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The Cardiorenal Protective Effects of Nonsteroidal Mineralocorticoid Receptor Antagonist (Finerenone) in Diabetic Kidney Disease

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Abstract

Diabetic kidney disease (DKD) affects nearly half of individuals with diabetes and is the leading cause of chronic kidney disease (CKD) globally. Traditionally, renin-angiotensin system (RAAS) inhibitors have been critical for DKD management. In recent years, sodium-glucose cotransporter-2 inhibitors (SGLT2is) have elicited promising renal outcomes in controlled clinical trials. Nevertheless, despite the combined use of RAAS inhibitors and SGLT2is, renal complications remain common, and these medications only delay kidney failure. In diabetes, mineralocorticoid receptor dysregulation exacerbates cardiovascular and renal pathologies. Steroidal mineralocorticoid receptor antagonists (MRAs) exert cardiorenal benefits in individuals with DKD but increase the risks of hyperkalemia and other adverse effects. Nonsteroidal MRAs have a distinct pharmacological profile that enables them to provide cardiorenal protection and minimize hyperkalemia risks in patients with CKD. These novel agents are being investigated for heart failure treatment and possible synergistic effects with SGLT2is, presenting a promising therapeutic avenue for various cardiorenal disorders. This study reviewed the evidence on the cardiorenal protective benefits of nonsteroidal MRA—finerenone, examining molecular mechanisms and exploring applications in treating patients with DKD. Additionally, this review explored the use of nonsteroidal MRAs in combination with SGLT2is or glucagon-like peptide-1 receptor agonists as a strategy to reduce the risk of DKD.

Key Words: Finerenone; diabetic kidney disease; nonsteroidal mineralocorticoid receptor antagonists; cardiorenal protection; hyperkalemia; sodium-glucose cotransporter-2 inhibitors

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Introduction

Diabetic kidney disease (DKD) affects 40% of patients with diabetes and is the leading cause of kidney failure worldwide[1]. DKD is associated with increased mortality in individuals with diabetes that is independent of other risk factors[2,3]. Patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) face a 60% higher risk of cardiovascular mortality and a 50% higher risk of all-cause mortality compared with those with T2D without CKD[4]. Additionally, mortality risk in this population increases as renal function declines, underscoring the importance of timely detection and intervention[5].

Traditional treatments for DKD focus on optimizing lifestyle, blood glucose levels, blood pressure (BP), and lipid levels[6,7]. Cardiorenal protection is achieved primarily by managing hypertension with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin-2 receptor blockers (ARBs)[8]. Additionally, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) exhibit cardiorenal protective effects[9]. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) provide substantial cardiorenal benefits in addition to their effects on blood glucose levels[10]. The risks of CKD and cardiovascular disease (CVD) among patients with T2D are high[11,12], and additional treatment strategies should be developed.

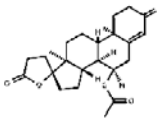
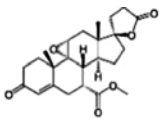
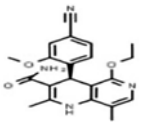
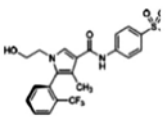
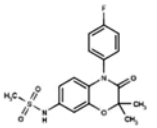
Steroidal mineralocorticoid receptor antagonists (MRAs) reduce albuminuria levels and BP, offering potential cardiorenal protection[13], with expanded indications in patients with heart failure (HF) with preserved ejection fraction (HFpEF)[14]. Steroidal MRAs pose a risk of hyperkalemia, especially in patients with DKD[13]. Consequently, efforts have shifted to developing nonsteroidal MRAs with greater receptor affinity, higher potency, and improved hyperkalemic safety and tolerability profiles[15]. Multiple novel compounds are already in clinical use including finerenone, esaxerenone, and apararenone (Table 1). These novel agents also offer potential cardiorenal protective benefits. Notably, finerenone, the first nonsteroidal MRA, was approved by the US Food and Drug Administration (FDA) in 2021 for patients with DKD to reduce kidney disease progression and cardiovascular complications. Finerenone was approved by the European Medicines Agency (EMA) in 2022[16]. Similar to steroidal MRAs, these drugs reduce fibrosis, inflammation, metabolic disorders, and adverse remodeling in the vasculature, heart, and kidneys[17]. This study reviewed the latest evidence on finerenone's cardiorenal protective effects, assessing its molecular mechanisms and clinical implications in the progression of DKD.

The pathophysiological implications of mineralocorticoid receptor activation on kidney and cardiovascular system

The mineralocorticoid receptor primarily interacts with aldosterone and cortisol, playing a crucial function in physiological homeostasis. This receptor is widely expressed in various tissues and cells, such as smooth muscle cells, vascular endothelial cells, cardiomyocytes, macrophages, and renal tubular epithelial cells[17]. In the distal renal tubules, aldosterone binds to mineralocorticoid receptor to form aldosterone-mineralocorticoid receptor complex, thereby promoting sodium reabsorption and facilitating the excretion of potassium and hydrogen ions. This mechanism suggests mineralocorticoid receptor's essential function in maintaining fluid and electrolyte balance, regulating blood pressure, and controlling circulating blood volume[17].

Excessive mineralocorticoid receptor activation drives inflammation, oxidative stress, and fibrosis, contributing to myocardial hypertrophy, renal injury, vascular dysfunction, and hypertension[17]. It promotes inflammatory cell differentiation and chronic inflammation, accelerating disease

Table 1. Key Differences in the Mechanism of Action and Pharmacological Properties between Steroidal and Nonsteroidal Mineralocorticoid Receptor Antagonists (MRAs)

Agent	Spironolactone	Eplerenone	Finerenone	Esaxerenone	Apararenone
Structure					
Pharmacokinetics	• Steroidal, nonselective competitive antagonist • > 90% oral bioavailability • t1/2: 1.4 hours • Tmax: 2.6-3.05 hours • Multiple actives metabolites	• Steroidal, selective competitive antagonist • 70% oral bioavailability • t1/2: 4-6 hours • Tmax: 1.5 hours • No active metabolites	• Nonsteroidal, selective competitive antagonist • High selectivity for the MR • 86.5% oral bioavailability • t1/2: 1.7-2.8 hours • Tmax: 0.75-1 hour • No active metabolites	• Nonsteroidal, selective competitive antagonist • Strong MR binding affinity • 90% oral bioavailability • t1/2: 20-30 hours • Tmax: 1.5-4 hours • Metabolite with low activity	• Nonsteroidal, selective competitive antagonist • t1/2: 275-285 hours; >1000 hours for active metabolite • Tmax: 4 hours • Metabolite with low activity
Heart-kidney distribution ratio	1:6	1:3	1:1 (cannot across the BBB)	1:1	
MR IC50 (mM)	24	990	17.8		
Hyperkalemia	High risk	High risk	Low risk	Low risk	Low risk
Excretion	< 1% unchanged drug recovered in urine; 10-15% of dose excreted in urine form of metabolites	66% of dose is excreted via urine; < 3% unchanged recovered from urine	80% of dose is excreted via urine; < 1% unchanged drug excreted in urine	38.5% of dose excreted in urine; < 2% unchanged drug excreted in urine	< 14% of dose excreted in urine
Dose adjust based on kidney function	Excretion by the kidney	Cannot be removed by hemodialysis	Decrease dose in patients with eGFR ≤ 60 and prohibit when eGFR < 25		
Sexual side-effects	++	+	-		
Cardiorenal benefits	Reduces cardiac fibrosis, lowers BP, improves HF (HFrEF), and protects kidneys in CKD	Reduces post-MI mortality, lowers BP, prevents vascular fibrosis, and improves cardiorenal outcomes	Reduces albuminuria, slows CKD progression, lowers CV risk, and improves HF outcomes	Lowers albuminuria, reduces BP, prevents cardiac and renal fibrosis	Reduces renal inflammation, fibrosis, and improves DKD
Clinical applications	HTN; hypokalemia; PA; HF; edema	Congestive HF; HTN	T2D with CKD; ESRD; CVD; congestive HF	DKD (clinical trial phase); HTN	DKD

Note. Adapted from "Cardiovascular-renal protective effect and molecular mechanism of finerenone in type 2 diabetic mellitus" by Lv R, et al, 2023, Front Endocrinol 2023, 14, 1125693, P.5-6IC50, half-maximal inhibitory concentration; Tmax, median time to maximum plasma concentration; t1/2, geometric mean terminal half-life; BBB, Blood-Brain Barrier; HTN, hypertension; PA, primary aldosteronism; HF, heart failure; T2DM, type 2 diabetes; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; MR, mineralocorticoid receptor; BP, blood pressure; HFrEF, heart failure with reduced left ventricular ejection fraction; MI, myocardial infarction

progression and targeting organ damage[18]. Specific pathways, such as mineralocorticoid receptor-VEGFR1 and mineralocorticoid receptor-Rac1, mediate vascular fibrosis and glomerular hyperfiltration[18]. Studies indicate that blocking mineralocorticoid receptor overactivation could help mitigate inflammation, fibrosis, and associated complications, offering potential therapeutic benefits[18].

Steroidal MRAs as treatments for CVD

3.1 Cardiovascular outcomes of the steroidal MRAs

The use of MRAs as a treatment strategy began in the early 1960s with the approval of steroidal MRAs as diuretics. Spironolactone and eplerenone, 2 steroidal MRAs in clinical use, are "passive" MRAs due to their binding mechanism, which induces an unstable receptor conformation that inhibits mineralocorticoid receptor corepressor binding[19,20]. This mechanism is distinct from that of the "bulky" nonsteroidal MRAs[21]. This difference in binding mechanism may explain the variations in pharmacological effects observed between steroidal and nonsteroidal MRAs[20,21].

In 1999, spironolactone was shown to reduce morbidity and mortality in patients with severe HF. The RALES trial demonstrated that spironolactone treatment reduced all-cause mortality by 30% in patients with HF with reduced ejection fraction (HFrEF; ejection fraction <35%) with New York Heart Association Class III-IV symptoms[22]. Subsequent trials involving patients who had experienced a myocardial infarction (MI) or who had early-stage CKD, hemodialysis, or resistant hypertension demonstrated spironolactone's ability to reverse cardiac remodeling, reduce left ventricular (LV) mass index, and decrease arterial stiffness[23]. Additionally, in the anti-remodeling effect of canrenone in patients with mild chronic HF (AREA IN-CHF) randomized trial and the observational study on canrenone's effects on cardiovascular mortality in patients with congestive heart failure (COFFEE-IT), canrenone, a spironolactone derivative, reduced mortality and cardiovascular remodeling in patients with HFrEF and HFpEF[24,25]. However, the early aldosterone blockade in acute myocardial infarction (ALBATROSS) and MRA pretreatment and early posttreatment to minimize reperfusion injury after ST-elevation following an MI (MINIMIZE STEMI) trials demonstrated no additional benefit of intravenous potassium canrenoate or spironolactone beyond those for standard post-MI care[26,27]. Other ongoing trials evaluating spironolactone are the postpercutaneous coronary colchicine and spironolactone in patients with an MI SYNERGY stent registry (CLEAR-SYNERGY; NCT03048825) and the perioperative atrial fibrillation occurrence in cardiac surgery patients (ALDOCURE; NCT03551548) trial for patients who have received an arterial bypass graft.

Eplerenone, a second-generation MRA, was developed as a more selective version of spironolactone[28]. Two large randomized clinical trials of eplerenone, the eplerenone post-acute MI HF efficacy and survival study (EPHESUS) and the eplerenone in patients with systolic HF and mild symptoms (EMPHASIS), demonstrated similar benefits in patients who had experienced an MI with HF or LV systolic dysfunction with less severe symptoms, respectively[29,30]. These results led to MRAs receiving a Level 1A recommendation for use in HFrEF across international guidelines[31]. Nevertheless, the early eplerenone treatment in patients with acute ST-elevation following an MI without HF (REMINDER) trial uncovered no clinical benefit of eplerenone in patients without HF who had experienced an MI[32].

To date, no clinical study has demonstrated improved outcomes in patients with HFpEF, the predominant HF type in patients with CKD. For example, the treatment of preserved cardiac func-

tion in HF with an aldosterone antagonist (TOPCAT) trial uncovered no statistically significant reduction in the primary endpoints of cardiovascular mortality, hospitalization for HF, or cardiac arrest incidence following treatment with spironolactone in patients with HFpEF ≥45%[33]. However, a subsequent subgroup analysis by region revealed significant improvements in North and South American patients[34], resulting in a Class IIb level B-R recommendation in US guidelines[31]. Despite the positive effects of MRAs in HF trials, adverse effects such as gynecomastia and hyperkalemia often limit their clinical use[22,29,30].

The spironolactone initiation registry randomized interventional trial in HFpEF (SPIRRIT-HFpEF; NCT02901184) and spironolactone in the treatment for HF (SPIRIT-HF; NCT04727073) studies currently ongoing for patients with HFpEF and HF with midrange ejection fraction may provide additional insights into the effectiveness of spironolactone in this clinical context.

3.2 Renal outcomes of steroidal MRA usage

Several short-term clinical studies have evaluated the effects of adding steroidal MRAs to ACEis or ARBs in individuals with CKD. A 3-month randomized study of 41 patients with proteinuria > 1.5 g/day treated with ACEis demonstrated that adding spironolactone significantly reduced the incidence of proteinuria; nevertheless, triple therapy with ACEis, ARBs, and spironolactone yielded no additional benefit over dual therapy[35]. A 2-month randomized study of 20 patients with DKD revealed that spironolactone reduced albuminuria by 32% compared with placebo (p<0.001), with a reversible 3 mL/min/1.73m^2 decline in glomerular filtration rate. Hyperkalemia occurred only in patients receiving a placebo, indicating the acceptable tolerability of spironolactone when combined with ACEis or ARBs[36]. This short-term study suggests that spironolactone, when combined with antihypertensive treatment involving ACEis or ARBs, is well tolerated and induces renal protection by reducing albuminuria levels in patients with DKD and nephrotic-range albuminuria[36]. Similarly, a study randomized 81 patients with DKD receiving lisinopril and spironolactone, losartan, or placebo for 48 weeks[37]. Spironolactone and losartan reduced urine-albumin-to-creatinine ratios (UACRs) by 34.0% (p=0.007) and 16.8% (p=0.20), respectively. During the treatment period, 52% of patients who received a combination of spironolactone and a high-dose ACEi developed clinically significant hyperkalemia. Additionally, another randomized controlled trial indicated that the administration of spironolactone did not prevent the onset of microalbuminuria among patients with T2D who were at high risk of developing microalbuminuria[38]. Specifically, hyperkalemic episodes were reported in only 9% of the 102 patients randomly assigned to receive spironolactone, compared with 1% of the 107 patients who received a placebo[38]. Although possibly underpowered, the study suggests that steroidal MRAs may not prevent DKD and that eplerenone exhibits renal protective properties in patients with DKD[38]. Finally, in a study of 268 patients with T2D and albuminuria (UACR≥50 mg/g), 50 or 100 mg/day eplerenone added to enalapril for 12 weeks resulted in reductions of UACR by 41% and 48.4% versus 7.4% for placebo (p<0.001 for both eplerenone groups), without significant differences in the incidence of hyperkalemia[39].

Hyperkalemia limits the use of steroidal MRAs in individuals with DKD and contraindicates their use in individuals with severe or end-stage renal disease (ESRD). Eplerenone is also contraindicated as an antihypertensive in patients with T2D with microalbuminuria due to increased hyperkalemia risk[40]. These restrictions have driven the search for alternative mineralocorticoid receptor inhibition strategies that retain cardioprotective benefits and reduce hyperkalemia and off-target effects in

individuals with DKD. However, no large-scale outcome trials to date have assessed the long-term effects of steroidal MRAs in individuals with DKD.

Cardiorenal benefits of finerenone in patients with DKD

Nonsteroidal MRAs possess physicochemical, pharmacodynamic, and pharmacokinetic properties distinct from those of steroidal MRAs[28,41]. Developed to reduce hyperkalemia and off-target effects, nonsteroidal MRAs typically exhibit high affinity, improved mineralocorticoid receptor specificity, and higher therapeutic indexes[23]. Currently, 3 nonsteroidal MRAs—finerenone, esaxerenone, and apararenone—have undergone clinical trials in patients with DKD. Of these, the most extensive clinical data have been reported for finerenone and esaxerenone, which are approved for treatment in several regions[23]. The development of finerenone is the most comprehensive, supported by data from studies involving over 15,000 patients[42-44,46,47]. Table 2 presents a summary of key clinical trials evaluating the cardiorenal effects of nonsteroidal MRAs in patients with DKD.

4.1 Finerenone

4.1.1 Phase II trials

Finerenone has been clinically evaluated in patients with diabetes, CKD, and HF. In the Phase II MRA tolerability study (ARTS) trial (*n*=458), finerenone reduced albuminuria and cardiac biomarkers as effectively as spironolactone after 4 weeks in patients with chronic HF and mild-to-moderate CKD[42]. Finerenone also significantly reduced serum potassium levels and hyperkalemia incidents compared with spironolactone[42]. In the ARTS-HF trial (*n*=1,066), 3 months of finerenone versus eplerenone treatment in patients with HFrEF with T2D or CKD concurrently receiving an ACEi or ARB revealed similar HF biomarker reductions[43]. The results of an exploratory analysis indicated a lower event rate for all-cause death, cardiovascular hospitalizations, or emergency presentations for worsening HF with finerenone, although the study lacked the power to detect statistical differences[43]. Notably, both drugs had comparable safety profiles, with hyperkalemia rates of 4.3%[43]. In the ARTS-DN trial (*n*=823), patients with DKD concurrently receiving an ACEi or ARB treated with finerenone for 3 months exhibited a reduction of between 21% and 38% in UACR, with minimal hyperkalemia-related discontinuations (0%-3.2%), although no discontinuations were reported in the placebo group[44]. Therefore, although promising, finerenone's influence on clinical outcomes and hyperkalemia requires further investigation.

The combination effect of finerenone and empagliflozin in participants with DKD with a UACR endpoint (CONFIDENCE) trial (NCT05254002) is the first Phase II study evaluating the combined effect of finerenone and an SGLT2i on slowing kidney function decline compared with each treatment alone in individuals with DKD already receiving maximized renin-angiotensin-aldosterone system (RAAS) inhibition. Short-term reductions in albuminuria are strongly correlated with long-term cardiorenal improvements[45]. If the CONFIDENCE trial uncovers a substantial additive effect in reducing albuminuria, the trial will provide a robust scientific rationale supporting the combination of these therapies to enhance cardiorenal protection in patients with DKD.

4.1.2 Phase III trials

The finerenone in reducing kidney failure and disease progression in DKD (FIDELIO-DKD) and the finerenone in reducing cardiovascular mortality and morbidity in DKD (FIGARO-DKD) phase III trials investigated the efficacy and safety of finerenone in individuals with DKD, focusing on kidney failure and cardiovascular outcomes, respectively, combined with maximized ACEi or ARB therapy[46,47]. Participants in the finerenone group

Table 2. Summary of Main Clinical Trials Evaluating Cardiorenal Effects of Nonsteroidal Mineralocorticoid Receptor Antagonists (MRAs) in patients with Type 2 Diabetes (T2D) and Chronic Kidney Disease (CKD)

Clinical trial	Study design	Inclusion criteria	Intervention	Sample size and duration	Major findings	Major adverse events	Conclusion
Finerenone							
ARTS-HF[43]	Randomized, double-blind, phase IIb multicenter study	• HFrEF, T2D and/or CKD • eGFR > 30 mL/min/1.73m^2 in patients with T2D or 30-60 L/min/1.73 m^2 in those without T2D • Therapy for HF for at least 3 months • LVEF 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	1066 people 90 days	*Primary endpoint:* Percentage of patients with >30% decline in NT-proBNP: no significant differences were observed across groups *Secondary endpoint:* All-cause death, CV hospitalization, or acute worsening HF was less common with finerenone than with eplerenone (HR 0.56; $p = 0.016$), except for finerenone 2.5→5 mg/day group. All-cause death ($p = 0.062$) and CV death ($p = 0.011$) occurred less frequently in the finerenone group than the eplerenone group.	Hyperkalemia (serum potassium ≥ 5.6 mmol/L): Finerenone 2.5→5 mg Once daily: 6 (3.6%) Finerenone 5→10 mg Once daily: 6 (3.8%) Finerenone 7.5→15 mg Once daily: 6 (3.7%) Finerenone 10→20 mg Once daily: 6 (3.6%) Finerenone 15→20 mg Once daily: 10 (6.3%) Eplerenone: 10 (4.7%) Serum potassium level at day 90 was greater in the eplerenone group (+0.262 mmol/L) than in each of the finerenone dose groups (+0.119-0.202 mmol/L	Administering finerenone at a starting dose of 10 mg per day, gradually increasing to 20 mg per day after 30 days, may achieve a favorable balance between safety and efficacy; further investigation in larger clinical trials is required. Finerenone was associated with a greater reduction in the composite clinical endpoints than eplerenone. Serum potassium levels in patients receiving finerenone exhibited a dose-dependent pattern consistent with those observed in the eplerenone group.
ARTS-DN[44]	Randomized, double-blind, phase IIb multinational study	• DKD • HbA1c ≤12% • UACR ≥ 30 mg/g, eGFR 30-90 mL/min/1.73 m^2 • Serum potassium ≤ 4.8 mmol/L • Minimum recommended ACEi/ARB dose	•Finerenone 1.25, 2.5, 5, 7.5, 10, 15, 20 mg/day •Placebo	823 people 90 days	*Primary endpoint: changes in UACR* UACR day 90/baseline ratio (90% CI; *P* value): 7.5 mg/day: 0.79 (0.68-0.91; $p = 0.004$) 10 mg/day: 0.76 (0.65-0.88; $p = 0.001$) 15 mg/day: 0.67 (0.58-0.77; $p < 0.001$) 20 mg/day: 0.62 (0.54-0.72; $p < 0.001$)	Discontinuation due to hyperkalemia (serum potassium ≥ 5.6 mmol/L): 2.1% in the 7.5 mg group, 0% in the 10 mg group, 3.2% in the 15 mg group 1.7% in the 20 mg group, 1.5% in the placebo group	The reduction in UACR was dose-dependent in the group receiving finerenone compared with the placebo group. The introduction of finerenone led to a significant improvement in UACRs not observed in the placebo group.
FIDELIO-DKD[46]	Randomized, double-blind, phase III, placebo-controlled, multinational study	• Age ≥ 18 years • DKD UACR 30-300 mg/g, eGFR 25-90 mL/min/1.73 m^2, and DR, or UACR 300-5,000 mg/g and eGFR 25-75 mL/min/1.73m^2 • Maximal tolerated ACEi/ARB dose • Serum potassium ≤ 4.8 mmol/L • No diagnosis of symptomatic chronic HFrEF	• Finerenone eGFR 25-60 mL/min/m^2 10 mg/day (1 month later up titrated to 20 mg based on serum potassium and eGFR) eGFR ≥ 60 mL/min/m^2 20 mg/day • Placebo	5734 people 2.6 years	*Primary composite outcome:* kidney failure, eGFR decrease of ≥40% from baseline or death from renal causes occurred: • finerenone: 17.8% • placebo: 21.1% HR 0.82; 95% CI 0.73-0.93; $p = 0.001$ *Major secondary composite outcome:* death from CV causes, MI, stroke, or hospitalization for HF: • finerenone: 13.0% • placebo: 14.8% HR 0.86; 95% CI 0.75-0.99; $p = 0.03$	Serum potassium ≥ 5.5 and 6.0 mmol/L: • finerenone: 21.7%,4.5% • placebo: 9.8%, 1.4% AKI: • finerenone: 4.6% • placebo: 4.8% Discontinuation due to Hyperkalemia • finerenone: 2.3% • placebo: 0.9%	Finerenone was associated with significant improvements in cardiovascular and kidney outcomes for patients with T2D and CKD at stages 3-4 with moderately elevated albumin levels, and those at stages 2-4 with severely elevated albumin levels. Although the use of finerenone was linked with a higher risk of hyperkalemia compared with placebo, discontinuation of the treatment due to hyperkalemia was rare.

FIGARO-DKD[47]	Randomized, double-blind, phase III, placebo-controlled, multinational study	• Age ≥ 18 years • DKD UACR 30-300 mg/g, eGFR 25-90 mL/min/1.73 m², and DR, or UACR 300-5000 mg/g and eGFR ≥ 60 mL/min/1.73m² • Maximal tolerated ACEi/ARB • Serum potassium ≤ 4.8 mmol/L	• Finerenone eGFR 25-60 mL/min/m² 10 mg/day (1 month later up titrated to 20 mg based on serum potassium and eGFR) eGFR ≥ 60 mL/min/m² 20 mg/day • Placebo	7437 people 3.4 years	*Primary composite outcomes:* death from CV causes, MI, nonfatal stroke, hospitalization for HF: • finerenone: 12.4% • placebo: 14.2% HR 0.87; 95% CI 0.76-0.98; $p = 0.03$ *Major secondary composite outcomes:* kidney failure, a sustained decrease of ≥40% in eGFR from baseline, or death from renal causes: • finerenone: 9.5% • placebo: 10.8% HR 0.87; 95% CI 0.76-1.01	Hyperkalemia (serum potassium ≥ 5.6 mmol/L): • finerenone: 10.8% • placebo: 5.3% *AKI: • finerenone: 2.5% • placebo: 2.7% Discontinuation due to hyperkalemia: • finerenone: 1.2% • placebo: 0.4%	Finerenone improved cardiovascular outcomes for patients with T2D and stage 2-4 CKD with moderately elevated albuminuria and those with stage 1 or 2 CKD experiencing severely elevated albuminuria. Although finerenone was linked to an increased risk of hyperkalemia compared with placebo, cases requiring discontinuation of the trial regimen due to hyperkalemia were rare.
FIDELITY[51]	Meta-analysis (FIDELIO-DKD and FIGARO-DKD)	• Age ≥ 18 years • DKD UACR 30-300 mg/g, eGFR 25-90 mL/min/1.73 m², and DR, or UACR 300-5000 mg/g and eGFR ≥ 60 mL/min/1.73 m² • Maximal tolerated ACEi/ARB • Serum potassium ≤ 4.8 mmol/L	•Finerenone eGFR 25-60 mL/min/m² 10 mg/day (1 month later up titrated to 20 mg based on serum potassium and eGFR) eGFR ≥ 60 mL/min/m² 20 mg/day •Placebo	13 026 people 3.0 years	*Major cardiovascular composite outcomes:* CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF failure: • finerenone: 12.7% • placebo: 14.4% HR 0.86; 95% CI 0.78-0.95; $p = 0.0018$. *Major renal composite outcomes:* kidney failure, a sustained ≥ 57% decrease in eGFR from baseline over ≥ 4 weeks, or renal death: • finerenone: 5.5% • placebo: 7.1% HR 0.77; 95% CI 0.67-0.88; $p = 0.0002$	Hyperkalemia (serum potassium ≥ 5.6 mmol/L): • finerenone: 8.8% • placebo: 3.8% *AKI: • finerenone: 3.4% • placebo: 3/6% Discontinuation due to hyperkalemia: • finerenone: 1.7% • placebo: 0.6%	Finerenone reduced the risk of clinically important cardiovascular and kidney outcomes versus placebo across the spectrum of CKD in patients with T2D.
Esaxerenone							
CS3150-B-J204[59]	Randomized, double-blind, phase II, placebo-controlled	• Age > 20 years • DKD UACR 45-300 mg/g eGFR ≥30 mL/min/1.73 m² • Treated with ACEi/ARB at highest usual dose for ≥3 months • HbA1c < 8.4% • Serum potassium 3.5-5.1 mmol/L for patients with eGFR ≥ 45 mL/min/1.73 m² or serum potassium 3.5-4.8 mol/L for patients with eGFR 30-45 mL/min/1.73 m²	• Esaxerenone 0.625, 1.25, 2.5, or 5 mg/day • Placebo	365 people 12 weeks	*Primary endpoint:* Change in UACR from baseline to week 12: • 0.625 mg: −21% • 1.25 mg: −38% ($p < 0.001$) • 2.5 mg: −50% ($p < 0.001$) • 5 mg: −56% ($p < 0.001$) • placebo: −7% *Secondary endpoints:* UACR remission rate (defined as UACR < 30 mg/g at the end of treatment and ≥ 30% decrease from baseline) at weeks 11 and 12: • 0.625 mg: −8% • 1.25 mg: −12% • 2.5 mg: −21% ($p = 0.004$) • 5 mg: −21% ($p = 0.004$) • placebo: −3%	Serum potassium increase: • 0.625 mg: 3% • 1.25 mg: 7% • 2.5 mg: 14% • 5 mg: 21% • placebo: 3% Discontinuation due to hyperkalemia: • 0.625 mg: 3% • 1.25 mg: 3% • 2.5 mg: 3% • 5 mg: 10% • placebo: 1%	Administering esaxerenone at dosages of 1.25, 2.5, and 5 mg/day for a duration of 12 weeks, in conjunction with an existing ACEi/ARB, significantly reduced UACR in patients with T2D and microalbuminuria.

ESAX-DN[60]	Randomized, double-blind, phase III, placebo-controlled	• Age ≥ 20 years • DKD UACR 45-300 mg/g eGFR ≥ 30 mL/min/1.73 m^2 • HbA1c < 8.4% • Serum potassium 3.5-5.1 mmol/L for patients with eGFR ≥ 45 L/min/1.73 m^2 or serum potassium 3.5-4.8 mmol/L for patients with eGFR 30-45 mL/min/1.73 m^2	• Esaxerenone 1.25 mg/day up titrated to 2.5 mg/day on basis of serum potassium levels • Placebo	455 people 52 weeks	*Primary endpoint:* Percentage of patients achieving UACR remission (UACR < 30 mg/g, 30% reduction from baseline): • Esaxerenone: 22% • Placebo: 4% difference 18%; 95% CI 12%-25%; $p < 0.001$ for esaxerenone versus placebo *Major secondary endpoint:* Change in UACR from baseline to end of treatment: • esaxerenone: −58% • placebo: +8% $p < 0.001$ for esaxerenone versus placebo	Serum potassium increase: • esaxerenone: 12% • placebo: 2% Serum potassium ≥ 6.0 or ≥ 5.5 mmol/L on 2 consecutive measurements: • esaxerenone: 9% • placebo: 2% Discontinuation due to hyperkalemia: • esaxerenone: 4.0% • placebo: 0.4%	Adding esaxerenone to existing ACEi/ARB therapy for patients with T2D and microalbuminuria significantly increased the likelihood of albuminuria returning to normal levels and reduced the progression of albuminuria to higher levels.
JapicCTI-173696[61]	Multicenter, single-arm, open-label phase III study	• Age ≥ 20 years • T2D and Hypertension • Received ACEi/ARB treatment for at least 3 months • 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 potassium levels • Single-arm study	56 people 28 weeks	*Primary endpoint:* Changes in UACR: UACR decreased by 54.6% (95% CI 46.9%-61.3%) on average from baseline (544.1 mg/g) to the end of treatment (246.8 mg/g) Percentage of UACRs <300 mg/g and ≥30% reduction: 51.8%	Hyperkalemia (serum potassium ≥ 5.5 or 6.0 mmol/L): 5.4% eGFR change at week 24: −8.3 mL/min/1.73 m^2	Adding esaxerenone to an ACEi/ARB leads to a reduction in UACRs in patients with T2D and a UACR ≥ 300 mg/g. Although esaxerenone increased serum potassium levels and decreased eGFR, these effects were reversible.
Apararenone							
MT-3995-J05/6[62]	Two-part phase II study Part A: dose–response, parallel-group, randomized, double-blind, placebo-controlled, multicenter study Part B: open-label, uncontrolled, extension study.	• Age 20-75 years • DKD UACR ≥ 50 mg/g in casual urine sample and median UACR 50-300 mg/g; and eGFR ≥ 30 mL/min/1.73m^2 • HbA1c ≤ 10.5% • SBP < 160 mmHg • DBP < 100 mmHg	Apararenone: Part A (dose–response study): 2.5, 5, or 10 mg or placebo orally once a day Part B (extension study): 2.5, 5, or 10 mg orally once a day	293 people 24 weeks (part A), a 28-week extension (part B)	*Primary endpoint:* From baseline to week 24, UACR (95% CI) as a percentage of baseline level at week 24: • 2.5 mg: 62.9% (54.6-72.5) • 5 mg: 50.8% (44.1-58.4) • 10 mg: 46.5% (40.4-53.5) • Placebo: 113.7% (98.5-131.2) $p < 0.001$ for all apararenone groups versus placebo *Secondary endpoints:* Percentage of patients with UACR remission (UACR<30 mg/g, ≥30% reduction from baseline) at 24 weeks (dose–response study) (95% CI): • 2.5 mg: 7.8% (2.6-17.3) • 5 mg: 29.0% (18.7-41.2) • 10 mg: 28.1% (17.6-40.8) • Placebo: 0.0% (0.0-5.6) * UACR remission maintained up to week 52 (extension study) Percent change from baseline in UACR at 52 weeks after randomization: • 2.5 mg: −37.3% • 5 mg: −56.1% • 10 mg: −55.3%	Part A (dose–response study) discontinuation due to hyperkalemia: • 2.5 mg: 2.7% • 5 mg: 0.0% • 10 mg: 4.1% • Placebo: 0.0% Part B (extension study) Serum potassium increased: • 2.5 mg: 0% • 5 mg: 4.7% • 10 mg 1.6%	Apararenone administered once daily for 24 weeks reduced UACR levels in patients with stage 2 DN. Additionally, administration of the treatment for 52 weeks was safe and well tolerated.

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor. AKI, acute kidney injury. ARB, angiotensin receptor blocker. CI, confidence interval. CKD, chronic kidney disease. CV, cardiovascular. DBP, diastolic blood pressure. DKD, diabetic kidney disease. DN, diabetic nephropathy. DR, diabetic retinopathy. eGFR, estimated glomerular filtration rate. HbA1c, glycated hemoglobin. HF, heart failure. HFrEF, heart failure with reduced left ventricular ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction. MI, myocardial infarction. MRAs, mineralocorticoid receptor antagonists. NT-proBNP, N-terminal pro-B-type natriuretic peptide. SBP, systolic blood pressure. T2D, type 2 diabetes. UACR, urine-albumin-to-creatinine ratio.

received 10 or 20 mg/day on the basis of their estimated glomerular filtration rate (eGFR) at screening (≤60 mL/min/1.73 m²). After 1 month, dosage escalation from 10 to 20 mg/day was recommended if serum potassium levels were ≤4.8 mmol/L and eGFR remained stable.

The FIDELIO-DKD trial, a large randomized, assessed finerenone's effect on renal function and kidney outcomes in individuals (*n*=5,734) with advanced DKD[46]. The trial had a median follow-up duration of 2.6 years. The incidence of the primary composite outcome—time to kidney failure, sustained eGFR decline > 40%, or renal death—was significantly lower with finerenone (17.8% vs 21.1%; hazard ratio [HR] 0.82; 95% confidence interval [CI] 0.73-0.93; *p*=0.001)[46]. The incidence of the major secondary composite outcomes—CVD death, nonfatal MI, nonfatal stroke, or HF hospitalization—was also reduced (HR 0.86; 95% CI 0.75-0.99; *p*=0.03). Adverse event rates were similar between groups (87.5% vs 87.5%), as were severe adverse event rates (31.9% vs 34.3%), although hyperkalemia was more frequent with finerenone (15.8% vs 7.8%), leading to a small percentage of treatment discontinuations (2.3% vs 0.9%)[46].

A prespecified subgroup analysis of the FIDELIO-DKD trial indicated that finerenone's influence on cardiorenal outcomes in patients with DKD was not affected by positive HF status at baseline[48]. Because symptomatic HFrEF was an exclusion criterion, patients with a history of HF in the FIDELIO-DKD study (comprising 7.7% of the total population) were diagnosed with either HF with mildly reduced ejection fraction or HFpEF. Over a median follow-up of 2.6 years, the effect of finerenone versus placebo on the composite cardiovascular outcome was consistent in patients with and without a history of HF (HR 0.73; 95% CI 0.50-1.06 and HR 0.90, 95% CI 0.77-1.04, respectively; $P_{interaction}$=0.33)[48]. Similarly, the renal outcome was consistent across groups (HR 0.79; 95% CI 0.52 to 1.20 with HF, and HR 0.83; 95% CI 0.73-0.94 without; $P_{interaction}$=0.83)[48]. Although post hoc and underpowered, these findings may suggest hypotheses. Notably, another prespecified analysis of the FIDELIO-DKD trial revealed that finerenone reduced new-onset atrial fibrillation or flutter (HR 0.71; 95% CI 0.53-0.94) [49].

The FIGARO-DKD trial, which involved a comparable cohort of patients (n=7,437) with less advanced CKD, focused on cardiovascular morbidity and mortality as the primary composite outcomes and DKD progression as a secondary outcome. After an average follow-up of 3.4 years, the incidence of the primary composite outcomes—CVD-related death, nonfatal MI, nonfatal stroke, and HF-related hospitalization—was significantly lower with finerenone than placebo (12.4% vs 14.2%; HR 0.87; 95% CI 0.76-0.98; *p*=0.03), primarily due to fewer HF hospitalizations (3.2% vs 4.4%; HR 0.71; 95% CI 0.56-0.90). The incidence of the secondary renal outcomes of kidney failure, substantial decline of ≥40% eGFR from baseline, or renal-related mortality was also lower in the finerenone group, although the difference was not statistically significant (9.5% vs 10.8%; HR 0.87; 95% CI 0.76-1.01) [47]. As in the FIDELIO-DKD trial, comparable incidences of adverse events (85.1% vs 85.5%) and serious adverse events (31.4% vs 33.2%) were observed across treatment groups. However, the rates of hyperkalemia (10.8% vs 5.3%) and discontinuation due to hyperkalemia (1.2% vs 0.4%) were higher in the finerenone group than in the placebo group[47]. Additionally, the results of a subanalysis revealed a significant reduction in new-onset HF (HR 0.68; 95% CI 0.50-0.93), and the results of an exploratory analysis indicated a greater benefit for patients on SGLT2is at baseline[50].

The FIDELITY pooled analysis combined data from the FIDELIO-DKD and FIGARO-DKD trials to provide robust estimates of finerenone's efficacy and safety across the spectrum of patients with DKD[51]. The results of the analysis verified

significant reductions in composite cardiovascular outcomes (HR 0.86; 95% CI 0.78-0.95) and composite renal outcomes (HR 0.77; 95% CI 0.67-0.88) among patients already on maximum tolerated RAAS inhibitor doses[51,52]. The observed cardiovascular benefits were primarily attributed to reduced HF hospitalizations (HR 0.78; 95% CI 0.66-0.92)[51]. Hyperkalemia, affecting 14% of patients, was the primary adverse effect, although the incidence of treatment discontinuation due to hyperkalemia was low (1.7%), suggesting that serum potassium monitoring and dose adjustments effectively managed hyperkalemic risks[51]. Notably, finerenone consistently improved renal outcomes compared with placebo, except for time to death from renal causes. Moreover, significant reductions were observed in sustained ≥57% eGFR from baseline (by 30%), ESRD (by 20%), eGFR below 15 mL/min/1.73 m² (by 19%), and kidney failure (by 16%)[51]. Therefore, the results of the FIDELITY analysis demonstrated finerenone's efficacy in improving cardiovascular and renal failure outcomes across a broad population of patients with DKD. Furthermore, in a subgroup analysis of patients with stage 4 CKD (eGFR <30mL/min/1.73m²), finerenone demonstrated significant cardiovascular benefits, consistent with the findings observed in the overall population, although no significant difference in composite renal endpoints was observed compared with placebo[53]. Finally, despite a higher hyperkalemia incidence (26%) in this subgroup, treatment discontinuation rates remained low at 3%[53]. On the basis of these trials, finerenone received FDA approval in July 2021 and EMA approval in February 2022 for its ability to reduce the risks of eGFR decline, ESRD, cardiovascular mortality, nonfatal MI, and HF hospitalization in patients with DKD[54].

Further evidence of the efficacy and safety of finerenone versus placebo in individuals with HF is expected from the ongoing finerenone trial to investigate efficacy and safety superior to placebo in patients with HF (FINEARTS-HF) trial, which is evaluating finerenone in patients with HF and LV ejection fraction ≥40%, to determine its efficacy in ejection fraction ranges not covered by current MRA guidelines[55]. Additionally, the ferinject assessment in patients with iron deficiency anemia and nondialysis-dependent CKD (FIND-CKD), an ongoing phase III trial, is investigating finerenone's effectiveness in preventing kidney disease progression in individuals with nondiabetic CKD[56].

Overall, the clinical data suggest finerenone is a promising treatment for cardiorenal diseases, providing BP-independent protection by inhibiting fibrosis, inflammation, and remodeling[23]. The FIGARO-DKD and FIDELIO-DKD trials demonstrate its benefits in DKD patients on ACEis or ARBs. Further research is needed to compare nonsteroidal and steroidal MRAs in HFrEF to evaluate efficacy and safety differences[23].

Cardiorenal benefits of other nonsteroidal MRAs in patients with DKD

5.1 Esaxerenone

Esaxerenone, another nonsteroidal MRA, shows potential for renal protection in preclinical studies and may be a beneficial adjunctive treatment for DKD[57,58]. For example, one Phase II trial (n=365) evaluated esaxerenone's efficacy and safety in patients with T2D and microalbuminuria (UACR of 45 to <300 mg/g) with or without hypertension treated with ACEis or ARBs and an eGFR of ≥30 mL/min/1.73m². After 12 weeks, esaxerenone at 1.25, 2.5, and 5 mg/d reduced UACR by 38%, 50%, and 56%, respectively, compared with 7% with placebo (all $p<0.001$)[59]. UACR remission rates were 21% for the 2.5- and 5-mg/d groups versus 3% for placebo (both $p<0.05$)[59]. Unlike finerenone, esaxerenone significantly reduced BP in a dose-dependent manner, with systolic BP reductions of between −3.7 and −9.7 mmHg versus −2.3 mmHg for placebo and diastolic BP reductions of between −1.5 and −4.1

mmHg versus −1.1 mmHg for placebo. The incidence of hyperkalemia, the most common drug-related adverse event, was also dose-dependent[59].

A phase III trial (*n*=455) examined esaxerenone's effects on UACR in individuals with T2D and albuminuria treated with RAAS inhibitors for at least 12 weeks[60]. The primary endpoint was the percentage of patients achieving UACR remission. Over 52 weeks, a significantly higher percentage of patients achieved UACR remission with esaxerenone than with placebo (22% vs 4%; 95% CI 12%-25%; $p<0.001$). Consistent with the results observed for finerenone[46], UACRs decreased within 4 months and were maintained at lowered levels thereafter[60]. Additionally, during the first 24 weeks of treatment with esaxerenone, eGFR gradually declined and stabilized for the remainder of the study. At the end of treatment, the average reduction in eGFR was approximately 10%, and the percentage of patients experiencing a reduction of ≥30% in eGFR on 2 consecutive occasions was 5% in the esaxerenone group and 2% in the placebo group[60]. Esaxerenone was also associated with higher UACR remission rates in those receiving concomitant SGLT2i (22% vs 4%) or dipeptidyl peptidase-4 inhibitors (23% vs 3%). Furthermore, BP reductions were notable with esaxerenone (systolic blood pressure −10 mmHg, 95% CI −12 to −9; diastolic blood pressure −5 mmHg, 95% CI −6 to −4). Adverse event rates were similar between groups (78% vs 77%)[60]. However, the incidence of hyperkalemia was significantly higher with esaxerenone than placebo (8.8% vs 2.2%), although discontinuations due to hyperkalemia were relatively low (4.0% vs 0.4%)[60]. In a Phase III finerenone study, a rapid eGFR decline was observed until month 24, and significant renal protective effects were observed in patients with higher baseline eGFR[46,48]. Nevertheless, the duration of follow-up in this trial may be insufficient to adequately observe the extent of this reduction.

A phase III trial in Japan (*n*=56) explored esaxerenone's effects on UACRs in patients with T2D and macroalbuminuria (UACR≥300 mg/g) receiving RAAS inhibitors[61]. Specifically, esaxerenone reduced UACRs by 54.6% (95% CI 46.9%-61.3%) on average from baseline (544.1 mg/g) to the end of the 28-week treatment (246.8 mg/g). Additionally, 51.8% of patients exhibited improvement in early nephropathy, suggesting esaxerenone may prevent nephropathy progression and ESRD. Moreover, systolic BP decreased from 143.3±9.4 to 132.6±12.4 mmHg, and diastolic BP decreased from 83.5±10.2 to 78.5±10.3 mmHg, with significant reductions of 10.7 (95% CI 8.2-13.2) and 5.0 (95% CI 3.4-6.7) mmHg, respectively. Finally, hyperkalemia occurred in 5.4% of patients in addition to decreased eGFR. Initiating esaxerenone at 1.25 mg/d and titrating to 2.5 mg/d after monitoring serum potassium levels may minimize these risks[61].

5.2 Apararenone

Apararenone, a highly selective nonsteroidal MRA, is associated with promising improvements in efficacy and safety[62]. In a randomized Phase II trial and open-label extension study involving patients with DKD (*n*=293), apararenone treatment (between 2.5 and 10 mg) led to a dose-dependent decrease in average UACRs of between 37% and 55% over 24 weeks, whereas the placebo group experienced a 14% increase ($p<0.001$ for all apararenone groups), regardless of concomitant ACEi/ARB use)[62]. At 24 weeks, UACR remission rates in placebo and apararenone 2.5, 5, and 10 mg groups were 0.0%, 7.8%, 29.0%, and 28.1%, respectively. Additionally, apararenone was associated with a reversible reduction of between 5% and 10% in eGFR, possibly due to hemodynamic effects. Throughout the trial, apararenone was associated with dose-dependent BP reductions in patients with hypertension at baseline but not in those without. Specifically, patients with an initial systolic BP of 130 mmHg or higher experienced a decrease in systolic BP ranging from −7.5 to

−13.3 mmHg when treated with apararenone versus −5.2 mmHg for placebo. Similarly, in patients with a diastolic BP of 80 mmHg or higher at baseline, diastolic BP declined by between −3.5 and −8.7 mmHg (vs −4.3 mmHg for placebo). The anti-hypertensive effects of apararenone were more pronounced in patients with hypertension who were also receiving ACEi or ARB therapy, with systolic BP reductions of −9.6 versus −6.9 mmHg and diastolic BP reductions of −4.3 versus −2.5 mmHg for the 10 mg dose. Additionally, during the first 12 weeks of treatment with apararenone, patients experienced a median increase in serum potassium levels of between 0.1 and 0.3 mmol/L from baseline, followed by stabilization or a decrease. Over the 24 weeks of the trial, only 5 patients (2.3%) discontinued treatment because of hyperkalemia[62].

Future perspective: Integrating non-steroidal MRAs with SGLT2is or GLP-1 RAs to mitigate the risk of DKD

SGLT2is were initially developed to manage metabolic processes in individuals with T2D[63]. SGLT2is have since become a first-line treatment for DKD, offering blood-glucose-lowering, cardiorenal protective effects without increasing hyperkalemia risk[64-66]. Similarly, GLP-1 RAs confer cardiorenal benefits, such as reduced BP, lower albuminuria, and slower eGFR decline, making them a recommended first-line therapy with SGLT2is for patients with T2D and CVD[67]. Despite the availability of these therapies, morbidity and mortality from cardiorenal diseases linked to DKD remain challenging to reduce. MRAs, with their anti-inflammatory and antifibrotic effects, complement the natriuretic and antiedematous properties of SGLT2i's and GLP-1RAs[28], and may improve cardiorenal outcomes in patients with DKD.

A crossover trial of dapagliflozin and eplerenone demonstrated that patients who did not respond to monotherapy often exhibited reduced albuminuria under combined treatment[68]. The BP-lowering effects of MRAs and SGLT2is likely contributed to this reduction[68]. However, the dapagliflozin and prevention of adverse outcomes in HF (DAPA-HF) trial, which evaluated dapagliflozin in patients with HFrEF, revealed similar efficacy and safety regardless of baseline MRA use[69]. Similarly, in the dapagliflozin in patients with CKD (DAPA-CKD) trial, which included 229 patients (5.3%) receiving steroidal MRAs at baseline, the composite renal outcomes—sustained ≥50% eGFR decline, ESRD, renal or cardiovascular death, or hyperkalemia—were not significantly affected by MRA use[70]. Additionally, the results of a network meta-analysis of 17 studies (n=34,412) revealed that SGLT2i and MRA combination therapy produced greater reductions in UACRs than did SGLT2is, MRAs, or placebo alone (mean differences [95% CI]: −34.19 [−27.30 to −41.08], −32.25 [−24.53 to −39.97], and −65.22 [−57.97 to −72.47], respectively; p<0.001 in each comparison)[71]. Moreover, treatment with SGLT2is and MRAs was associated with a greater reduction in systolic BP than treatment with SGLT2is, MRAs or placebos alone (mean difference [95% CI]: −5.80 [−9.53 to −2.06], −5.90 [−9.64 to −2.17] and −9.13 [−12.87 to −5.39], respectively; p<0.001 in each comparison)[71].

In the FIDELITY pooled analysis, 877 patients (6.7%) received SGLT2is, and finerenone's cardiovascular outcomes were similar regardless of SGLT2i use, indicating that SGLT2is did not alter finerenone's effect on the primary endpoint.[51] Additionally, the results of a subgroup analyses from the FIDELIO-DKD trial revealed that finerenone's albuminuria-lowering effects were consistent irrespective of whether patients received SGLT2is[72]. However, SGLT2i users experienced a lower incidence of hyperkalemia than those who did not receive these medications, suggesting that adding SGLT2is to treatment regimens may reduce finere-

none-associated hyperkalemia[73].

One study pooled data from 2 SGLT2i trials (the canagliflozin cardiovascular assessment [CANVAS] and canagliflozin and renal events in diabetes with established nephropathy clinical evaluation [CREDENCE]), 2 nonsteroidal MRA trials (FIDELIO-DKD and FIGARO-DKD), and 8 GLP-1 RA trials to evaluate the effects of combination therapy versus conventional care (RAAS blockade and traditional risk factor control) on cardiovascular, kidney, and mortality outcomes in individuals with T2D and albuminuria[74]. The combination of nonsteroidal MRAs and SGLT2is significantly reduced major adverse cardiovascular events (MACEs), HF hospitalization, and cardiovascular death, with HRs of 0.75 (95% CI 0.65-0.87), 0.50 (0.39-0.64), and 0.74 (0.60-0.91), respectively. CKD progression and all-cause mortality were also reduced, with HRs of 0.49 (95% CI 0.38-0.61) and 0.76 (0.64-0.90)[64]. Moreover, the combination of SGLT2is, GLP-1 RAs, and nonsteroidal MRAs lowered MACE risk (HR 0.65; 95% CI 0.55-0.76), with a 3-year absolute risk reduction of 4.4% (95% CI 3.0-5.7) and a number needed to treat of 23 (95% CI 18-33). Similarly, compared with conventional care, the combination of SGLT2is, GLP-1 RAs, and nonsteroidal MRAs significantly reduced CKD progression and all-cause mortality (HRs of 0.42 [95% CI 0.31-0.56] and 0.67 [95% CI 0.55-0.80], respectively)[74]. These findings suggest that combining nonsteroidal MRAs, SGLT2is, and GLP-1 RAs may offer substantial cardiorenal benefits for individuals with T2D and moderate albuminuria[74]. However, additional research is required to verify the long-term effects of these combinations on cardiorenal outcomes in patients with DKD.

Potential mechanisms of cardiorenal benefits of finerenone

The mineralocorticoid receptor, found in the distal nephron and various cell types, is activated by aldosterone, driving inflammation, oxidative stress, metabolic disorders, and fibrosis[75]. Finerenone provides therapeutic benefits for diabetes and related cardiorenal diseases through mechanisms affecting adipose tissue, the heart, and the kidneys (Figure 1).

7.1 Natriuresis and fluid homeostasis

Aldosterone plays a crucial role in the distal nephron by promoting sodium reabsorption and water retention and facilitating potassium and magnesium excretion to regulate extracellular volume and BP[76]. Mineralocorticoid receptor activation in renal epithelial cells increases the expression of epithelial sodium channel subunits and upregulates serum- and glucocorticoid-regulated kinase 1 (Sgk1), which enhances sodium transport in epithelial tissues. Sgk1 phosphorylates Nedd4-2, which regulates cell sodium channel turnover, preventing it from binding to cells and promoting sodium influx[77].

Natriuresis—a natural process that lowers blood sodium levels—benefits individuals with cardiorenal diseases by reducing BP. In a preclinical study, nonsteroidal MRAs such as finerenone provided dose-dependent natriuretic effects, protecting against cardiorenal damage[20]. The activation of neurohumoral mechanisms, such as RAAS, the sympathetic nervous system, and vasopressin, drives sodium retention and extracellular volume overload, key contributors to chronic HF and renal failure. Mineralocorticoid receptor antagonism can inhibit these processes[17]. For example, in a murine model of CKD progression associated with T2D, finerenone effectively reduced Sgk1 levels[78].

Sodium retention in skin reservoirs may also trigger inflammation[79]. Sodium accumulation in the skin, particularly with aging, may promote proinflammatory immune activity and suppress anti-inflammatory responses[79]. Additionally, one study reported that patients on dialysis with higher muscle and skin sodium levels exhibited elevated plasma interleukin (IL)-6 and high-sensitivity C-reactive

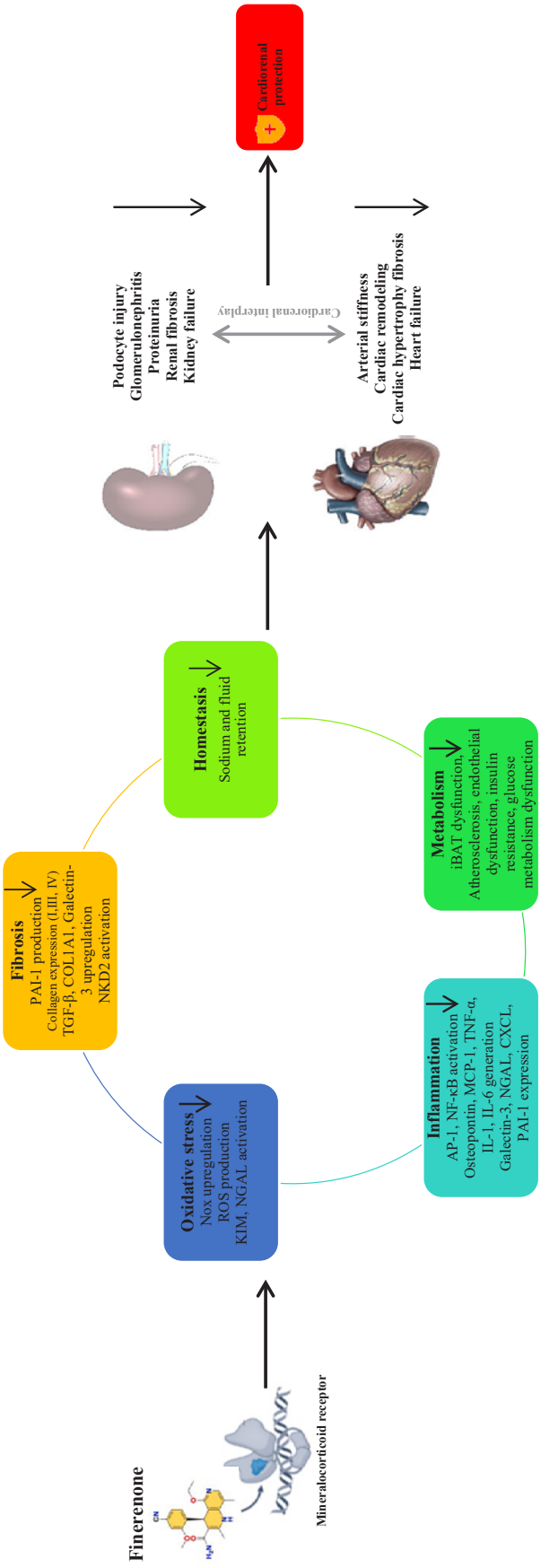


Figure 1. Potential mechanisms of cardiorenal protection by finerenone in diabetic kidney disease

Abbreviations: AP-1, activator protein-1. COL1A1, collagen type I 1 chain. iBAT, interscapular brown adipose tissue. IL, interleukin. KIM-1, kidney injury molecule 1. MCP-1, monocyte chemoattractant protein-1. MRA, mineralocorticoid receptor antagonists. NGAL, neutrophil gelatinase-associated lipocalin. NF-κB, nuclear factor-κB. PAI-1, plasminogen activator inhibitor-1. TNF-α, tumor necrosis factor-α.

protein compared with controls without kidney disease[80], suggesting sodium regulates immune function. Hence, reducing local sodium levels by blocking mineralocorticoid receptors may offer therapeutic benefits for autoimmune conditions and CVD[79].

7.2 Metabolic disorders

DKD—a predominant contributor to ESRD—is caused by various metabolic disturbances affecting renal function[81]. The aldosterone–mineralocorticoid receptor system is vital for metabolism, and its overactivation is linked to impaired glucose metabolism, atherosclerosis, and endothelial dysfunction[82]. In addition to their protective effects against traditional indications such as HF and hypertension, MRAs exert protective effects on adipose tissue in individuals with diabetes and obesity by preventing glucose metabolism dysfunction[83]. For example, in mice models of high-fat-diet-induced obesity, finerenone activated brown adipose tissue through the adenosine-5-monophosphate-activated-protein-kinase-adipose-triglyceride-lipase-uncoupling protein-1 signaling pathway, protecting against adverse metabolic parameters[84]. Similarly, in mouse models of ovariectomy-induced metabolic profile alterations and cardiovascular dysfunction, finerenone reduced weight gain, improved insulin resistance, lowered glucose tolerance, and enhanced cardiovas-

cular function and exercise capacity[85]. These findings suggest that finerenone may improve glycemic control and prevent cardiorenal complications in individuals with diabetes and obesity by directly affecting adipocytes. Nonsteroidal MRAs may thus also benefit patients with obesity and related metabolic comorbidities[86].

7.3 Inflammation

Inflammation drives DKD progression, making its prevention key to MRAs' benefits. Specifically, mineralocorticoid receptor activation in immune cells fuels systemic and local inflammation, causing fibrosis and tissue damage[87]. This damage increases the expression of proinflammatory cytokines such as osteopontin, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), IL-1, and IL-6[88,89]. Mineralocorticoid receptor activation also promotes the transcription of genes associated with inflammation and facilitates macrophage infiltration, enhancing the DNA binding activity of transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1[87]. However, a preclinical model demonstrated that nonsteroidal MRAs can inhibit the transcription of proinflammatory genes in the kidney, heart, and other organs[17].

Cardiomyocyte-specific mineralocorticoid receptor knockdown in various animal models has highlighted the role of mineralocorticoid receptor signaling in the initiation and progression of cardiac inflammation[90-92]. Specifically, mice lacking mineralocorticoid receptors in cardiomyocytes exhibited a diminished early innate inflammatory response, suppressed overall inflammatory response, and reduced recruitment of monocytes, macrophages, and lymphocytes[90]. By contrast, mineralocorticoid receptor activation-maintained inflammation through the NF-κB pathway, promoting proinflammatory cytokine expression[93]. Additionally, in Dahl salt-sensitive rats fed a high-salt diet, esaxerenone treatment significantly downregulated TNF-α, IL-6, and CXCL-8, key regulators of cardiac inflammation, demonstrating the beneficial effects of nonsteroidal MRAs[94]. Moreover, in a murine model of isoproterenol-induced inflammation and fibrosis, finerenone significantly inhibited cardiac macrophage infiltration and reduced cardiac mRNA expression of galectin-3[95], a protein associated with renal diseases such as DKD[96]. Finerenone also attenuated the synthesis of neutrophil gelatinase-associated lipocalin (NGAL), a target of mineralocorticoid receptor activation involved in mediating cardiac damage following an MI in both human cardiac fibroblasts and mouse models[97]. Nevertheless, further studies are necessary to clarify the role of nonsteroidal MRAs in regulating cardiac inflammation.

In CKD, nonsteroidal MRAs partially protect against renal damage through anti-inflammatory mechanisms. For example, in a murine model of renal ischemia-reperfusion injury, finerenone increased IL-4 receptor expression, promoting M2 macrophage polarization to potentially slow CKD progression[93]. Finerenone also reduced the messenger RNA (mRNA) expression of TNF-α and the M1 macrophage marker IL-1β[93]. Additionally, in a murine model of antiglomerular basement membrane glomerulonephritis, BR-4628—a precursor to finerenone—provided renal protection by reducing the accumulation of glomerular macrophages, T-cells, and proinflammatory and profibrotic molecules, leading to improved renal function and reduced fibrosis[98]. Notably, this protective effect was linked to a significant reduction in kidney gene expression of proinflammatory (chemokine ligand 2, TNF-α, interferon gamma) and profibrotic (collagen I, fibronectin) molecules. This inhibition reduced the deterioration of renal function, tubular damage, and the development of renal fibrosis[98]. Moreover, in a murine model of uninephrectomy and deoxycorticosterone-acetate-salt exposure, the administration of finerenone downregulated kidney

retinoid-related orphan receptor gamma t-positive T-cells, an outcome associated with a significant reduction in UACR, indicating finerenone's substantial renal protective effects[99]. Furthermore, both NGAL and MCP-1 contribute to the progression of CKD in humans[17]. Finerenone lowered MCP-1 levels and renal NGAL expression in a deoxycorticosterone-acetate-salt model of cardiorenal damage, reducing inflammation and tubular injury markers[17]. Another study indicated that the proinflammatory cytokine osteopontin may be involved in the progression of CKD, noting elevated plasma concentrations of osteopontin in the early stages of CKD[100]. Finerenone also reduced the expression of renal osteopontin in a rat model of CKD induced by deoxycorticosterone-acetate-salt administration[101]. Finally, in a murine model of CKD progression associated with T2D (uninephrectomized mice with T2D fed a high-salt diet), finerenone protected against podocyte injury by reducing the expression of fibronectin and inflammatory markers such as MCP-1 and plasminogen activator inhibitor-1 (PAI-1) in the glomeruli[78]. Nevertheless, further studies are required to elucidate the effects of nonsteroidal MRAs in regulating renal inflammation in individuals with DKD.

7.4 Oxidative stress

Studies involving MRAs and models with cell-specific mineralocorticoid receptor knockout or overexpression indicate the roles of aldosterone- and mineralocorticoid receptor-mediated oxidative stress in cardiac damage[102]. Notably, mineralocorticoid receptor activation increases the regulation of nicotinamide adenine dinucleotide phosphate oxidase (Nox) subunits in a ligand-dependent manner, which drive reactive oxygen species (ROS) production[103]. Animal studies have investigated ROS in the heart and mineralocorticoid receptor antagonism. For example, in Zucker fatty rats, finerenone enhanced myocardial perfusion, reduced oxidative stress, increased nitric oxide bioavailability, and induced long-term structural changes[104]. Additionally, Dahl salt-sensitive rats fed a high-salt diet exhibited a strong immunoreactivity for the 4-hydroxynonenal upregulated Nox components $gp47^{phox}$ and $p22^{phox}$ and increased lipid peroxidation indicated by sharply increased levels of malondialdehyde in cardiac tissues, whereas treatment with esaxerenone significantly downregulated the expression of these genes[94]. Additionally, a mouse model of cardiac fibrosis induced by isoproterenol injection revealed that the administration of finerenone reduced Nox activity in RacET transgenic mice exhibiting constitutive activation of Rac1 in myocardial tissues[95]. Finally, in a postmenopausal ovariectomized mouse model, the administration of finerenone reversed superoxide-induced endothelial dysfunction at the level of the coronary arteries[85].

Mineralocorticoid receptor overactivation in the kidneys increases ROS levels by upregulating Nox, producing superoxide that damages vasculature and tubules, while hydrogen peroxide disrupts preglomerular function[17]. For example, in a T2D, high-salt-intake KK-Ay mouse model, levels of renal oxidative stress markers were elevated, specifically Nox activity and mRNA levels of Nox subunits; esaxerenone administration mitigated this salt-induced oxidative stress[105]. Additionally, ischemia-induced renal injury linked to oxidative stress alters the endothelin B receptor, reducing endothelial nitric oxide synthase activation; the nonsteroidal MRA BR-4628 exhibited protective effects against such renal dysfunction and tubular injury in a rat model of renal ischemia/reperfusion injury[106].

Arterial stiffness is an independent predictor of cardiovascular events linked to the onset of DKD[86]. Albuminuria development is linked to arterial stiffness, influenced by elastin changes, oxidative stress, elevated matrix metalloproteinase (MMP)-9 activity, and endothelial dysfunction. An in vivo CKD study conducted in Munich Wistar Frömter rats dem-

onstrated that the amelioration of intrinsic arterial stiffness through finerenone treatment was accompanied by modifications in elastin organization, the reinstatement of MMP-2 and MMP-9 activities, and a decrease in oxidative stress[107]. Additionally, deleting the mineralocorticoid gene in smooth muscle cells or administering finerenone reduced oxidative stress production[108]. Furthermore, finerenone inhibited the expression of kidney injury markers, kidney injury molecule 1, and NGAL in a mouse model[108]. Oxidative stress in the cytoplasm and mitochondria has also been implicated in CKD in the absence of diabetes, and selective nonsteroidal MRAs may mitigate these oxidative processes. Nevertheless, few studies have assessed the effects of oxidative stress on diabetic kidney injury, and additional studies are required to elucidate the involvement of oxidative stress in DKD[86].

7.5 Fibrosis

Mineralocorticoid receptor overactivation contributes to fibrosis by stimulating collagen expression and increasing PAI-1 production, which inhibits plasmin and leads to extracellular matrix buildup. The prevention of fibrosis is a key benefit of MRAs for individuals with CVD and DKD.

Aldosterone's profibrotic effects and the antifibrotic effects of MRAs are well established[28]. Extensive preclinical evidence has indicated that nonsteroidal MRAs may exert cardioprotective effects by reducing fibrosis. For example, finerenone significantly downregulated proinflammatory and profibrotic biomarker genes, including PAI-1, monocyte chemoattractant protein-1, osteopontin, and MMP-2, compared to deoxycorticosterone-acetate-salt treatment in rats [101]. Moreover, in a post-MI HF mouse model, 2 months of finerenone treatment improved LV compliance and reduced interstitial fibrosis[109]. Additionally, in a transgenic mouse model of LV and left atrial fibrosis, finerenone reduced transforming growth factor beta (TGF-β) mRNA expression and myocardial fibrosis after 5 months[110]. Myocardial fibrosis was also reduced following finerenone treatment[110]. Furthermore, in a murine model of isoproterenol-induced cardiac fibrosis, finerenone significantly reduced cardiac collagen accumulation and mitigated increases in tenascin-X, a protein involved in collagen regulation[95]. Finally, finerenone attenuated the upregulation of TGF-β, collagen type I 1 chain (COL1A1), and galectin-3 caused by isoproterenol[95].

Mineralocorticoid receptors contribute to atrial fibrosis and atrial fibrillation. Research shows increased hydroxyproline—a fibrosis marker—in affected hearts. Finerenone reduces fibrosis by lowering connective tissue growth factor expression, inhibiting remodeling, and blocking collagen cross-linking[110].

Renal fibrosis contributes to CKD and renal failure by damaging tubules and blood vessels. Preclinical models show mineralocorticoid receptors play a role, while finerenone helps reduce fibrosis. For example, in a chronic-hyperaldosteronism-induced end-organ injury model, finerenone provided dose-dependent protection against glomerular, tubular, and vascular injury, with the greatest effect at 10 mg/kg/day[101]. Additionally, finerenone exhibited direct antifibrotic properties that reduced myofibroblast and collagen deposition, renal PAI-1, and naked cuticle homolog 2 (NKD2) expression in a mouse model of progressive kidney fibrosis, even at dosages independent of BP[111]. Moreover, NKD2 is a specific marker for myofibroblasts in human renal fibrosis[112]. Furthermore, in a mouse model of CKD with unilateral, ischemia/reperfusion-induced tubulointerstitial fibrosis, finerenone markedly decreased the extent of renal fibrosis by reducing the expression of the profibrotic cytokine TGF-β and fibronectin[93]. Similarly, in a rat model of chronic CKD with renal dysfunction, increased proteinuria, and substantial tubule-interstitial fibrosis, finerenone administration restricted renal fibrosis

and collagen deposition, as assessed through histopathological scoring[15]. Finally, in a rat model of cardiorenal syndrome and hypertension, finerenone reduced renal fibrosis and the expression of profibrotic COL1A1 in renal tissue[113].

These preclinical studies suggest finerenone offers cardiorenal benefits by reducing fibrosis and highlighting the interplay of inflammation and oxidative stress in DKD. However, limited research in diabetes models emphasizes the need for further investigation into their antifibrotic effects in DKD.

Conclusions

DKD is a growing global public health concern that is strongly associated with a high incidence of CVD and ESRD. Nonsteroidal MRAs, a novel class of pharmaceutical agents, exhibit high potency and selectivity with fewer off-target side effects compared with steroidal MRAs. These agents effectively reduce UACRs in individuals with DKD. Clinical trials such as FIDELIO-DKD and FIGARO-DKD also demonstrate finerenone's ability to slow renal disease progression and mitigate adverse cardiovascular events compared with placebo. Consequently, finerenone was approved by the FDA in July 2021 and the EMA in February 2022 to treat DKD, prevent disease progression, and improve cardiovascular outcomes.

MRAs achieve these effects through anti-inflammatory, antioxidant, and antifibrotic mechanisms, offering benefits beyond glucose and BP control. Evidence suggests that combining SGLT2is and nonsteroidal MRAs may provide synergistic renal protection, although further clinical data are required to verify this hypothesis. Proactively monitoring serum potassium levels and adjusting dosages during treatment with nonsteroidal MRAs such as finerenone is essential. Future studies should identify ideal candidates for therapy, explore novel treatment strategies, and evaluate the benefits of combining nonsteroidal MRAs with SGLT2is or GLP-1 RAs to improve cardiorenal outcomes in individuals with DKD.

Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

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非類固醇性礦物皮質激素受體拮抗劑（Finerenone）在糖尿病腎臟病中的應用

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摘要

糖尿病腎臟病變影響著近半數的糖尿病患者，是全球慢性腎臟疾病的主要成因。傳統上，腎素 - 血管張力素系統抑制劑在糖尿病腎臟病變的治療中扮演著重要角色。近年來，鈉 - 葡萄糖共同轉運蛋白 2 抑制劑在臨床試驗中已顯示出令人鼓舞的腎臟保護療效。然而，儘管腎素 - 血管張力素系統抑制劑與鈉 - 葡萄糖共同轉運蛋白 2 抑制劑的合併使用，腎臟疾病之併發症仍然普遍存在著，同時這些藥物的使用也只能延緩腎臟衰竭的進展。在糖尿病之下，礦物皮質素受體調節失調會加劇心血管和腎臟之病變。雖然類固醇礦物皮質素受體拮抗劑能降低糖尿病腎臟病變患者多重心腎的益處，但同時也增加了高鉀血症等不良反應的風險。非類固醇礦物皮質素受體拮抗劑擁有獨特的藥理特性，可提供心腎保護作用，同時將高鉀血症的風險最小化。這些新型藥物正被用於探討心臟衰竭治療的成效，以及探索其與鈉 - 葡萄糖共同轉運蛋白 2 抑制劑的合併是否有協同效應，以期能為心腎疾病提供多種潛在的治療方式。本研究綜合回顧非類固醇礦物皮質素受體拮抗劑 finerenone 在心腎保護中的效益，探索其可能之分子機制以及其運用在糖尿病腎臟病變患者治療的可行性。此外，本研究同時探討了以非類固醇性礦物質皮質激素受體拮抗劑結合鈉 - 葡萄糖協同轉運蛋白 2 抑制劑或胰高血糖素樣肽 -1 受體促效劑作為策略，以降低糖尿病腎臟病風險的效果。