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Review

What's Missing In Diabetes Treatment? A Novel Agent Finerenone?

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Abstract

Diabetic kidney disease represents a leading cause of chronic kidney disease and end-stage renal disease worldwide. The pathogenesis is primarily driven by persistent hyperglycemia, which induces oxidative stress, low-grade chronic inflammation, and activation of profibrotic signaling pathways. These mechanisms promote mesangial expansion, podocyte injury, and tubular epithelial-to-mesenchymal transition, culminating in glomerulosclerosis and tubulointerstitial fibrosis. Fibrosis is a hallmark of progressive diabetic kidney disease, characterized by excessive deposition of extracellular matrix components, leading to structural distortion and progressive decline in glomerular filtration rate.

Proteinuria, a key clinical manifestation of diabetic kidney disease, reflects dysfunction of the glomerular filtration barrier and serves as both a marker and mediator of disease progression. Filtered proteins exert direct cytotoxic effects on proximal tubular epithelial cells, inducing proinflammatory and profibrotic responses that exacerbate tubulointerstitial injury and accelerate fibrosis.

Despite standard-of-care therapy with renin-angiotensin-aldosterone system blockade, a significant proportion of patients exhibit residual proteinuria and progressive renal fibrosis, underscoring the need for additional therapeutic interventions. Mineralocorticoid receptor overactivation has emerged as a critical driver of renal inflammation and fibrosis in diabetic kidney disease. Finerenone, a novel non-steroidal, selective mineralocorticoid receptor antagonist, has demonstrated potent antifibrotic and antiproteinuric effects by attenuating the transcription of proinflammatory and profibrotic mediators, including transforming growth factor-beta and connective tissue growth factor. Finerenone reduces macrophage infiltration, extracellular matrix accumulation, and fibrosis in glomerular and tubulointerstitial compartments.

The landmark FIDELIO-DKD and FIGARO-DKD trials established the efficacy of finerenone in reducing albuminuria and slowing the progression of kidney disease in patients with type 2 diabetes and chronic kidney disease. By directly targeting key pathophysiological mechanisms of renal fibrosis and proteinuria, finerenone offers a novel and evidence-based therapeutic strategy to mitigate kidney disease progression in this high-risk population.

Keywords: Finerenone, Diabetes Mellitus, Nephropathy, Proteinuria, Hyperkalemia

INTRODUCTION

Diabetes mellitus is a complex metabolic disease with a high global prevalence and represents a leading cause of chronic kidney disease (CKD) and cardiovascular morbidity and mortality. Despite intensive glycemic control, many patients experience progressive microvascular and macrovascular complications, including diabetic nephropathy and cardiovascular disease, which substantially contribute to increased mortality and morbidity rates (1,2). Traditional management strategies have focused primarily on glycemic control through the use of oral antidiabetic agents and insulin therapy. However, although these approaches effectively reduce hyperglycemia, they often fail to prevent or adequately slow the progression of diabetes-related end-organ complications, particularly renal and cardiovascular outcomes (3).

The pathophysiology of diabetic complications

is multifactorial and involves chronic low-grade inflammation, oxidative stress, and endothelial dysfunction. These mechanisms drive the progression of both microvascular complications—such as diabetic nephropathy and retinopathy—and macrovascular complications, including ischemic heart disease and stroke (1,2). In particular, persistent oxidative stress and inflammation activate fibrotic signaling pathways that contribute to mesangial matrix expansion, podocyte injury, and tubulointerstitial fibrosis, ultimately resulting in glomerulosclerosis and progressive decline in glomerular filtration rate (4).

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have emerged as a cornerstone therapy in diabetic kidney disease, offering significant cardio-renal protection independent of glycemic control. These agents have been shown to reduce the risk of hospitalization for heart failure and slow the progression of CKD, irrespective of preexisting atherosclerotic cardiovascular disease or heart failure history (5). Current guidelines recommend initiating SGLT-2 inhibitors in patients with type 2 diabetes mellitus and albuminuria—defined as a urine albumin-to-creatinine ratio (UACR) >300 mg/g—particularly when estimated glomerular filtration rate (eGFR) is greater than 30 mL/min/1.73 m², to reduce the risk of both cardiovascular events and CKD progression (6).

Nevertheless, despite optimized renin-angiotensin-aldosterone system (RAAS) blockade and SGLT-2 inhibitor therapy, many patients exhibit persistent albuminuria and progressive kidney fibrosis, highlighting the need for additional therapeutic interventions. One important mechanism contributing to this residual risk is the phenomenon of aldosterone breakthrough, whereby chronic RAAS blockade becomes insufficient to suppress plasma aldosterone levels. Elevated aldosterone promotes overactivation of mineralocorticoid receptors, which plays a central role in mediating renal inflammation, oxidative stress, and fibrogenesis (7,8).

Mineralocorticoid receptor antagonists (MRAs) have demonstrated efficacy in attenuating these pathological processes by blocking mineralocorticoid receptor activation. MRAs inhibit the transcription of key pro-inflammatory and pro-fibrotic mediators, including transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), osteopontin, platelet-derived growth factor (PDGF), plasminogen activator inhibitor-1 (PAI-1), and CC-chemokine ligand 2 (CCL2). This results in reduced macrophage infiltration, decreased collagen deposition, and suppression of extracellular matrix accumulation within both glomerular and tubulointerstitial compartments (9). In addition, MRAs have been shown to attenuate fibroblast activation, reactive oxygen species generation, mesangial expansion, and glomerular hypertrophy—key pathological features of diabetic nephropathy (10).

Clinical studies have established the role of MRAs as adjunctive therapy to RAAS inhibitors and SGLT-2 inhibitors in diabetic nephropathy. Beyond their nephroprotective effects, MRAs confer additional cardiovascular benefits, particularly in reducing the risk of hospitalization for heart failure, a common comorbidity among diabetic patients (11).

Among MRAs, finerenone has emerged as a novel non-steroidal selective antagonist with high affinity for the mineralocorticoid receptor. Finerenone exhibits a more favorable safety profile compared to traditional steroidal MRAs, such as spironolactone, with a lower incidence of hyperkalemia and fewer off-target effects, including gynecomastia (12,13). These properties make finerenone a suitable option for patients with diabetic nephropathy and reduced kidney function. Current guidelines recommend the use of finerenone in patients with diabetic nephropathy who are at high risk of cardiovascular events or CKD progression, particularly when serum potassium levels are ≤4.8 mmol/L or in cases where SGLT-2 inhibitors are contraindicated or not tolerated (14).

Finerenone has demonstrated significant reductions in albuminuria and slowed CKD progression in patients with type 2 diabetes mellitus and albuminuric CKD, as evidenced by the FIDELIO-DKD and FIGARO-DKD trials (15,16). Through its potent anti-inflammatory and anti-fibrotic effects, finerenone offers a mechanistically distinct and evidence-based approach for reducing residual albuminuria and mitigating renal fibrosis in diabetic kidney disease.

METHODS

This review was designed as a systematic narrative review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to comprehensively evaluate the efficacy, safety, and clinical application of finerenone, a non-steroidal mineralocorticoid receptor antagonist, in patients with type 2 diabetes mellitus and chronic kidney disease, with an emphasis on renal and cardiovascular outcomes.

Data Sources and Search Strategy

A comprehensive search of the literature was conducted using four major electronic databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Cochrane Library

The search was performed for studies published from January 2010 to March 2025, using a combination of controlled vocabulary (MeSH terms) and free-text

keywords. The following search terms were used in various combinations:

"Finerenone", "Mineralocorticoid receptor antagonist", "Non-steroidal MRA", Diabetic kidney disease", "Chronic kidney disease", "Albuminuria", "Proteinuria" "Cardiorenal outcomes", "Cardiovascular disease", "Heart failure", "SGLT-2 inhibitors", RAAS blockade"

Inclusion Criteria

- Study type: Randomized controlled trials (RCTs), meta-analyses, systematic reviews, and large observational studies.
- Population: Adult patients (≥18 years) with type 2 diabetes mellitus and chronic kidney disease (CKD), with or without cardiovascular disease.
- Interventions: Studies evaluating finerenone as monotherapy or in combination with other agents (e.g., RAAS blockers, SGLT-2 inhibitors).
- Outcomes: Studies reporting renal endpoints (e.g., eGFR decline, albuminuria/proteinuria reduction, end-stage renal disease) and/or cardiovascular outcomes (e.g., cardiovascular death, hospitalization for heart failure).

Exclusion Criteria

- Case reports, case series, editorials, letters to the editor, conference abstracts, and non-peer-reviewed articles.
- Preclinical or animal studies not directly translatable to clinical outcomes.
- Studies exclusively focused on non-diabetic kidney disease, unless relevant to mineralocorticoid receptor mechanism of action.

RENAL OUTCOMES

The renoprotective effects of finerenone have been clearly demonstrated in two pivotal, large-scale, randomized, double-blind, placebo-controlled trials: the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) study (14,15) (**Table 1**).

The FIDELIO-DKD trial was specifically designed to evaluate the impact of finerenone on renal and cardiovascular outcomes in patients with type 2 diabetes mellitus and chronic kidney disease. The study enrolled patients with stage 3 to 4 chronic kidney disease, defined by an estimated glomerular filtration rate (eGFR) of 25 to 60 mL/min/1.73 m² and a urine albumin-to-creatinine ratio (UACR) greater than 300 mg/g, all of whom were receiving optimized renin-angiotensin-aldosterone system (RAAS) blockade therapy with either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB). Over a median follow-up period of 2.6 years, finerenone significantly reduced the risk of the primary composite renal outcome, which included a sustained ≥40% decline in eGFR from baseline, progression to end-stage renal disease (ESRD), or renal death, by 18% compared to placebo (14). In addition, finerenone produced a substantial reduction in albuminuria, as evidenced by a significant decrease in UACR levels when compared with placebo (14).

The FIGARO-DKD study extended these findings by enrolling patients with earlier stages of chronic kidney disease (CKD stages 1 to 4) and a broader range of albuminuria (UACR 30 to 5000 mg/g). Over a median follow-up of 3.4 years, finerenone demonstrated a significant reduction in the primary composite cardiovascular outcome, which included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (15). Although cardiovascular outcomes were the primary focus of FIGARO-DKD, the trial also confirmed finerenone's renoprotective benefits as a key secondary endpoint, particularly in patients with more severe albuminuria (15).

In the FIDELIO-DKD study, finerenone was associated with a clear slowing of eGFR decline and a meaningful reduction in albuminuria. However, an increased incidence of hyperkalemia was reported compared to placebo, though this was generally manageable with regular monitoring and dose adjustments (14). Similarly, in the FIGARO-DKD trial, while the incidence of hyperkalemia was higher in the finerenone group, the rates of treatment discontinuation due to hyperkalemia remained low (15).

Secondary renal outcome analyses from FIGARO-DKD demonstrated that finerenone reduced the risk of ESRD

Table 1. Renoprotective effects of finerenone

Study	Population	Primary Renal Endpoint	Outcome (Risk Reduction)
FIDELIO-DKD	Type 2 Diabetes + CKD Stages 3-4, UACR >300 mg/g	≥40% eGFR decline, ESRD, or renal death	18% relative risk reduction in renal outcomes (HR 0.82)
FIGARO-DKD	Type 2 Diabetes + CKD Stages 1-4, UACR 30-5000 mg/g	Secondary outcome: ESRD or sustained eGFR decline by 40%, renal death	36% reduction in progression to ESRD in patients with severely increased albuminuria
FIDELITY (Pooled Analysis)	Combined population from FIDELIO-DKD and FIGARO-DKD	Composite of renal outcomes	Consistent renal benefit across CKD stages (HR 0.86)

CKD; Chronic Kidney Disease, **UACR;** Urine Albumin-to-Creatinine Ratio, **eGFR;** Estimated Glomerular Filtration Rate, **ESRD;** End-Stage Renal Disease, **HR;** Hazard Ratio.

progression by 36% in patients with severely increased albuminuria, and also provided significant benefits in those with moderately increased albuminuria, with the greatest effect observed in patients with higher baseline albuminuria levels (16).

In patients already receiving RAAS blockade, finerenone was shown to further reduce UACR levels and slow the progression of renal disease, while exhibiting a lower incidence of hyperkalemia compared to steroidal mineralocorticoid receptor antagonists (MRAs) such as spironolactone (13,17). A slight decline in eGFR is commonly observed following initiation of MRAs; however, in the Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS), finerenone was associated with smaller reductions in eGFR and a lower incidence of worsening renal function compared to spironolactone (11,17).

Mineralocorticoid receptor overactivation is a key driver of inflammation and fibrosis in the diabetic kidney. By selectively blocking these receptors, MRAs mitigate these pathogenic processes. Finerenone's high affinity for the mineralocorticoid receptor, coupled with its non-steroidal structure, enhances its anti-fibrotic and anti-inflammatory efficacy while minimizing off-target effects (13).

Both the FIDELIO-DKD and FIGARO-DKD trials required patients to be on maximally tolerated doses of ACE inhibitors or ARBs for at least four weeks prior to enrollment, ensuring that the demonstrated benefits of finerenone were additive to optimized RAAS blockade (14,16).

The FIDELITY pooled analysis of the FIDELIO-DKD and FIGARO-DKD studies reinforced these findings by demonstrating that finerenone provided consistent renoprotective effects across overlapping stages of CKD in patients with type 2 diabetes mellitus. This analysis confirmed reductions in albuminuria and slowed progression to kidney failure when compared with placebo (18).

Based on these robust clinical data, the 2022 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease recommend the use of finerenone in patients with an eGFR of at least 25 mL/min/1.73 m², persistent albuminuria (UACR ≥30 mg/g), and normal serum potassium concentrations (≤4.8 mmol/L), despite treatment with the maximum tolerated dose of RAAS inhibitors (8).

CARDIOVASCULAR OUTCOMES

Cardiovascular disease remains the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus and chronic kidney disease (CKD). Persistent hyperglycemia, oxidative stress, and chronic low-grade inflammation contribute to accelerated atherosclerosis, endothelial dysfunction, and myocardial fibrosis, which collectively increase the risk of cardiovascular events in this population. Despite optimized glycemic control and renin-angiotensin-aldosterone system (RAAS) blockade, substantial residual cardiovascular risk persists, necessitating novel therapeutic interventions that address the underlying pathophysiological mechanisms (1,2) (Table 2).

Mineralocorticoid receptor (MR) overactivation plays a central role in the development and progression of cardiovascular disease in patients with diabetic kidney disease. Excess aldosterone activity promotes myocardial fibrosis, vascular inflammation, and remodeling, thereby contributing to increased arterial stiffness, left ventricular hypertrophy, and heart failure. Mineralocorticoid receptor antagonists (MRAs) attenuate these processes by inhibiting MR-mediated transcription of proinflammatory and profibrotic mediators, such as transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), and osteopontin, thereby reducing myocardial fibrosis and improving vascular compliance (5,7).

Finerenone, a novel, selective, non-steroidal MRA, has demonstrated significant cardiovascular benefits in large randomized controlled trials. In the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial,

Table 2. Cardioprotective effects of finerenone

Study	Population	Primary Cardiac Outcomes	Risk Reduction	Follow-up, years
FIGARO-DKD	Type 2 Diabetes + CKD Stages 1-4, UACR 30-5000 mg/g	Cardiovascular death, nonfatal MI, nonfatal stroke, HF hospitalization	13% reduction in cardiovascular events (HR 0.87)	3.4
FIDELIO-DKD	Type 2 Diabetes + CKD Stages 3-4, UACR >300 mg/g	Secondary outcome: Composite cardiovascular events	14% reduction in CV events (HR 0.86) (secondary endpoint)	2.6
FIDELITY (Pooled Analysis)	Combined population from FIDELIO-DKD and FIGARO-DKD	Composite of CV death, nonfatal MI, stroke, HF hospitalization	14% reduction in CV events (HR 0.86), primarily driven by lower HF hospitalization rates	Varied

CKD; Chronic Kidney Disease, **UACR;** Urine Albumin-to-Creatinine Ratio, MI; **Myocardial Infarction, HF;** Heart Failure, **CV;** Cardiovascular, **HR;** Hazard Ratio.

finerenone significantly reduced the risk of the primary composite cardiovascular outcome—defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure—by 13% compared to placebo (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.76–0.98; p=0.03) (15). Notably, the benefit was consistent across different baseline estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) categories, including patients with earlier stages of CKD and moderately increased albuminuria.

In the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, finerenone also reduced the risk of cardiovascular events as a key secondary endpoint, with a hazard ratio of 0.86 (95% CI, 0.75–0.99), further confirming its cardioprotective potential in patients with more advanced CKD and higher levels of albuminuria (14).

The FIDELITY pooled analysis, which combined data from both FIDELIO-DKD and FIGARO-DKD, reinforced these findings by demonstrating that finerenone significantly reduced the risk of cardiovascular events by 14% compared to placebo across a broad population of patients with type 2 diabetes mellitus and CKD (hazard ratio [HR], 0.86; 95% CI, 0.78–0.95) (18). The reduction in cardiovascular risk was primarily driven by a lower incidence of hospitalization for heart failure, reflecting the antifibrotic effects of finerenone on the myocardium and its capacity to mitigate cardiac remodeling (18).

Steroidal MRAs such as spironolactone and eplerenone have long been established in the treatment of heart failure with reduced ejection fraction (HFrEF), demonstrating reductions in mortality and heart failure hospitalizations (19,20). However, their use in patients with CKD is often limited by the increased risk of hyperkalemia and worsening kidney function. Finerenone, due to its non-steroidal structure, balanced distribution in cardiac and renal tissues, and higher selectivity for the mineralocorticoid receptor, provides a favorable safety profile with a lower incidence of hyperkalemia compared to traditional MRAs (13,17).

The KDIGO 2022 Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease recommend finerenone for patients with type 2 diabetes mellitus, persistent albuminuria (UACR ≥30 mg/g), and high cardiovascular risk, particularly in those who cannot tolerate or are ineligible for sodium-glucose cotransporter-2 (SGLT-2) inhibitor therapy (8). In addition, current heart failure guidelines recommend SGLT-2 inhibitors as first-line therapy for patients with heart failure with preserved ejection fraction (HFpEF). In cases of persistent symptoms despite optimized therapy, the addition of finerenone may be considered, particularly in patients at risk for progressive cardiorenal dysfunction (19,20).

Beyond its established role in reducing heart failure hospitalizations, finerenone may also provide long-term cardiovascular protection by preventing myocardial fibrosis and reducing arterial stiffness—two key mechanisms underlying heart failure with preserved and reduced ejection fraction (21). Ongoing studies are evaluating the potential benefits of combining finerenone with other cardioprotective agents, including SGLT-2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, in patients with diabetes and cardiorenal syndromes (9,19,22).

SAFETY and ADVERSE OUTCOMES

Finerenone binds to mineralocorticoid receptors with better selectivity and higher affinity and has non-steroidal structure. As a result, the side effect profile is better compared to other MRA. Additionally, different from steroidal MRA, it displays more balanced distribution in cardiac and renal tissues (23).

As with other MRA, hyperkalemia may be observed linked to finerenone. As a result, regular monitoring of serum potassium levels is required. But the hyperkalemia risk is lower compared to spironolactone and generally is at tolerable levels (17). In the FIDELIO-DKD study, hyperkalemia was observed after finerenone use that required lower rates of drug cessation relative to other

Table 3. Comparison of adverse events among MRAs

Parameter	Finerenone	Steroidal MRAs (Spironolactone / Eplerenone)
Hyperkalemia incidence	10.8% to 18.3% (lower than spironolactone)	Higher hyperkalemia incidence, especially in CKD
Hyperkalemia-related treatment discontinuation	1.7% to 3.2% (lower discontinuation rates vs. steroidal MRAs)	Higher discontinuation rates due to hyperkalemia
Gynecomastia and endocrine-related adverse events	Minimal due to non-steroidal structure	Common (gynecomastia, menstrual irregularities)
Blood pressure effects	Mild reduction in systolic BP, less than spironolactone	Stronger BP lowering effect
Drug interactions	CYP3A4 metabolism, caution with inhibitors/inducers	Less prone to CYP interactions, but broader side effect profile
Use in advanced CKD (eGFR <25 ml/min/1.73m²)	Not recommended (evidence limited in eGFR <25 ml/min/1.73m²)	Not preferred in advanced CKD due to hyperkalemia risk

MRA antagonists and the incidence was reported to vary from 1.7% to 3.2% (14). The hyperkalemia side effect risk with the addition of finerenone to treatment of patients using RAAS blockers was observed at lower rates compared to treatment with two RAAS blockers (14,24). The FIDELITY combined analysis reported that the simultaneous use of SGLT-2 inhibitors in patients using RAAS blocker and finerenone may reduce the hyperkalemia side effect risk (18) (**Table 3**).

The United States Food and Drug Administration (FDA) recommends initiating Finerenone therapy at potassium levels <5 mmol/L. The recommendation of the KDIGO 2022 Clinical Practice Guidelines for Management of Diabetes in Chronic Renal Disease is presented in Table 1 (8).

The reduction in systolic blood pressure and increase in serum aldosterone levels in patients receiving finerenone were lower than observed in patients receiving spironolactone. This situation may be an additional benefit for patients with blood pressure controlled well or at low levels with first-choice antihypertensive drugs like RAAS blockers (17).

Due to the selective structure of finerenone, observation of side effects like gynecomastia and feminization, that may be observed after spironolactone use, is not expected (20). Potential drug interactions may occur with finerenone, which is metabolized mainly by cytochrome P450-3A4 enzyme and binds to protein at high rates (25).

Steroidal MRA are drugs with proven efficacy for treatment of low ejection fraction heart failure and primary hyperaldosteronism. They are effective for refractory hypertension (26). For these indications, finerenone cannot take the place of steroidal MRA (8).

Limitations of The Review

Despite the promising evidence supporting the use of finerenone in patients with diabetic kidney disease and cardiovascular risk, several limitations warrant consideration when interpreting the available data and translating it into clinical practice.

First, the majority of evidence regarding the efficacy and safety of finerenone is derived from randomized controlled trials, specifically the FIDELIO-DKD and FIGARO-DKD studies. Although these trials were well-designed and included large, diverse populations, they primarily enrolled patients with type 2 diabetes mellitus, moderately to severely increased albuminuria, and relatively preserved renal function (eGFR ≥25 mL/min/1.73 m²). As a result, the generalizability of these findings to patients with non-diabetic chronic kidney disease, normoalbuminuric diabetic kidney disease, or those with advanced kidney failure (eGFR <25 mL/min/1.73 m²) remains uncertain.

Second, while finerenone has demonstrated a favorable safety profile compared to steroidal mineralocorticoid receptor antagonists, the risk of hyperkalemia persists. Although manageable in controlled clinical trial settings with frequent monitoring and protocol-driven dose adjustments, real-world data on hyperkalemia incidence and management strategies in broader clinical practice are still limited. Patients at higher risk for hyperkalemia, such as those with advanced CKD, heart failure, or concomitant use of potassium-sparing diuretics, require close monitoring, which may present challenges in routine care.

Third, the long-term outcomes beyond the median follow-up durations of the FIDELIO-DKD (2.6 years) and FIGARO-DKD (3.4 years) trials are not yet known. While these studies demonstrated a reduction in surrogate renal and cardiovascular endpoints, further evidence is needed to confirm the durability of these benefits over longer time horizons, particularly regarding progression to end-stage renal disease and long-term cardiovascular mortality.

Additionally, although the concurrent use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors was allowed in both FIDELIO-DKD and FIGARO-DKD, the proportion of patients receiving combination therapy was relatively low. More data are required to assess the efficacy, safety, and potential synergistic effects of combining finerenone with SGLT-2 inhibitors, glucagon-like peptide-1 receptor agonists, and other emerging therapies in patients with diabetic kidney disease.

Finally, there is limited evidence regarding the use of finerenone in specific subpopulations, such as patients with type 1 diabetes mellitus, elderly patients with frailty, and those with significant comorbidities, including liver disease or malignancy. Further studies are necessary to clarify finerenone's role in these groups and to identify additional biomarkers for predicting treatment response and safety.

CONCLUSION

Finerenone represents a significant advancement in the management of patients with type 2 diabetes mellitus and chronic kidney disease. By selectively antagonizing the mineralocorticoid receptor, finerenone addresses key pathophysiological mechanisms—namely inflammation and fibrosis—that drive the progression of diabetic kidney disease and contribute to cardiovascular morbidity and mortality. Robust evidence from the FIDELIO-DKD and FIGARO-DKD trials demonstrates that finerenone reduces albuminuria, slows the decline in estimated glomerular filtration rate, and lowers the risk of cardiovascular events, including hospitalization for heart failure.

Compared to traditional steroidal mineralocorticoid receptor antagonists, finerenone offers a more favorable safety profile, with a reduced incidence of hyperkalemia and fewer endocrine-related adverse effects. These features make finerenone a valuable therapeutic option, particularly for patients who remain at high residual cardiorenal risk despite optimized renin-angiotensin-aldosterone system blockade and, where appropriate, the use of sodium-glucose cotransporter-2 inhibitors.

Current clinical practice guidelines endorse finerenone as an adjunctive therapy in patients with diabetic kidney disease, persistent albuminuria, and high cardiovascular risk. However, further research is needed to confirm its long-term efficacy and safety in broader patient populations, explore its role in combination therapy with other novel agents, and clarify its potential benefits in non-diabetic kidney disease.

In summary, finerenone offers a novel, mechanism-driven approach to cardiorenal protection in patients with type 2 diabetes mellitus and chronic kidney disease, with the potential to improve clinical outcomes and fill an important therapeutic gap in this high-risk population.

DECLARATIONS

Ethics committee approval: In this review, the authors confirm that there are no ethical concerns or conflicts of interest. Authors have contributed to the study in compliance with ethical guidelines, and no aspect of the research involves activities that could present ethical issues.

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AI: The integrity of the content and flow of the text was assessed by operating AI chatbox. However, the final decision on including the AI-driven suggestions was considered by the author.

REFERENCES

1. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. *Clin J Am Soc Nephrol.* 2017;12(12):2032-2045. doi:10.2215/CJN.11491116
2. Strain WD, Paldánius PM. Diabetes, cardiovascular disease and the microcirculation [published correction appears in Cardiovasc Diabetol. 2021 Jun 11;20(1):120. doi: 10.1186/s12933-021-01307-5.]. *Cardiovasc Diabetol.* 2018;17(1):57. Published 2018 Apr 18. doi:10.1186/s12933-018-0703-2
3. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials [published correction appears in Lancet. 2019 Jan 5;393(10166):30. doi: 10.1016/S0140-6736(18)33206-9.]. *Lancet.* 2019;393(10166):31-39. doi:10.1016/S0140-6736(18)32590-X
4. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):323-334. doi:10.1056/NEJMoa1515920
5. Barrera-Chimal J, Estrela GR, Lechner SM, et al. The myeloid mineralocorticoid receptor controls inflammatory and fibrotic responses after renal injury via macrophage interleukin-4 receptor signaling. *Kidney Int.* 2018;93(6):1344-1355. doi:10.1016/j.kint.2017.12.016
6. Staessen J, Lijnen P, Fagard R, Verschueren LJ, Amery A. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *J Endocrinol.* 1981;91(3):457-465. doi:10.1677/joe.0.0910457
7. Barrera-Chimal J, Lima-Posada I, Bakris GL, Jaisser F. Mineralocorticoid receptor antagonists in diabetic kidney disease - mechanistic and therapeutic effects. *Nat Rev Nephrol.* 2022;18(1):56-70. doi:10.1038/s41581-021-00490-8
8. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int.* 2022;102(5S):S1-S127. doi:10.1016/j.kint.2022.06.008
9. Pitt B, Anker SD, Böhm M, et al. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. *Eur J Heart Fail.* 2015;17(2):224-232. doi:10.1002/ejhf.218
10. de Boer IH, Khunti K, Sadusky T, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care.* 2022;45(12):3075-3090. doi:10.2337/dci22-0027
11. Currie G, Taylor AH, Fujita T, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol.* 2016;17(1):127. Published 2016 Sep 8. doi:10.1186/s12882-016-0337-0
12. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol.* 2006;1(5):940-951. doi:10.2215/CJN.00240106
13. Bakris GL, Agarwal R, Chan JC, et al. Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy: A Randomized Clinical Trial. *JAMA*. 2015;314(9):884-894. doi:10.1001/jama.2015.10081
14. Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med.* 2020;383(23):2219-2229. doi:10.1056/NEJMoa2025845
15. Ruilope LM, Agarwal R, Anker SD, et al. Design and Baseline Characteristics of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial. *Am J Nephrol.* 2019;50(5):345-356. doi:10.1159/000503712
16. Ruilope LM, Pitt B, Anker SD, et al. Kidney outcomes with finerenone: an analysis from the FIGARO-DKD study. *Nephrol Dial Transplant.* 2023;38(2):372-383. doi:10.1093/ndt/gfac157
17. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J.* 2013;34(31):2453-2463. doi:10.1093/eurheartj/eht187
18. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis [published correction appears in Eur Heart J. 2022 May 21;43(20):1989. doi: 10.1093/eurheartj/ehab886.]. *Eur Heart J.* 2022;43(6):474-484. doi:10.1093/eurheartj/ehab777
19. Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med.* 2024;391(16):1475-1485. doi:10.1056/NEJMoa2407107
20. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med.* 2023;389(12):1069-1084. doi:10.1056/NEJMoa2306963
21. Gil-Ortega M, Vega-Martín E, Martín-Ramos M, et al. Finerenone Reduces Intrinsic Arterial Stiffness in Munich Wistar Frömter Rats, a Genetic Model of Chronic Kidney Disease. *Am J Nephrol.* 2020;51(4):294-303. doi:10.1159/000506275
22. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J.* 2016;37(27):2105-2114. doi:10.1093/eurheartj/ehw132
23. Bärfacker L, Kuhl A, Hillisch A, et al. Discovery of BAY 94-8862: a nonsteroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases. *ChemMedChem.* 2012;7(8):1385-1403. doi:10.1002/cmdc.201200081
24. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy [published correction appears in N Engl J Med. 2014;158:A7255]. *N Engl J Med.* 2013;369(20):1892-1903. doi:10.1056/NEJMoa1303154
25. Rico-Mesa JS, White A, Ahmadian-Tehrani A, Anderson AS. Mineralocorticoid Receptor Antagonists: a Comprehensive Review of Finerenone. *Curr Cardiol Rep.* 2020;22(11):140. Published 2020 Sep 10. doi:10.1007/s11886-020-01399-7
26. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370(15):1383-1392. doi:10.1056/NEJMoa1313731