Modifying chronic kidney disease progression with the mineralocorticoid receptor antagonist finerenone in patients with type 2 diabetes

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Abstract

In patients with type 2 diabetes, chronic kidney disease (CKD) is the most common cause of kidney failure. With its increasing prevalence and limited treatment options, CKD is a major contributor to the global burden of disease. Although recent guidelines for the control of hypertension and hyperglycaemia, as well as the use of renin-angiotensin system inhibitors and, more recently, sodium-glucose co-transporter-2 inhibitors, have improved outcomes for patients with CKD and diabetes, there is still a high residual risk of CKD progression and adverse cardiovascular events. In this review, we discuss the recently published FIDELIO-DKD and FIGARO-DKD studies and FIDELITY prespecified individual patient analysis. Together, these studies have established finerenone, a novel non-steroidal mineralocorticoid receptor antagonist, as an effective treatment for kidney and cardiovascular protection and welcome addition to the pillars of treatment to slow CKD progression in patients with type 2 diabetes.

Keywords
chronic kidney disease, mineralocorticoid receptor antagonist, type 2 diabetes

1 INTRODUCTION

In the next 20 years, the number of patients with diabetes mellitus is estimated to rise by 51%, reaching 700 million or 10.9% of the global population by 2045. Patients with diabetes are at risk for developing chronic complications that affect multiple organs and contribute to diabetic comorbidities and the global burden of the disease. Diabetic kidney disease (DKD) is one of the most common complications arising from diabetes, affecting approximately 40% of patients with diabetes. DKD typically develops after diabetes duration of 10 years in type 1 diabetes but may be present at the time of diagnosis in type 2 diabetes (T2D). DKD is defined as abnormalities of kidney structure or function, present for >3 months, and requires one of two criteria: estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m² or persistent albuminuria. The term DKD has been used to refer to chronic kidney disease (CKD) caused by the diabetes; however, the differential diagnosis of DKD can be challenging because CKD in patients with diabetes can present with highly heterogeneous clinical and laboratory abnormalities, i.e. 15%-20% do not manifest albuminuria. Current screening guidelines recommend assessment of both albuminuria and eGFR because both are independently and synergistically associated with mortality and progression to end-stage kidney disease (ESKD). DKD is the most common cause of ESKD, and both diabetes and DKD are strongly associated with cardiovascular disease (CVD) and CVD-related adverse outcomes.

The treatment of hypertension, in particular blockade of the renin-angiotensin system (RAS), has been the cornerstone of treatment of DKD. However, despite optimized blood pressure control...
with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) and optimized glycaemic control, there is still an unmet need to reduce the risk of progression to ESKD and development of DKD-related CVD. Advances in the understanding of DKD pathophysiology and identification of new targets beyond the RAS have opened new treatment possibilities. Sodium-glucose cotransporter-2 inhibitors (SGLT-2is) have emerged as a new class of antidiabetic medications that can both slow the progression of DKD and reduce cardiovascular (CV) events in patients with T2D and existing CV disease or CV risk factors; however, the uptake of the SGLT-2is has been slow.

Over the past two decades, deleterious effects of aldosterone in the pathophysiology of cardiorenal disease have been increasingly recognized and blockade of its mineralocorticoid receptor (MR) has arisen as a therapeutic approach. Steroidal MR antagonists (MRAs) showed protective effect in non-diabetic and diabetic CKD animal models and reduced proteinuria or albuminuria and slowed CKD progression in clinical applications, albeit with increased risk of hyperkalaemia and renal dysfunction. In this review, we will focus on finerenone, the novel non-steroidal MRA (NS-MRA) with a favourable side effect profile and discuss its potential benefits as a novel disease-modifying agent for the treatment of patients with CKD and T2D.

2 | PATHOPHYSIOLOGY OF DIABETIC KIDNEY DISEASE

Chronic hyperglycaemia is the key risk factor for development and progression of CKD, and the phenotype of DKD is only observed in this context. If the glycated haemoglobin A1c, biomarker of long-term glycaemic control, remains below 6.5%, microvascular complications, including DKD, do not develop. High glucose concentrations affect various resident cells in the kidney, with endothelial cells, cells lining the vasculature and the renal tubules being particularly susceptible to glucose-induced toxicity. High intracellular glucose concentrations activate multiple metabolic and inflammatory pathways in these cells that lead to the generation of toxic intermediates, advanced glycation end products, reactive oxygen species, inflammatory cytokines, and growth and fibrotic factors. Prolonged exposure to such a toxic environment exerts deleterious effects on kidney function and morphology. Tubular and glomerular hypertrophies are characteristic features of DKD associated with a decline in kidney function. Of note, in animal models of DKD, tubular hypertrophy precedes glomerular hypertrophy, and inhibition of the tubular hypertrophy with an inhibitor of ornithine decarboxylase (the rate-limiting enzyme of polyamine synthesis) prevents glomerulosclerosis and development of DKD. Hypertrophy of the proximal tubule and high filtered load of glucose drive increased reabsorption of glucose and sodium chloride by the SGLT-2 in the proximal tubule, resulting in decreased sodium delivery to the macula densa cells of the juxtaglomerular apparatus (JGA). Decreased delivery of sodium to the JGA results in: (a) intrarenal activation of renin-angiotensin-aldosterone system (RAAS) cascade, leading to efferent arteriolar vasoconstriction, increased intraglomerular pressure, and glomerular hyperfiltration, and (b) inhibition of adenosine production, resulting in absence of vasodilatation, increased renal plasma flow, and further exacerbation of the increase in intraglomerular pressure and glomerular hyperfiltration. Over time, hyperfiltration and increased intraglomerular pressure introduces mechanical stress and increased oxygen demand, resulting in glomerular injury and development and progression of DKD. In addition, and increasingly appreciated, intrarenal RAAS stimulation activates a variety of downstream proinflammatory and profibrotic pathways. Aldosterone released from the visceral adipocytes, particularly in obese people, has been shown to contribute to inflammation and kidney injury as reflected by increases in albuminuria. Evidence came from a large, multicentre, prospective study of over a thousand newly diagnosed hypertensive patients that addressed the relationship between body mass index, aldosterone, plasma renin activity and aldosterone-renin ratio. Clear elevations of aldosterone were noted in this cohort, with stronger association in patients who were overweight and obese, thus suggesting a pathophysiological link between aldosterone production and fat deposition. This association was not found in patients with primary aldosteronism. Furthermore, an early increase in aldosterone signalling has been shown in animal models of metabolic syndrome.

3 | TREATMENT OF DIABETIC KIDNEY DISEASE

DKD usually manifests as a decline in GFR, persistent albuminuria and hypertension. Early diagnosis of DKD is essential to introduce measures to slow or halt the disease progression and its related complications, particularly CV. Multiple treatment strategies used in combination are required and include glycaemic control, blood pressure control (<130/80 mmHg) and management of dyslipidaemia, together with lifestyle changes. RAS inhibitors, ACEIs and ARBs, which reduce blood pressure, intraglomerular hypertension and albuminuria, are recommended in the setting of diabetes, established CKD, and hypertension because of their beneficial effects on renal and CV outcomes. ACEIs/ARBs have been shown to slow, but not halt, the progression of DKD, and this incomplete response of DKD to the RAS inhibitors may be because of angiotensin escape, which has been reported in up to 53% of patients after 1 year of RAAS blockade. Aldosterone breakthrough has been associated with an accelerated decline in eGFR in both patients with T2D and with type 1 diabetes nephropathy and is frequent in patients treated with short-acting ARBs. Aldosterone breakthrough has also been associated with reversal of the beneficial effects of ACEIs on LV hypertrophy and functional capacity.

Glycaemic control initiated early in the course of diabetes is well established for the prevention of DKD. The latest glucose-lowering therapies, such as SGLT-2is, show benefits beyond blood glucose control. Recent CV and renal outcome studies showed that the SGLT-2i class of antidiabetic medications can both slow the progression of DKD (CREDiT and DAPA-CKD) and reduce CV events in
patients with T2D and existing CV disease or CV risk factors (EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58). In CREDENCE and DAPA-CKD, SGLT-2i therapy slowed the decline in eGFR in patients with diabetes and eGFR down to 30 and 25 ml/min/1.73 m², respectively, and a re-analysis of the CREDENCE data indicates that canagliflozin retards the progression of DKD in patients with T2D and an eGFR <30 ml/min/1.73 m². Trials evaluating glucagon-like peptide-1 receptor agonists (GLP-1 RAs) also showed beneficial effects on CV outcomes, particularly in patients with T2D and CVD or who are at high risk for CVD. However, their renoprotective mechanisms are less well established and not well understood.

4 | FINERENONE

In addition to the RAS blockers and SGLT-2is, a new class of agents called NS-MRAs is now available (Figure 1) because of efforts to identify new potent, selective and cardioprotective MRAs with a favourable safety profile. Steroidal MRAs have documented clinical benefit in patients with hypertension, heart failure and left ventricular dysfunction. RALES, the first trial to investigate steroidal MRAs, showed the CV and renal benefits of spironolactone, while the subsequent EPHESUS trial showed benefits of eplerenone, a more selective but less potent steroidal MRA. The beneficial effect of MRAs on proteinuria or albuminuria in patients treated with RAS inhibitors has also been shown by small-scale clinical trials. The wider use of spironolactone and eplerenone in patients with CKD has been limited because of associated complications such as antiandrogenic side effects, hyperkalaemia and worsening of kidney function. These complications were not a limiting factor for the use of finerenone as shown in the phase II ARTS programme (ARTS, ARTS-HF and ARTS-DN). In patients with T2D and DKD, finerenone reduced albuminuria and N-terminal pro B-type natriuretic peptide, with a lower risk of hyperkalaemia than observed with steroidal MRAs. Recently, finerenone has been approved by the US Food and Drug Administration to reduce the risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks and hospitalization for heart failure in people with T2D. It is the only MRA available for this indication. The finerenone programme included two phase 3 trials that had complementary protocols: FIDELIO-DKD (Finnenone in reducing kiDney failure and disease prOgression in Diabetic Kidney Disease) and FIGARO-DKD (Finnenone in reducinG cArdiovascular morTality and mOrbidity in Diabetic Kidney Disease). These were independent, event-driven, randomized, double-blind, placebo-controlled trials with similar designs and reciprocal primary and key secondary outcomes (i.e. the primary endpoint in one trial corresponds with the key secondary endpoint in the other). FIDELIO-DKD investigated the efficacy and safety of finerenone in delaying CKD progression in advanced CKD, whereas FIGARO-DKD evaluated the efficacy and safety of finerenone in reducing CV morbidity and mortality in earlier stages of CKD. In addition, the finerenone programme included a prespecified individual patient analysis of both trials, FIDELITY. The primary outcomes were defined as CV endpoints and renal endpoints, including doubling of serum creatinine and time to ESKD.

4.1 | Efficacy

In FIDELIO-DKD, the effects of finerenone were investigated on cardio renal morbidity and mortality in patients with CKD and T2D, treated with a maximally tolerated dose of an ACEI or ARB. Patients with T2D were eligible if they had a serum potassium level ≤4.8 mmol/L and if they met the CKD criteria of either urinary albumin-to-creatinine ratio (UACR) between ≥30 (but <300) mg/g and eGFR of 25 to <60 ml/min/1.73 m² and a history of diabetic retinopathy, or UACR of ≥300 mg/g (but ≤5000 mg/g) and eGFR of 25 to <75 ml/min/1.73 m². In total, 5734 patients were randomized to receive oral finerenone or placebo.

Results from FIDELIO-DKD showed that in patients with DKD and T2D, treatment with finerenone significantly slowed the progression of DKD. During a median follow-up of 2.6 years, finerenone compared with placebo decreased the primary composite outcome (kidney failure, sustained GFR decrease by ≥40%, death from renal cause) by 18% [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.73-0.93, p = .001]. Finerenone also significantly reduced the key secondary composite outcome (CV death, non-fatal myocardial infarction, non-fatal stroke, or heart failure hospitalization) by 14% (HR 0.86, 95% CI 0.75-0.99, p = .03) compared with placebo. These effects were seen as early as 1 month into the trial and persisted throughout, indicating that finerenone protects against adverse CV outcomes in patients with DKD and T2D. Finerenone had a modest effect to reduce systolic blood pressure (decrements from baseline to month 1 and to month 12 were −3.0 and −2.1 mmHg, respectively, compared with −0.1 and 0.9 mmHg, respectively, with placebo). Finerenone had no effect on glycated haemoglobin A1c, indicating that the drug's beneficial
renoprotective effects were mediated via non-glycaemic mechanisms (see subsequent discussion and mechanism of action).

In the FIGARO trial, which was similar in design to FIDELIO, the primary composite outcome was CV (CV death, non-fatal myocardial infarction, non-fatal stroke, hypertensive heart failure), whereas the key secondary outcome was renal (kidney failure, sustained GFR decrease ≥40%, death from renal causes), i.e. the mirror image of FIDELIO.48 During a mean follow-up of 3.4 years, the primary outcome was reduced by 13% (HR 0.87, 95% CI 0.76-0.98, p = .03) and the secondary composite outcome was reduced by 13% (HR 0.87, 95% CI 0.76-1.01). In a post-hoc, propensity-matched analysis of FIDELIO with CREDENCE, Agarwal et al. compared the cardiorenal outcome to a subgroup of FIDELIO diabetic subjects who had similar inclusion and exclusion criteria to those in CREDENCE.19 In the FIDELIO CREDENCE like-population (finerenone vs. placebo) the cardiorenal endpoint (HR 0.74, 95% CI 0.63-0.87, p = .0003) was similar to that in CREDENCE (HR 0.70, 95% CI 0.59-0.82).19

The FIDELITY analysis included over 13,026 people followed for a median of 3 years.36 The analysis focused on time-to-event efficacy outcomes, which were (a) a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, and (b) a composite of kidney failure, a sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death. The analyses showed a 23% risk reduction in doubling (≥57% reduction) in serum creatinine, and a 20% risk reduction in ESKD. In addition, there was a 14% risk reduction in CV events, primarily driven by reduction in heart failure hospitalization and reduction in CV death.66 The blood pressure changes in FIDELITY were modest (2.5 mmHg mean systolic blood pressure reduction) but cannot explain the CV and renal protective effects of finerenone.

4.2 | Safety

The total incidence of treatment-emergent adverse events was similar between the finerenone and placebo groups.47,48 Hyperkalaemia-related adverse events were twice as frequent with finerenone compared with placebo in FIDELIO (18.3% vs. 9.0%) and FIGARO (10.8% vs. 5.3%). In FIDELIO, the serum potassium levels increased by a maximum of 0.23 mmol/L and remained steady throughout the study.47 The FIDELITY pooled analysis indicated that hyperkalaemia led to permanent treatment discontinuation more frequently in patients receiving finerenone (1.7%) than placebo (0.6%). Among patients with an eGFR ≥60, the discontinuation rate was 0.9% for finerenone versus 0.4% for placebo. Other than hyperkalaemia, no clinically significant side effects were observed with finerenone in FIDELIO and FIGARO, including gynecomastia, impotence and menstrual irregularities, which have been reported with steroidal MR agonists.

The effect of finerenone versus other MRAs has been examined in two studies.41,43 In 392 patients with heart failure with reduced ejection fraction and moderate CKD, the mean increase in serum potassium with finerenone (0.04-0.30 meq/L) was significantly less than with spironolactone (0.45 meq/L) (p < .01) and the incidence of hyperkalaemia was significantly less (5.3% vs. 12.7%, p < .05).41 In the ARTS-HF trial, the mean increase in serum potassium with eplerenone (0.262 meq/L) was greater than in each of the five finerenone groups (0.119-0.202 meq/L).53 Serum potassium at any time during the study was 4.7% in the eplerenone group compared with 3.6%-3.8% in the finerenone groups receiving <15 mg/day.

4.3 | Mechanism of action

The MR is a ligand-induced transcription factor from the nuclear receptor superfamily that is expressed in many tissues/cell types, including the heart, kidneys and vasculature.12 Binding of its physiological ligand, the steroid hormone aldosterone, promotes conformational change in MR and its translocation from the cell cytoplasm to the nucleus, where it binds to specific hormone-response elements and recruits transcriptional cofactors, allowing transcription or repression of its target genes.12,50 Finerenone acts as a bulky-passive NS-MRA and impairs MR signalling at various levels.50,51 Upon binding, finerenone induces a conformational change in the receptor that inhibits the binding of aldosterone and other mineralocorticoids. This diminishes the nuclear accumulation of MR and its turnover and inhibits recruitment of the transcriptional cofactors.12,50 Recent reviews provide greater detail regarding how NS-MRAs interact with the aldosterone receptor and how they are different from steroidal MRAs.13,14 Unlike RAS inhibitors and the SGLT-2is, the renoprotective effect of finerenone is not known to be mediated by altered renal haemodynamics or altered tubuloglomerular feedback, but rather by its anti-inflammatory, antifibrotic and antioxidative actions.15,33,52 Therefore, one might expect it to be completely additive to ACEIs/ARBs and SGLT-2is, as was shown in the FIDELIO-DKD study.47

In response to injury, cortical and medullary fibrosis is a common endpoint of CKD caused by various insults. Aldosterone infusion in rats increases NADPH oxidase activity and reactive oxygen species and directly stimulates superoxide anion generation in mesangial cells.54 Aldosterone also promotes mesangial apoptosis,55 stimulates collagen synthesis in mesangial cells both in vivo and in vitro,36,57 promotes podocyte damage,58 causes endothelial dysfunction and increases oxidative stress in the vasculature.60 MR inhibition reduces podocyte damage, decreases proteinuria, retards glomerulosclerosis, and decreases proteinuria and fibrosis, and these beneficial effects are reversed with aldosterone administration.61-65 In the heart, aldosterone promotes apoptosis of cardiomyocytes and myocardial fibrosis, leading to abnormal cardiac remodelling and impaired contractility.66

In streptozotocin-induced diabetic rats and db/db mice, MR blockade with both spironolactone and eplerenone reduces collagen deposition in glomerular, tubulointerstitial, and perivascular areas and decreases albuminuria.66-69 Similar results have been reported with finerenone.70 In a variety of models of kidney injury, finerenone has been shown to inhibit proinflammatory and profibrotic pathways, decreases proteinuria and block interstitial fibrosis71,72 without change in blood pressure. Finerenone also inhibits profibrotic and proinflammatory gene expression in the heart, prevents myocardial fibrosis, and improves myocardial...
function at non-blood pressure-lowering doses. Similar results have been reported with other MRAs and MR knockout. In summary, a considerable body of preclinical evidence indicates that the protective effects of finerenone and other MRAs are mediated via their anti-inflammatory, antifibrotic and antioxidative stress properties (Figure 1).

4.4 | Comparison with other mineralocorticoid receptors

In preclinical studies, NS-MRAs showed a different pharmacological profile from steroidal MRAs. Finerenone had greater MR selectivity than spironolactone and higher receptor binding affinity than eplerenone. Binding of finerenone and eplerenone led to differential MR cofactor modulation, resulting in differential gene expression profiles. In patients with chronic heart failure and mild-to-moderate CKD, a head-to-head study with spironolactone showed that finerenone had comparable effects on efficacy markers and cardiac biomarkers of haemodynamic stress and albuminuria and reduced rates of adverse effects, such as hyperkalaemia and renal dysfunction. The lower potential for side effects with finerenone is because of differences in selectivity toward MRs. The less selective MRA spironolactone can unspecifically bind and antagonize androgen and progesterone receptors, leading to anti-androgenic and pro-gestational side effects.

5 | OTHER THERAPIES: ADDITIVE WITH FINERENONE

5.1 | Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Antihypertensive agents such as ACEIs and ARBs are recommended as first-line drugs in the management of CKD of both diabetic and non-diabetic origin. RAS inhibitors are effective in all stages of CKD and recommended for patients presenting with either hypertension, proteinuric CKD, or reduced eGFR <60 ml/min/1.73 m² and UACR ≥300 mg/g. Combination therapy with an ACEI and an ARB is associated with an increased risk of serious adverse events, including acute kidney injury and hyperkalaemia, and is not recommended for the treatment of CKD. MRAs in combination with RAS inhibitors have been shown to reduce albuminuria and lower risk of CKD progression, independently of blood pressure control, in patients with CKD and T2D. In the ARTS-DN trial, addition of finerenone to RAS inhibitors in patients with diabetes and proteinuric CKD reduced UACR in a dose-dependent manner with low rates of hyperkalaemia. Results from the FIDELIO-DKD and FIGARO trials in patients with T2D and CKD confirmed that finerenone on a background of maximal RAS blockade therapy reduced albuminuria and slowed the progression of GFR decline. If hyperkalaemia develops during treatment with MRAs in combination with RAS blockade therapies, a number of therapeutic options are available, including decreased dietary potassium intake, correction of acidosis with bicarbonate, and use of diuretics and newer potassium binders, such as patiromer and sodium zirconium cyclosilicate.

5.2 | Sodium-glucose co-transporter-2 inhibitors

SGLT-2is have been shown to improve cardiorenal outcomes in diabetic and non-diabetic patients. When used with RAS blockers in patients with T2D and moderate CKD, SGLT-2is reduce the risk of CVD and CKD progression regardless of glycaemic control. SGLT-2 is a high-capacity, low-affinity transporter that is expressed almost exclusively in the initial segment of the proximal tubule and is responsible for the majority of glucose resorption. Upregulation of SGLT-2 expression increases the renal threshold for glucose excretion, thereby contributing to the maintenance of hyperglycaemia. The main mechanism of action of SGLT-2is is to block glucose reabsorption by the SGLT-2, causing glucosuria and natriuresis. Glucosuria reduces the plasma glucose concentration, whereas increased sodium delivery to the macula densa cells of the JGA corrects the disturbance in tubuloglomerular feedback by causing afferent arteriolar vasoconstriction and efferent arteriolar vasodilatation. This results in decreased intraglomerular pressure, reduced glomerular hyperfiltration, decreased albuminuria and diminished rate of decline in GFR. SGLT-2is also exert multiple other renoprotective effects, which have recently been reviewed. It is important to keep in mind, however, that while all of this is true when the GFR is above 45 ml/min/1.73 m², SGLT-2is still have benefits down to a GFR of 30 ml/min/1.73 m². Hence, it is not their glucose-lowering effect that is driving the renal protective benefit.

Treatment with a combination of finerenone and SGLT-2is in the setting of T2D and CKD may offer increased renal and CV protection. A recent study that combined finerenone and SGLT-2 inhibition by empagliflozin in an animal model of hypertension-induced end-organ damage provided clear evidence of additive benefit to reduce cardiac fibrosis and albuminuria, as well as to reduce certain aspects of renal fibrosis. In the FIDELIO-DKD study, 4.4% of patients received finerenone on a background of SGLT-2is, and, in this limited number of participants, the renoprotective effect appeared to be similar to that in non-SGLT-2i-treated subjects, suggesting an additive effect. Moreover, SGLT-2is also reduce the incidence of hyperkalaemia associated with finerenone in this trial.

6 | CARDIOVASCULAR DISEASE AND CHRONIC KIDNEY DISEASE

Patients with CKD, both diabetic and non-diabetic, are at high risk for developing adverse CV complications. In people with diabetes, the presence of CKD markedly increases CV risk, and it is CVD, not ESKD, that is the leading cause of death in these patients. Nevertheless, CVD often remains underdiagnosed and undertreated in patients with CKD. CKD causes a systemic, chronic proinflammatory state
contributing to vascular and myocardial remodelling processes that result in accelerated atherogenesis, vascular calcification and vascular senescence, as well as myocardial fibrosis and calcification of cardiac valves.\textsuperscript{9} Therapies to decrease the risk of CVD in CKD have recently been updated, raising the hope that CV risk in patients with CKD can be reduced in the future.\textsuperscript{5} At the moment, however, data from CV outcomes trials in the high-risk group of patients with CKD, particularly those with advanced CKD, are limited. CV outcomes trials with glucose-lowering SGLT-2is or GLP-1 RAs consistently show CV benefits in patients with T2D at high CV risk.\textsuperscript{11,35} Results from the FIDELIO-DKD trial showed that finerenone has the potential to provide a new treatment option for patients with CKD and T2D, with and without history of atherosclerotic CV disease.\textsuperscript{89} FIDELIO-DKD showed the benefit of finerenone for both primary and secondary prevention of CV events in patients with T2D and CKD, and well-controlled blood pressure and blood glucose levels, when used in combination with the optimized RAS blockade therapy.\textsuperscript{89} Results from FIGARO-DKD show that the addition of finerenone to standard medical therapy significantly reduces the risk of CV mortality and other CV events in patients with CKD and T2D.\textsuperscript{47}

7  |  CONCLUSION

DKD affects a large proportion of the population globally. It is a chronic, progressive disease with a complex pathophysiology that is not fully understood. Identification of novel underlying mechanisms of DKD has revealed potential druggable targets and has led to the development of new therapeutic approaches. Data regarding the use of SGLT-2is, MRAs and their combinations with RAS inhibitors are evolving and impacting standard-of-care options. Safety and efficacy data available for NS-MRA finerenone support its clinical use alongside these therapies. In the near future, the results of trials with GLP-1 RAs will help to clarify whether they represent another therapeutic class with renal benefit. After 20 years of treatment scarcity in nephrology, SGLT-2is and the NS-MRA finerenone are at hand to further slow CKD progression from diabetes. Nephrologists now have the opportunity to use pillars of therapy, much like cardiologists do in heart failure, to improve prognosis and slow disease progression.

8  |  USE OF FINERENONE IN MODIFYING CHRONIC KIDNEY DISEASE PROGRESSION: OPINION

ACEIs and ARBs have long been considered preferred first-line agents for patients with diabetes with GFR <60 ml/min/1.73 m\textsuperscript{2} (stage 3) and UACR ≥30 mg/g Cr because of their proven benefit, and this is unlikely to change in the absence of head-to-head studies with other renal protective medications. However, the ACEIs and ARBs are rarely titrated to their maximum dose to achieve optimal renal benefit. Because the aetiology of CKD is multifactorial,\textsuperscript{15} once a stable dose of the ACEI or ARB has been achieved, the authors believe that a second renal protective agent should be added without delay. Both the SGLT-2is and finerenone slow the progression of DKD and provide CV protection against hospitalization for heart failure. Because the SGLT-2is are approved for slowing kidney disease progression, reducing CV risk and reducing plasma glucose concentration if GFR is above 45 ml/min/1.73 m\textsuperscript{2}, we favour addition of the SGLT-2i if glycaemic control is needed within 4 weeks after the ACEI or ARB dose has been maximized. Nonetheless, CKD can continue to progress despite combined SGLT-2i/ACEI or ARB therapy. Therefore, we advocate the addition of finerenone within 4 weeks as the third pillar of therapy. If glycaemic control is adequate or SGLT-2is are contraindicated, finerenone should be added to the ACEI or ARB.

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data supporting the concept in this article can be found in the references cited in the text and, thus, are readily available to the public. Data sharing is not applicable to this article as no new data were created or analyzed.

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