease in eGFR, all-cause mortality, change in UACr,	Finerenone and placebo groups had a primary event occur at 12.4% vs 14.2% respectively. (95% CI, 0.76-0.98; p=0.03) This difference was primarily driven by reduced heart failure hospitalizations in the Finerenone treated group.

		onset of kidney failure. Composite endpoint is onset of kidney failure, sustained decrease in eGFR, all-cause mortality, all-cause hospitalization, and change in UACR.	
FIDELIO-DKD	Randomized, double-blind, placebo-controlled phase 3 multicenter study Adults with T2DM and CKD on maximal dose of ACEi/ARB were randomly assigned in a 1:1 ratio to receive either oral Finerenone 10 mg or placebo. The dose was uptitrated to Finerenone 20mg after 1 month and placebo dose adjustment if no hyperkalemia. N = 5674	Primary outcome was time to kidney failure, time to sustained eGFR decrease of at least 40% from baseline, or death from renal cause. Secondary outcomes measured in time-to-event include composite of death from cardiovascular cause, nonfatal MI, nonfatal stroke, or heart failure hospitalization.	Incidences of primary composite outcome significantly lower in the Finerenone group than in placebo. 17.8% vs 21.1% (95% CI 0.73-0.93; p=0.001) Incidence of secondary outcomes was consistently lower with Finerenone than with placebo. 13.0% vs 14.8% (95% CI 0.75-0.99; p=0.03) Number needed to treat at the end of 3 years was 29.
ARTS-DN	Randomized, double-blind, phase 2b multicenter study Adults with T2DM and diabetic nephropathy receiving a RAAS blocker. Patients randomized to receive 1.25, 2.5, 5, 7.5, 10, 15, or 20mg Finerenone or placebo. N = 821	Primary outcome was change in UACR over 90 days Secondary outcomes were adverse events including changes of potassium and eGFR from baseline	UACR reduction was dose-dependent in the Finerenone group compared to placebo. Significant reductions were in the 7.5 (0.79; 90% CI, 0.68-0.91; p=.004), 10 (0.76, 90% CI, 0.65-0.88; p=.001), 15 (0.67; 90% CI, 0.58-0.77; p<0.001), 20mg (0.62; 90% CI, 0.54-0.72; p<0.001) Finerenone groups Hyperkalemia (>5.6mmol/L) occurred in the 1.25, 2.5, 5, 7.5, 15, and 20mg groups (2.1, 1.1, 1.0, 2.1, 3.2, and 1.7% respectively)
ARTS-DN Japan	Randomized, double-blind, phase 2b multicenter study Adults with T2DM and diabetic nephropathy receiving a RAAS blocker. Patients randomized to receive 1.25, 2.5, 5, 7.5, 10, 15, or 20mg Finerenone or placebo. N = 96	Primary outcome was change in UACR over 90 days Secondary outcomes were adverse events including hyperkalemia ≥5.6mmol/L, decrease in eGFR	UACR reduction was Finerenone dose-dependent compared to placebo. The ratio of UACR reduction of 20mg Finerenone to placebo was 0.67 (p=0.024) Small increases in serum potassium were noticed in the Finerenone groups compared with placebo (0.025–0.167 mmol/L) however no instances of hyperkalemia.

ED=Emergency Department; T2DM=Type 2 Diabetes Mellitus; MI=Myocardial Infarction; CKD=Chronic Kidney Disease; UACR= Urine Albumin-Creatinine Ratio; GFR=Glomerular Filtration Rate; RAAS= Renin-Angiotensin-Aldosterone System; ARTS-HF= Mineralocorticoid Receptor Antagonist Tolerability Study-Heart Failure; FIGARO-DKD= Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; FIDELIO-DKD= Finerenone in Reducing Kidney Failure and Disease progression in Diabetic Kidney Disease