Clinical perspective—evolving evidence of mineralocorticoid receptor antagonists in patients with chronic kidney disease and type 2 diabetes

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Chronic kidney disease (CKD) in type 2 diabetes is a large and growing problem leading to end-stage kidney disease, atherosclerotic cardiovascular disease, and heart failure (HF). Aldosterone is a key risk factor in promoting inflammation and fibrosis, which causes cardiorenal failure. Treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers does not prevent overactivation of the mineralocorticoid receptor. Therapeutic options and challenges with blocking MR overactivation by aldosterone are reviewed herein. Whereas classic steroidal mineralocorticoid receptor antagonists (MRAs) reduced albuminuria in short-term studies of diabetic and nondiabetic CKD, long-term studies evaluating hard endpoints such as loss of kidney function were not conducted in CKD because of side effects (primarily hyperkalemia). Novel nonsteroidal MRAs reduce proteinuria and markers of HF, with lower risk of hyperkalemia and without renal impairment, in comparison to steroidal MRAs. Furthermore, recent clinical trials have demonstrated the efficacy of the novel, selective, nonsteroidal MRA finerenone to delay progression of kidney and cardiovascular disease, including HF, in patients with CKD and type 2 diabetes. Concomitantly, the safety profile of finerenone is good, with few patients discontinuing treatment because of hyperkalemia, even among study participants with a low estimated glomerular filtration rate (>25 ml/min per 1.73 m²). Novel nonsteroidal MRAs such as finerenone hold the potential to be an attractive addition to the treatment paradigm in the management of patients with CKD and type 2 diabetes, targeting the unmet need of managing increased inflammation and fibrosis attributable to MR overactivation.


KEYWORDS: chronic kidney disease; finerenone; mineralocorticoid receptor; mineralocorticoid receptor antagonist; type 2 diabetes

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Diabetes is the leading cause of chronic kidney disease (CKD), which occurs in 30%–40% of diabetic individuals. Globally, 537 million individuals, or 1 in 10, have diabetes, and the numbers are expected to increase to 783 million by 2040. Thus, even as we have seen better control of cardiorenal risk factors and implementation of renin–angiotensin system (RAS) inhibitor therapy, which has reduced the individual risk for cardiovascular (CV) disease and end-stage kidney disease (ESKD), the incidence of CKD in diabetes with excess CV mortality and development of ESKD has not declined. Important to note is that the majority of individuals who develop CKD in diabetes die from CV disease, including atherosclerotic disease and heart failure (HF). At age 30 years, the occurrence of diabetes and CKD shortens the life span by approximately 15 years in men and 17 years in women. US population-based data have demonstrated that a 28% reduction in risk for ESKD in diabetes occurred from 1990 to 2010, but the number of patients referred for ESKD treatment increased from ~17,000 to 50,000 during this period. These data reflect a need for better prevention and treatment of CKD in diabetes. This includes a need for improved screening for CKD.

The sodium–glucose co-transporter-2 inhibitors (SGLT-2i’s) are a relatively new treatment option. Initially, CV safety studies in patients with type 2 diabetes (T2D) and a history of CV disease demonstrated reductions in CV events with the SGLT-2i empagliflozin, but reduced progression of CKD as a secondary outcome was also observed. Subsequent primary kidney outcome studies in patients with T2D and CKD demonstrated reduced progression of CKD and CV disease; however, despite treatment with an SGLT-2i in addition to RAS inhibitor therapy, a significant proportion of patients continued to progress.

Optimizing blockade of the RAS

Until recent data from studies of SGLT-2i’s or glucagon-like peptide-1 receptor agonists (GLP-1RAs) were presented, the standard of care for patients with CKD and diabetes for almost 20 years has been RAS inhibitor therapy with angiotensin-converting enzyme (ACE) inhibitors (ACEi’s) or angiotensin receptor blockers (ARBs) in addition to blood glucose management. Although this management strategy improved renal and CV outcomes (development of doubling of serum creatinine level or ESKD, and hospitalization for HF), with up to 50% of patients reported to reach the
primary endpoint after 4 years in the treated group, these data come from a study completed almost 20 years ago.\textsuperscript{12}

The insufficient effect on renal and CV outcomes is partly explained by RAS blockade being incomplete; ACE inhibition can be bypassed by angiotensin II formation from chymases, and angiotensin II type 1 receptor blockade may be incomplete.\textsuperscript{13} This finding led to exploration of dual inhibitor therapy with a combination of ACEi’s and ARBs. Dual blockade reduced proteinuria, compared with single-agent intervention, but did not provide long-term renal benefits in patients with CKD and T2D in the VA NEPHRON-D (Diabetes in Nephropathy) study, which was stopped due to futility and side effects, including hyperkalemia.\textsuperscript{14} Addition of renin inhibition did not prevent CV and renal events in the long-term, as reported in the ALTIITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) study, and the proportion of patients with hyperkalemia (serum potassium level ≥6 mmol/L) was significantly higher with aliskiren versus placebo (11.2% vs. 7.2%; $P < 0.001$).\textsuperscript{15} Furthermore, chymase inhibitors, which were developed to address the insufficient blockade of angiotensin II formation during ACE inhibition, did not reduce albuminuria in a clinical study.\textsuperscript{16}

**The importance of aldosterone**

The benefits of ACEi’s and ARBs in CKD have been ascribed to the reduction in systemic and intraglomerular blood pressure (BP) and proteinuria.\textsuperscript{17} However, focus has been increasing on the benefits of a reduction in aldosterone due to the deleterious effect of overactivation of mineralocorticoid receptors (MRs) by aldosterone in kidney and heart disease, resulting in inflammation and fibrosis.\textsuperscript{18} In HF with reduced ejection fraction, blocking aldosterone with the MR antagonists (MRAs) spironolactone\textsuperscript{19} and eplerenone\textsuperscript{20} reduced mortality, and effects on BP were documented in resistant hypertension in T2D.\textsuperscript{21}

In CKD, aldosterone is also proposed to be part of its pathophysiology. In 1982, aldosterone levels were shown to start to increase when the glomerular filtration rate (GFR) is reduced by 50%.\textsuperscript{22} A subsequent study\textsuperscript{23} reported aldosterone levels to be elevated up to 4-fold in patients with a mean GFR of 27 ml/min per 1.73 m\textsuperscript{2}. During long-term blockade of RAS, aldosterone escape or breakthrough is seen.\textsuperscript{24} In a study of patients with type 1 diabetes (T1D) and CKD treated with losartan for 3 years, the decline in GFR (\textsuperscript{51}Cr-EDTA plasma clearance) was 5.0 ml/min per 1.73 m\textsuperscript{2} per year in patients with aldosterone escape, compared with 2.4 ml/min per 1.73 m\textsuperscript{2} per year in patients without, and aldosterone levels were associated with the rate of decline of GFR.\textsuperscript{25} This finding suggests that blockade of aldosterone may be beneficial in CKD. In contrast to this observation, a *post hoc* analysis of the AMADEO (A prospective, randomized, double-blind, double-dummy, forced-titration, multicenter, parallel-group, 1-year treatment trial to compare telMisartan [80 mg] vs losArtan [100 mg] in hypertensive type-2 DiabEtic patients with Overt nephropathy) study\textsuperscript{26} did not determine an association between aldosterone breakthrough at 6 months and change in GFR between 6 and 12 months in a large cohort of patients with T2D and CKD.\textsuperscript{27} This difference might be due to a difference in follow-up or the lack of a common definition of breakthrough.

In addition to the effect on MRs in the classic location of the distal nephron, these effects are mediated through MRs on smooth muscle cells, endothelium, fibroblasts, podocytes, myeloid cells, and inflammatory cells.\textsuperscript{28} Further insights into the role of the MR in non-epithelial cells are discussed in detail in articles in this issue, by Nakamura *et al.* and Luther and Fogo.\textsuperscript{29,30} These effects result in reductions in tissue inflammation and fibrosis, which have been demonstrated in experimental studies, are blood pressure independent, and contribute to the cardiorenal benefits observed with MRA blockade.\textsuperscript{31} The interplay among microenvironment proteases, consequent inflammation, and an array of profibrotic cascades is likely to play a key role in promoting the chronic progression of fibrosis. These factors and their sites of action are summarized in Figure 2 of the article by Hollenberg and Epstein (see the numbered sites 3, 6, 8, and 9 in Figure 2 and the accompanying explanatory discussion of how they interact in a complementary manner to promote inflammation and fibrosis).\textsuperscript{32} Recently, cardiorenal syndrome was revisited, suggesting that factors such as diabetes and hypertension lead to inflammation and activate fibrosis, a common driver for cardiorenal damage and a potential target for intervention.\textsuperscript{33}

**Steroidal MRAs**

The correlation between aldosterone levels and breakthrough with decline in GFR supports aldosterone as a target for intervention in patients with CKD and T2D who are receiving ACEi’s or ARBs. Thus, it was proposed that the addition of spironolactone to RAS inhibitor therapy in patients with aldosterone breakthrough may offer additional albuminuria-lowering effects in patients with CKD and T2D and potentially would be beneficial for kidney and cardiac outcomes. The addition of spironolactone was reported to lead to a significant 40% reduction in albuminuria, demonstrating the benefit of preventing the activation of the MR.\textsuperscript{34} The steroidal MRA spironolactone is potent but also nonselective, causing gynecomastia.\textsuperscript{13} Spironolactone was further investigated in doses of 25–50 mg/d in combination with ACEi’s or ARBs in patients with T1D\textsuperscript{35} or T2D\textsuperscript{36,37} moderately increased albuminuria,\textsuperscript{38} severely increased albuminuria, or nephrotic range albuminuria (>2500 mg/24 h).\textsuperscript{39} A meta-analysis of 16 studies of spironolactone added to routine antidiabetic/renoprotective/antihypertensive treatment lasting 2–18 months demonstrated on average a significant reduction in end-of-treatment 24-hour urinary albumin/protein excretion (mean difference $= -61.48$; 95% confidence interval [CI], $-96.74$ to $-26.23$; $P = 0.0006$), with the major concern being a more than 5-fold increased risk for hyperkalemia, particularly in those with impaired renal function.\textsuperscript{40} Similar data with a 39% reduction in albuminuria/proteinuria were found in other meta-analyses of MRA, including patients with diabetic and nondiabetic CKD.\textsuperscript{41} A 72-week intervention study with 4 arms combining irbesartan 150 or 300 mg daily with spironolactone 20 mg or placebo confirmed a long-term antiproteinuric effect
(up to 30%) and safety in elderly patients with T2D and CKD (estimated GFR [eGFR] >45 ml/min per 1.73 m²) when spironolactone was used in combination with irbesartan.42

More recently, prevention of CKD with spironolactone was tested in the 3-year PRIORITY study (Proteomic Prediction and Renin–Angiotensin–Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Participants with Normoalbuminuria). The study included 1777 patients with T2D and normal to mildly increased albuminuria, of whom 218 had a high risk of CKD, as determined from a urinary proteomics-based risk pattern for CKD (CKD273). The high-risk individuals were randomized to receive placebo or spironolactone in addition to ongoing RAS inhibitor therapy. Only patients with a GFR >45 ml/min per 1.73 m² were included, to reduce the risk of hyperkalemia.45 The urinary proteomic pattern predicted progression of both albuminuria and development of CKD stage 3+, but spironolactone was not able to prevent progression (hazard ratio [HR] = 0.81; 95% CI, 0.49–1.34; P = 0.41). Possible reasons for this are a lack of statistical power, too short a trial duration, or that the disease process was in too early a stage for this mode of action to be effective.46 In a study of hemodialysis patients, the composite CV outcome of death from cardio-cerebrovascular events, aborted cardiac arrest, and sudden cardiac death was reduced with long-term, low-dose spironolactone with HR = 0.42; 95% CI, 0.26–0.78.45 However, these findings were not confirmed in the SPin-D (Safety and CV Efficacy of Spironolactone in Dialysis-dependent ESKD) study.46 Eplerenone is a second-generation, more-selective, but less-potent steroidal MRA. Eplerenone has documented benefits in HF with reduced ejection fraction47 and was considered promising for treating CKD in diabetes without the hormonal side effects of spironolactone, while still providing blockade of MR activation. Eplerenone was studied as an add-on to ACE inhibition in patients with T2D and CKD and demonstrated antiproteinuric effects similar to those seen with spironolactone,47,48 but efficient doses led to an increase in potassium levels, resulting in a recommendation against eplerenone in T2D with CKD (US and UK labels). Metanalyses of the steroidal MRAs in diabetic and nondiabetic CKD found consistent findings on proteinuria/albuminuria—a 20%–60% decline.41,49,50 Long-term studies aiming to prevent progression of established CKD have not been carried out, and therefore, whether the beneficial effect on albuminuria translates into prevention of ESKD is not known. The association between reduction in albuminuria after onset of anti-hypertensive therapy and long-term preservation of renal function was demonstrated years ago.51 Recent meta-regression analyses from large observational studies and intervention studies with a total of almost 30,000 patients support reduction in albuminuria as a surrogate endpoint. A 30% decrease in albuminuria, compared with that with placebo, will provide an average HR for the hard clinical endpoint of 0.68.52,53 Exceptions have also occurred, with interventions that have lowered albuminuria in phase II trials not demonstrating kidney protection in phase III trials,15 highlighting the need for well-designed, long-term phase III studies.14,15 A summary of the characteristics and effects of steroidal MRAs in patients with CKD and T2D is provided in Table 1.34,41,54–59

**Novel nonsteroidal MRAs**

As discussed above, blocking aldosterone may have several benefits. Spironolactone lowers BP in treatment-resistant hypertension in T2D21 and in CKD,41 and the physiological role of aldosterone is linked to regulation of volume and electrolyte status, but studies in HF and CKD found improved outcomes without lowering of BP.38,60 The benefits probably relate more to the antifibrotic and anti-inflammatory effects, which have been observed in experimental studies and seem to include effects on inflammatory and myeloid cells. Although the aldosterone-blocking benefits have been seen previously with drugs limited by hyperkalemia,41 the suggestion was made that agents with beneficial effects on progression of kidney and CV disease but a reduced effect on hyperkalemia could be developed. Novel nonsteroidal MRAs have since been developed, and agents such as esaxerenone, KBP-5074, and finerenone may have this profile.54–56,61 For a summary of the characteristics and effects of nonsteroidal MRAs in patients with CKD and T2D, see Table 1.

The development of finerenone is the most advanced, with large outcome studies recently completed. The difference in mode of action of finerenone compared with steroidal MRAs is explained by the different physiochemical properties affecting the following: (i) tissue distribution, pharmacokinetic properties, and cellular penetration; (ii) mode of binding to the MR; and (iii) blockade or recruitment of tissue-selective or ligand-specific cofactors leading to differential gene expression after blocking the MR.61 Finerenone is more selective and has a higher affinity to the MR than do spironolactone and eplerenone.54 A phase II program was conducted, and the ARTS (Mineralocorticoid Receptor antagonist Tolerability Study) evaluated various doses of finerenone for 28 days in 393 patients with CKD and chronic HF with reduced ejection fraction. Compared with spironolactone, a comparable reduction occurred in N-terminal pro-brain natriuretic peptide and albuminuria, but with a smaller increase in serum potassium, and a significantly lower rate of hyperkalemia (5.3% vs. 12.7%) and renal impairment (3.8% vs. 28.6%).52 The ARTS-DN (Mineralocorticoid Receptor antagonist Tolerability Study in Diabetic Nephropathy) study evaluated the effect on albuminuria of different doses of finerenone and placebo for 90 days in 823 patients with T2D and CKD (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g) on RAS inhibitor therapy. Treatment with finerenone led to a dose-dependent reduction in albuminuria (21%–38%). Adverse events were comparable to those observed with placebo. Hyperkalemia and subsequent discontinuation of study drug occurred in 1.8% of patients receiving finerenone, compared with no patients on placebo. In addition, no differences in the incidence of an eGFR decrease of ≥30% were seen between the groups.57
These data support the assumption that the antiproteinuric effect can be maintained with a limited effect on serum potassium. Thus, a phase III program was initiated to test if this would translate into prevention of kidney and CV events in patients with T2D and CKD in the FIGARO-DKD (Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease; NCT02540993) and the FIDELIO-DKD (Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease; NCT02545049) studies (Table 2).58,63 These companion studies have been the first to test if the antiproteinuric effect of aldosterone blockade translates safely into prevention of progression of kidney disease and prevention of CV events, including HF. The similarities in intervention, design, and endpoints will make it possible to analyze the combined cohort covering the spectrum of CKD in T2D, from early to late stages (Table 2).65,66,67

FIGARO-DKD was a randomized, double-blind phase III study of CV morbidity and mortality in T2D with CKD, and the primary endpoint was time to first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF. The key secondary composite outcome was time to kidney failure, a sustained ≥40% decrease in eGFR from baseline, or renal death. The key secondary composite CV endpoint was death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF. The primary endpoint was time to first occurrence of onset of kidney failure, a sustained ≥40% decrease in eGFR, or renal death. The key secondary composite CV outcome was death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF.63 FIDELIO-DKD included 5734 patients with CKD and T2D (UACR ≥30–<300 mg/g, eGFR ≥25–<75 ml/min per 1.73 m², and serum potassium ≤4.8 mmol/l). The primary composite kidney endpoint and the key secondary composite CV were significantly reduced with finerenone compared with placebo; HR = 0.82; 95% CI, 0.73–0.93, P = 0.001 and HR = 0.86; 95% CI, 0.75–0.99; P = 0.03, respectively. A secondary composite kidney endpoint including kidney failure, a sustained ≥57% decrease in eGFR, and renal death was also reduced with finerenone, compared with placebo (HR = 0.76; 95% CI, 0.65–0.90). During the study, no difference was seen in glycated hemoglobin, and systolic BP was reduced by 2–3 mm Hg with finerenone, compared with placebo. The primary endpoint findings were consistent across subgroups. UACR was reduced by 14% with finerenone and 117 patients (4.5%) treated with finerenone and 117 patients (4.5%)
Table 2 | Clinical characteristics and key outcomes of the phase III FIDELIO-DKD and FIGARO-DKD studies with the nonsteroidal MRA finerenone<sup>58,63–65</sup>

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<tr>
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<th>FIGARO-DKD</th>
<th>FIDELIO-DKD</th>
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<tr>
<td><strong>Key inclusion criteria</strong></td>
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<tr>
<td>Aged ≥18 yr with CKD and T2D</td>
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<tr>
<td>eGFR 25–&lt;90 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt; and UACR 30–&lt;300 mg/g OR eGFR ≥60 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt; and UACR ≥300–≤5000 mg/g</td>
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<td>Aged ≥18 yr with CKD and T2D</td>
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<td>Pretreated with optimized therapy, including an ACEi or ARB at the maximum tolerated labeled dose for ≥4 wk</td>
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<td>Pretreated with optimized therapy, including an ACEi or ARB at the maximum tolerated labeled dose for ≥4 wk</td>
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<td>Serum potassium ≤4.8 mmol/l</td>
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<td><strong>Key exclusion criteria</strong></td>
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<td>Nondiabetic kidney disease, including clinically relevant renal artery stenosis</td>
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<td>HFrEF with NYHA class II–IV</td>
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<td>HbA1c &gt;12%</td>
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<td>Uncontrolled arterial hypertension</td>
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<td>Stroke, transient ICA, ACS, or hospitalization for HF within ≤30 d</td>
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<td><strong>Primary endpoint</strong></td>
<td>0.87 (0.76–0.98)</td>
<td>0.82 (0.73–0.93)</td>
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<td>A composite of time to first occurrence of:</td>
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<td>CV death</td>
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<td>Nonfatal MI</td>
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<td>Nonfatal stroke</td>
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<td>Hospitalization for HF</td>
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<td><strong>Secondary endpoints</strong></td>
<td>0.87 (0.76–1.01)</td>
<td>0.86 (0.75–0.99)</td>
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<tr>
<td>A composite of time to first occurrence of kidney failure, a sustained ≥40% decrease in eGFR from baseline over ≥4 wk, or renal death</td>
<td></td>
<td>A composite of time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF</td>
</tr>
<tr>
<td>Time to all-cause hospitalization</td>
<td>0.97 (0.90–1.04)</td>
<td>Time to all-cause mortality</td>
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<tr>
<td>Time to all-cause mortality</td>
<td>0.89 (0.77–1.04)</td>
<td>Time to all-cause hospitalization</td>
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<tr>
<td>Change in UACR from baseline to month 4</td>
<td>0.68 (0.65–0.70)</td>
<td>Time to first occurrence of onset of kidney failure, a sustained decrease in eGFR ≥57% over ≥4 wk, or renal death</td>
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<tr>
<td></td>
<td>0.77 (0.60–0.99)</td>
<td>0.69 (0.66–0.71)</td>
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<tr>
<td>A composite of time to first occurrence of kidney failure, or a sustained ≥57% decrease in eGFR over ≥4 wk, or renal death</td>
<td></td>
<td>Change in UACR from baseline to month 4</td>
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ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease; FIGARO-DKD, Finerenone in reducing cardiovascular mortality and morbidity in Diabetic Kidney Disease; HbA1c, glycated hemoglobin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICA, ischemic cerebral attack; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

For endpoints, hazard ratios with 95% CIs are given, except for change in UACR, for which the ratio of the least-squares mean change from baseline to month 4 is given, with 95% CIs.
receiving placebo (HR = 0.71; 95% CI, 0.53–0.94; P = 0.016). 67

Microvascular damage is a generalized problem in diabetes, leading to not only CKD but also diabetic retinopathy, a leading cause of blindness, and a feared complication of diabetes. 1 A meta-analysis demonstrated that blocking the renin–angiotensin–aldosterone system could reduce diabetic retinopathy. 58 Also, the suggestion has been made that MRAs may reduce progression of retinopathy, 69 and substudies of the FIDELIO-DKD and FIGARO-DKD studies will investigate whether finerenone can reduce progression of non-proliferative diabetic retinopathy (NCT04477707, NCT04795726). These studies with finerenone are not designed specifically to investigate eye complications, and thus a positive signal would need to be confirmed in a dedicated study of diabetic retinopathy.

Another nonsteroidal MRA, esaxerenone, was recently registered in Japan for the treatment of hypertension. Esaxerenone was tested in a phase IIb study in Japanese patients with T2D and elevated urinary albumin excretion of 12 weeks. The study demonstrated that esaxerenone, when added to RAS inhibitors, dose-dependently reduced UACR by 38%–56%, compared with RAS inhibitors alone. Hyperkalemia was the cause of study discontinuation in 3%–10% of patients on esaxerenone. 59

The findings from the phase IIb study were extended in the phase III ESAX-DN (esaxerenone [CS-3150] in patients with T2D and microalbuminuria) study, in which the primary endpoint was the proportion of patients achieving remission of albuminuria (defined as UACR <30 mg/g creatinine and a ≥30% reduction in UACR from baseline at 2 consecutive time points). The study demonstrated that esaxerenone induced significant remission of moderately increased albuminuria in T2D (n = 455) when added to RAS inhibition for 52 weeks, compared with RAS inhibitors alone. 56 Overall, 49 patients (22%) and 9 patients (4%) in the esaxerenone and placebo groups, respectively, achieved UACR remission (normal to mildly increased albuminuria and a 30% decline in UACR from baseline [P < 0.001]). The change in UACR from baseline to end of treatment was a 58% reduction with esaxerenone versus 8% with placebo. Significant reductions occurred in systolic and diastolic BP, by −10 and −5 mm Hg, respectively, which were not associated with the reduction in UACR. In addition to remission of albuminuria, there was a significant improvement in the time to first transition to overt albuminuria (HR = 0.23; 95% CI, 0.11–0.48). Concerning safety, more patients had a serum potassium level of ≥6.0 mEq/l or ≥5.5 mEq/l on 2 consecutive measurements in the esaxerenone group (20 [9%]) versus placebo (5 [2%]), but these events were mostly asymptomatic and resolved after dosage reduction, and they resulted in drug discontinuation in just 4% of patients. After the end of treatment, there was a 4-week washout of medication; during this period, a significant difference in UACR remained between groups. These data suggest a lasting effect, in line with potential modification of inflammation and fibrosis, in contrast to a hemodynamic effect, which would be expected to be transient. A longer washout period may be required to substantiate these findings.

Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline for management of diabetes in patients with CKD recommended SGLT-2i’s in addition to lifestyle therapy, control of cardiorenal risk factors, and RAS inhibition for renoprotection in CKD and T2D. 70 The KDIGO guideline does not discuss the role of nonsteroidal MRAs in the treatment of CKD in diabetes, because the outcome studies were not published at the time that this guideline, and other contemporary guidelines, became available. Finerenone has been approved for CKD in T2D by the United States Food & Drug Administration and the European Medicines Agency. 71 The 2022 Standards of Medical Care in Diabetes from the American Diabetes Association recommend finerenone to reduce cardiovascular events and progression of kidney disease in people at high risk or who do not tolerate SGLT-2i’s. 72 When the FIDELIO-DKD and FIGARO-DKD studies were initiated, the use of SGLT-2i’s to reduce cardiorenal risk was not licensed in many countries, and the approved indication was for treatment initiation in patients with a higher eGFR level than the recommended guidelines (≥60 ml/min per 1.73 m2 vs. ≥30 ml/min per 1.73 m2, respectively). 70,73,74 In the FIDELIO-DKD study, the eGFR criteria for initiation of an SGLT-2i were met by only ~12% of patients. 75 Furthermore, SGLT-2i’s were used in only 259 of 5674 patients (4.6%) in the FIDELIO-DKD study at baseline. 58,76 After the start of the study, SGLT-2i treatment was initiated as a new medication in 328 patients (5.8%). Recent register-based study data from the US have demonstrated that <1% of patients with CKD and diabetes were treated with an SGLT-2i in 2019. 77 The recent guidelines 75,76 and data from dedicated renal studies with SGLT-2i’s 10,78 are anticipated to increase the use of SGLT-2i’s in patients with CKD and T2D. The mode of action of SGLT-2i’s probably involves hemodynamic actions reducing intraglomerular pressure, and improved oxygen tension in the kidney, which are different pathways than have been suggested for the MRAs in reducing inflammation and fibrosis. 79,80 Thus, the potential for the combination of these treatments may provide an interesting opportunity for patient management. In line with this possibility, the effect of finerenone and esaxerenone on outcomes was independent of the use of SGLT-2i’s, 56,58 demonstrating, for example, that the reduction in albuminuria with finerenone after 4 months was similar in patients with versus without SGLT-2i use at baseline in the FIDELIO-DKD study, and lower rates of hyperkalemia-related adverse events were observed in patients receiving both finerenone and an SGLT-2i, compared with those not receiving an SGLT-2i. 76 However, additional data are needed to clarify whether the beneficial effects can be combined.

The GLP-1RAs are another newer class of glucose-lowering agents. GLP-1RAs have demonstrated CV benefits in patients
with T2D, particularly in relation to atherosclerotic CV disease, and in patients with CKD and T2D, they may also have beneficial effects on kidney outcomes. 81 Although a dedicated kidney study with a GLP-1RA has not yet been completed, a study evaluating semaglutide is ongoing (NCT03819153) in patients with CKD and T2D. In the FIDELIO-DKD study, GLP-1RAs were used in 394 patients (6.9%) at baseline and were initiated as a new medication during the study in 368 patients (6.5%). 82 Again, the benefit of finerenone was independent of GLP-1RA use, suggesting that the agents may be combined to optimize benefits, although dedicated studies are lacking. Going forward, an improved understanding may be needed about optimization of patient selection for the nonsteroidal MRAs, together with its potential combination with SGLT-2i’s and/or GLP-1RA use. Data for treatment with finerenone for patients with T1D with CKD or nondiabetic CKD are not available.

Conclusions
For decades, the potential for a cardiorenal protective effect of aldosterone blockade in patients with CKD and T2D has been of interest. Study of this idea has been difficult due to the incidence of side effects with steroidal MRAs, such as hyperkalemia. In patients with established CKD, spironolactone and eplerenone reduced albuminuria, but trials were stopped due to hyperkalemia. The nonsteroidal MRAs finerenone and esaxerenone have demonstrated reduction in albuminuria in patients with CKD and T2D, with only minor potassium-related drug discontinuation. Finerenone demonstrated reduction in progression of kidney disease, and CV benefit, in patients with early to advanced CKD and T2D, with only minor incidence of drug discontinuation due to hyperkalemia. Finerenone has been approved and is now recommended in guidelines for management of CKD in T2D. These data suggest a role for finerenone and potentially other nonsteroidal MRAs across the spectrum of CKD in T2D.

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REFERENCES


