Diabetic kidney disease (DKD) affects approximately one-fifth of individuals with type 2 diabetes (T2D) and is associated with higher cardiovascular and all-cause morbidity and mortality. Current treatment targets primarily focus on improving glycemic control, reducing blood pressure, managing lipids, and addressing obesity, with special attention to other potentially modifiable risk factors. The choice of medications has traditionally been directed at those that provide specific renal benefits. Since 2020 SGLT2 inhibitors have been added to ACE inhibitors or ARBs to reduce renal and cardiovascular risk in individuals with T2D and albuminuria. Nevertheless, despite the standard of care, these patients often progress to dialysis, develop heart failure and die prematurely.

Recent years have witnessed the rapid pace of advancement in the treatment of diabetes and chronic kidney disease (CKD) with a surge of high-quality new information. This evoked an unprecedentedly rapid update of the KDIGO Clinical Practice Guideline for Diabetes Management in CKD in 2022, only two years after the original clinical practice guideline on this topic. The major changes in the new version were lowering the eGFR threshold for introducing SGLT2 inhibitors and the addition of non-steroidal mineralocorticoid antagonists (ns-MRA) for patients with T2D, albuminuria, and normal serum potassium.

Drivers of renal disease progression in T2DM
CKD progression is driven by combined effects of hemodynamic, metabolic, inflammatory, and fibrotic factors. The natural history of DKD includes glomerular hyperfiltration, progressive albuminuria, declining glomerular filtration rate (GFR), and, ultimately, end-stage renal disease. Metabolic changes associated with diabetes lead to glomerular hypertrophy, glomerulosclerosis, and tubulointerstitial damage and inflammation. Most current and emerging therapies for DKD have primarily focused on improving the management of hyperglycemia and intraglomerular pressure. However, despite the very efficient interventions in these areas, there remains a high residual risk of progression to end-stage renal disease and the development of cardiovascular complications. Thus, growing evidence suggests that the missing links to explain the course of the disease and associated morbidity are inflammation and fibrosis, which are caused by the overactivation of the mineralocorticoid receptor (MR).

The MR is a transcription factor of the family of steroid receptors. It is expressed in a variety of cells, including cardiomyocytes, fibroblasts, vascular (endothelial and smooth muscle) cells, immune cells, and subcutaneous adipocytes. MRs mediate fluid, electrolyte, hemodynamic homeostasis, and tissue repair. In addition, an increasing amount of clinical and experimental evidence shows that MR overactivation is associated with kidney and cardiovascular diseases. Several ligand and non-ligand MR activators can cause increased gene expression of pro-inflammatory...
and profibrotic factors leading to hypertension, glomerular injury, proteinuria, and CKD. Thus, under pathological conditions, MRs overactivation switches its activity from homeostatic regulator to pathophysiological mediator by promoting inflammation and fibrosis in tissues where it is expressed.

Mineralocorticoid receptor antagonists (MRA)
MRAs block the effects of aldosterone thus inducing natriuresis, lowering blood pressure, and reducing heart congestion. They improve survival and reduce morbidity in patients with heart failure, reduced ejection fraction, and mild-to-severe symptoms. Over the past few decades, several randomized controlled trials have also reported antiproteinuric and potentially renoprotective effects of MRAs in CKD. The steroidal MRAs spironolactone and eplerenone exert their therapeutic effects by lowering blood pressure and proteinuria. They also show blood pressure-independent anti-inflammatory and antifibrotic effects in patients with reduced left ventricular ejection fraction, thus lowering cardiovascular morbidity and mortality. However, their use in clinical practice is limited due to their safety profiles and labeling precautions (mainly hyperkalemia).

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Flerenone, which currently has the most available evidence, was recently approved to reduce the risk of kidney function decline, kidney failure, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure in adults with CKD associated with T2D. It is more selective for the MR than eplerenone and spironolactone and is at least as potent as spironolactone. Its specific bulkier structure completely covers the MR, thus reducing co-factor recruitment within the nucleus and hindering pro-inflammatory and pro-fibrotic gene expression. Furthermore, the effects of fherenone are independent of its antihypertensive action.

Clinical evidence of nsMRAs benefits
Since 2015 several large randomized controlled studies evaluated the effects of ns MRAs. The ARTS program comprising five phase II studies in over 2000 patients was designed to test the safety and tolerability of fherenone in patients with heart failure with reduced ejection fraction and mild-to-moderate CKD. Compared to spironolactone, fherenone better preserved renal function with fewer adverse events. It also reduced albuminuria in patients with CKD and T2D, independent of changes in blood pressure or eGFR, suggesting non-hemodynamic drug effects.

Based on the success of the Phase II ARTS studies and the biological plausibility of cardiorenal benefit, two phase III clinical trials were initiated in 2015: the Fherenone in reducing kidney failure and disease progression in Diabetic Kidney Disease (FIDELO-DKD) and Fherenone in reducing CARDiovascular morbidity and mortality in Diabetic Kidney Disease (FIGARO-DKD) studies. The FIDELO-DKD trial was primarily designed to detect a treatment effect of fherenone on kidney function endpoints, whereas the FIGARO-DKD trial aimed to detect an effect on a cardiovascular composite primary endpoint. The results of FIDELO-DKD suggest that fherenone effectively attenuated eGFR decline and decreased the risk of renal failure, as well as of key secondary outcome events (defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). Thus, fherenone appears to be an effective treatment for kidney and cardiovascular protection with a favorable safety profile in patients with CKD and T2D.

To overcome the limitations of steroidal MRAs, several nsMRAs have been developed with improved efficacy and tolerability. They are highly selective, remarkably potent, and with an even distribution between the kidneys and heart. Fherenone, which currently has the most available evidence, was recently approved to reduce the risk of kidney function decline, kidney failure, cardiovascular death, non-fatal heart attacks, and hospitalization for HF in adults with CKD associated with T2D. It is more selective for the MR than eplerenone and spironolactone and is at least as potent as spironolactone. Its specific bulkier structure completely covers the MR, thus reducing co-factor recruitment within the nucleus and hindering pro-inflammatory and pro-fibrotic gene expression. Furthermore, the effects of fherenone are independent of its antihypertensive action.

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of their results in the Finerenone in chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial program analysis (FIDELITY) analysis. This prespecified analysis from two randomized trials, which together included over 13,000 patients, found a reduction in both cardiovascular events and renal failure outcomes when finerenone was used on top of optimized RAS blockade in patients with T2D and CKD. Finerenone significantly reduced the hazard of a kidney composite outcome (time to kidney failure, sustained 57% or more decrease in eGFR from baseline, or kidney death) versus placebo. No synergistic effect was observed between finerenone and either SGLT2-inhibitors or GLP-1RA. Adverse events were similar between treatment arms. Hyperkalemia risk was negligible at eGFR≥60mL/min, but hyperkalemia leading to treatment discontinuation occurred significantly more frequently with finerenone versus placebo at eGFR<60mL/min. The risk for hyperkalemia was lower in patients with lower baseline potassium and those using diuretics and SGLT2 inhibitors. Still, there were no hyperkalemia-related deaths over 3 years of median follow-up. Based on these results, nsMRAs were introduced in the 2022 KDIGO Clinical practice guidelines for diabetes management in CKD, American Diabetes Association (ADA) guidelines on CKD and cardiovascular disease risk management, and American Heart Association (AHA) scientific statement as additional risk-based therapy. As for hyperkalemia, a simple protocol for potassium management by Wanner et al. highlights routine monitoring and provides practical recommendations for preventive measures.

**KEY POINTS**

1. Patients with DKD have higher cardiovascular and all-cause morbidity and mortality.

2. MR overactivation promotes inflammation and fibrosis and is a determinant of renal disease progression in T2DM.

3. Finerenone is a novel nsMRA that effectively attenuates eGFR decline, curtails albuminuria, and reduces cardiovascular morbidity and mortality in patients with T2DM.

4. Finerenone-related hyperkalemia is seldom critical. A simple protocol for potassium management can help avoid serious complications.

5. More studies (FINEARTS-HF, CONFIDENCE, FIND-CKD, FIONA) are underway to assess possible synergistic effects of finerenone and SGLT2-inhibitors, its effects on non-diabetic CKD and pharmacokinetics/pharmacodynamics of finerenone in a pediatric population with CKD.

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**Figure 4.**

The protocol for potassium management with finerenone

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The speaker approved the content.
Further readings


What can we learn from the FIDELIO-DKD and FIGARO-DKD Studies? A holistic/multidisciplinary approach