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REVIEW ARTICLE

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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.[1] 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.[1,2] Diabetic kidney disease (DKD) is one of the most common complications arising from diabetes, affecting approximately 40% of patients with diabetes.[2-4] 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).[5] 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 m^2 or persistent albuminuria.[4] 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.[6,7] 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).[5,7] 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.[2,8,9]

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 co-transporter-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.[10,11]

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.[12-14] 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.[12-14] 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.[15] If the glycated haemoglobin A1c, biomarker of long-term glycaemic control, remains below 6.5%, microvascular complications, including DKD, do not develop.[16] 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.[17] 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.[15,17] 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.[15,17] 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.[18] 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 afferent vasodilatation, increased renal plasma flow, and further exacerbation of the increase in intraglomerular pressure and glomerular hyperfiltration.[15] Over time, hyperfiltration and increased intraglomerular pressure introduces mechanical stress and increased oxygen demand, resulting in glomerular injury and development and progression of DKD.[15] In addition, and increasingly appreciated, intrarenal RAAS stimulation activates a variety of downstream proinflammatory and profibrotic pathways.[19] 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.[20] 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.[20,21] 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.[13,22]

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.[9] 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.[4,5,23] 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.[4,5] 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.[24,25] Aldosterone breakthrough has been associated with an accelerated decline in eGFR in both patients with T2D and with type 1 diabetes nephropathy,[24-27] and is frequent in patients treated with short-acting ARBs.[26,27] Aldosterone breakthrough has also been associated with reversal of the beneficial effects of ACEIs on LV hypertrophy[28] and functional capacity.[29]

Glycaemic control initiated early in the course of diabetes is well established for the prevention of DKD.[30] The latest glucose-lowering therapies, such as SGLT-2is, show benefits beyond blood glucose control.[15,31] Recent CV and renal outcome studies showed that the SGLT-2i class of antidiabetic medications can both slow the progression of DKD (CREDENCE 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).[11] 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 m^2, 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 m^2.[32-34] 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.[35]

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.[13,14,36] Steroidal MRAs have documented clinical benefit in patients with hypertension, heart failure and left ventricular dysfunction.[37,38] 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.[37,38] The beneficial effect of MRAs on proteinuria or albuminuria in patients treated with RAS inhibitors has also been shown by small-scale clinical trials.[13] 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.[37-40] 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).[41-43] 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.[42,43] 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 (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease) and FIGARO-DKD (FInerenone 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).[44,45] 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.[46] The primary outcomes were defined as CV endpoints and renal endpoints, including doubling of serum creatinine and time to ESKD.[46]

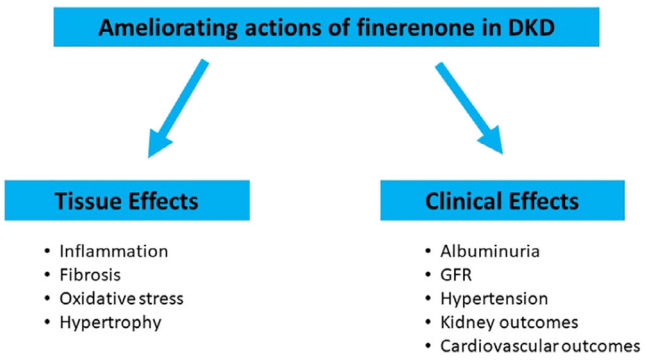

FIGURE 1 Current standard of care in diabetic kidney disease (DKD) focuses on glycaemic control and blood pressure management, while inflammation and fibrosis remain largely unaddressed. By blocking mineralocorticoid receptor-mediated sodium reabsorption and mineralocorticoid receptor overactivation, finerenone showed inhibitory activity against inflammatory, fibrotic, oxidative and hypertrophic processes in preclinical models. Finerenone has been licensed in the United States for reducing cardiorenal events in patients with chronic kidney disease associated with type 2 diabetes. GFR, glomerular filtration rate

4.1 | Efficacy

In FIDELIO-DKD, the effects of finerenone were investigated on cardiorenal morbidity and mortality in patients with CKD and T2D, treated with a maximally tolerated dose of an ACEI or ARB.[44,47] 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 m^2 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 m^2. In total, 5734 patients were randomized to receive oral finerenone or placebo.[44,47]

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, $p = .001$].[47] 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.[47] 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).[47] 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.[49] 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).[49]

The FIDELITY analysis included over 13 026 people followed for a median of 3 years.[46] 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.[46] 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).[43] 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[53] 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,[56,57] promotes podocyte damage,[58] causes endothelial dysfunction[59] 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.[36]

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, decrease proteinuria and block interstitial fibrosis[71,72] 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.[71,73] Similar results have been reported with other MRAs[74] and MR knockout.[75-77]

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.[14,51] Finerenone had greater MR selectivity than spironolactone and higher receptor binding affinity than eplerenone.[14,51] Binding of finerenone and eplerenone led to differential MR cofactor modulation, resulting in differential gene expression profiles.[73] 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.[41] 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.[51]

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.[78] 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 m^2 and UACR ≥300 mg/g.[5] 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.[79] 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.[42] 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.[47,48] 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.[80,81]

5.2 | Sodium-glucose co-transporter-2 inhibitors

SGLT-2is have been shown to improve cardiorenal outcomes in diabetic and non-diabetic patients.[11,32] 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.[11] 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.[15,31] Upregulation of SGLT-2 expression increases the renal threshold for glucose excretion, thereby contributing to the maintenance of hyperglycaemia.[31,82,83] The main mechanism of action of SGLT-2is is to block glucose reabsorption by the SGLT-2, causing glucosuria and natriuresis.[15,31] 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.[15] 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 m^2, SGLT-2is still have benefits down to a GFR of 30 ml/min/1.73 m^2.[11,33] 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.[13] 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.[84] 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.[47] Moreover, SGLT-2is also reduce the incidence of hyperkalaemia associated with finerenone in this trial.[85]

6 | CARDIOVASCULAR DISEASE AND CHRONIC KIDNEY DISEASE

Patients with CKD, both diabetic and non-diabetic, are at high risk for developing adverse CV complications.[2] 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.[2,86] Nevertheless, CVD often remains underdiagnosed and undertreated in patients with CKD.[87,88] 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.[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.[4] 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.[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.[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.[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.[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^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,[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^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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REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019.
2. Fried LF, Folkerts K, Smeta B, et al. Targeted literature review of the burden of illness in patients with chronic kidney disease and type 2 diabetes. *Am J Manag Care*. 2021;27(8 Suppl):S168-S177.
3. United States Renal Data System. *USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.

4. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;98(4S):S1-S115.
5. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes–2021. *Diabetes Care*. 2021;44(Suppl 1):S151-S167.
6. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA*. 2016; 316(6):602-610.
7. Amin AP, Whaley-Connell AT, Li S, et al. The synergistic relationship between estimated GFR and microalbuminuria in predicting long-term progression to ESRD or death in patients with diabetes: results from the kidney early evaluation program (KEEP). *Am J Kidney Dis*. 2013; 61(4 suppl 2):S12-S23.
8. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215-2222.
9. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. *Circulation*. 2021;143(11):1157-1172.
10. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults, 1999–2018. *N Engl J Med*. 2021;384(23): 2219-2228.
11. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6(2):148-158.
12. Bauersachs J, Jaisser F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. *Hypertension*. 2015;65(2):257-263.
13. Barrera-Chimal J, Bonnard B, Jaisser F. Roles of mineralocorticoid receptors in cardiovascular and cardiorenal diseases. *Annu Rev Physiol*. 2022;84(14):14.11-14.26.
14. Kintscher U, Bakris GL, Kolkhof P. Novel non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease. *Br J Pharmacol*. 2021. doi:10.1111/bph.15747. Online ahead of print.
15. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. *Nat Rev Nephrol*. 2021;17(5): 319-334.
16. International Expert Committee. International expert committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32(7):1327-1334.
17. Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. *Nat Rev Dis Primers*. 2015;1:15018.
18. Thomson SC, Deng A, Bao D, Satriano J, Blantz RC, Vallon V. Ornithine decarboxylase, kidney size, and the tubular hypothesis of glomerular hyperfiltration in experimental diabetes. *J Clin Invest*. 2001; 107(2):217-224.
19. Ruggenenti P, Cravedi P, Remuzzi G. The RAAS in the pathogenesis and treatment of diabetic nephropathy. *Nat Rev Nephrol*. 2010;6(6): 319-330.
20. Rossi GP, Belfiore A, Bernini G, et al. Body mass index predicts plasma aldosterone concentrations in overweight-obese primary hypertensive patients. *J Clin Endocrinol Metab*. 2008;93(7):2566-2571.
21. Hsueh WA, Wyne K. Renin-angiotensin-aldosterone system in diabetes and hypertension. *J Clin Hypertens (Greenwich)*. 2011;13(4): 224-237.
22. Nagase M, Yoshida S, Shibata S, et al. Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. *J Am Soc Nephrol*. 2006;17(12): 3438-3446.
23. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical Care in Diabetes–2021. *Diabetes Care*. 2021;44(suppl 1):S125-S150.
24. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol*. 2007;3(9):486-492.
25. Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension*. 2003; 41(1):64-68.
26. Moranne O, Bakris G, Fafin C, Favre G, Pradier C, Esnault VL. Determinants and changes associated with aldosterone breakthrough after angiotensin II receptor blockade in patients with type 2 diabetes with overt nephropathy. *Clin J Am Soc Nephrol*. 2013;8(10):1694-1701.
27. Schjoedt KJ, Andersen S, Rossing P, Tarnow L, Parving HH. Aldosterone escape during blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy is associated with enhanced decline in glomerular filtration rate. *Diabetologia*. 2004;47(11):1936-1939.
28. Sato A, Saruta T. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in essential hypertensive patients with left ventricular hypertrophy. *J Int Med Res*. 2001;29(1):13-21.
29. Cicoira M, Zanolla L, Franceschini L, et al. Relation of aldosterone "escape" despite angiotensin-converting enzyme inhibitor administration to impaired exercise capacity in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2002;89(4):403-407.
30. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589.
31. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. *Nat Rev Nephrol*. 2017; 13(1):11-26.
32. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15): 1436-1446.
33. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019; 380(24):2295-2306.
34. Bakris G, Oshima M, Mahaffey KW, et al. Effects of canagliflozin in patients with baseline eGFR <30 ml/min per 1.73 m(2): subgroup analysis of the randomized CREDENCE trial. *Clin J Am Soc Nephrol*. 2020;15(12):1705-1714.
35. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.
36. Kolkhof P, Bärfacker L. 30 years of the mineralocorticoid receptor: mineralocorticoid receptor antagonists: 60 years of research and development. *J Endocrinol*. 2017;234(1):T125-T140.
37. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone evaluation study investigators. *N Engl J Med*. 1999; 341(10):709-717.
38. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321.
39. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1): 11-21.
40. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized Aldactone evaluation study. *N Engl J Med*. 2004;351(6):543-551.
41. 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.
42. 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.

43. 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.
44. Bakris GL, Agarwal R, Anker SD, et al. Design and baseline characteristics of the Finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial. *Am J Nephrol*. 2019;50(5):333-344.
45. 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.
46. 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. *Eur Heart J*. 2021;43:474-484.
47. 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.
48. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *New Engl J Med*. 2021;385:2252-2263.
49. Agarwal R, Anker SD, Filippatos G, et al. Importance of trial design when investigating cardiorenal outcomes in patients with CKD and T2D: focus on CREDENCE and FIDELIO-DKD. *Am Heart J*. 2021;242:162.
50. Amazit L, Le Billan F, Kolkhof P, et al. Finerenone impedes aldosterone-dependent nuclear import of the mineralocorticoid receptor and prevents genomic recruitment of steroid receptor coactivator-1. *J Biol Chem*. 2015;290(36):21876-21889.
51. Fagart J, Hillisch A, Huyet J, et al. A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule. *J Biol Chem*. 2010;285(39):29932-29940.
52. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. *Kidney Int*. 2019;96(2):302-319.
53. Nishiyama A, Yao L, Nagai Y, et al. Possible contributions of reactive oxygen species and mitogen-activated protein kinase to renal injury in aldosterone/salt-induced hypertensive rats. *Hypertension*. 2004;43(4):841-848.
54. Miyata K, Rahman M, Shokoji T, et al. Aldosterone stimulates reactive oxygen species production through activation of NADPH oxidase in rat mesangial cells. *J Am Soc Nephrol*. 2005;16(10):2906-2912.
55. Mathew JT, Patni H, Chaudhary AN, et al. Aldosterone induces mesangial cell apoptosis both in vivo and in vitro. *Am J Physiol Renal Physiol*. 2008;295(1):F73-F81.
56. Diah S, Zhang GX, Nagai Y, et al. Aldosterone induces myofibroblastic transdifferentiation and collagen gene expression through the rho-kinase dependent signaling pathway in rat mesangial cells. *Exp Cell Res*. 2008;314(20):3654-3662.
57. Brilla CG, Zhou G, Matsubara L, Weber KT. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. *J Mol Cell Cardiol*. 1994;26(7):809-820.
58. Shibata S, Nagase M, Yoshida S, Kawachi H, Fujita T. Podocyte as the target for aldosterone: roles of oxidative stress and Sgk1. *Hypertension*. 2007;49(2):355-364.
59. Thum T, Schmitter K, Fleissner F, et al. Impairment of endothelial progenitor cell function and vascularization capacity by aldosterone in mice and humans. *Eur Heart J*. 2011;32(10):1275-1286.
60. Briet M, Schiffrin EL. Vascular actions of aldosterone. *J Vasc Res*. 2013;50(2):89-99.
61. Nagase M, Shibata S, Yoshida S, Nagase T, Gotoda T, Fujita T. Podocyte injury underlies the glomerulopathy of dahl salt-hypertensive rats and is reversed by aldosterone blocker. *Hypertension*. 2006;47(6):1084-1093.
62. Arai K, Tsuruoka H, Homma T. CS-3150, a novel non-steroidal mineralocorticoid receptor antagonist, prevents hypertension and cardiorenal injury in dahl salt-sensitive hypertensive rats. *Eur J Pharmacol*. 2015;769:266-273.
63. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest*. 1996;98(4):1063-1068.
64. Sun Y, Zhang J, Zhang JQ, Ramires FJ. Local angiotensin II and transforming growth factor-beta1 in renal fibrosis of rats. *Hypertension*. 2000;35(5):1078-1084.
65. Martin-Fernandez B, Rubio-Navarro A, Cortegano I, et al. Aldosterone induces renal fibrosis and inflammatory M1-macrophage subtype via mineralocorticoid receptor in rats. *PLoS ONE*. 2016;11(1):e0145946.
66. Fujisawa G, Okada K, Muto S, et al. Spironolactone prevents early renal injury in streptozotocin-induced diabetic rats. *Kidney Int*. 2004;66(4):1493-1502.
67. Guo C, Martinez-Vasquez D, Mendez GP, et al. Mineralocorticoid receptor antagonist reduces renal injury in rodent models of types 1 and 2 diabetes mellitus. *Endocrinology*. 2006;147(11):5363-5373.
68. Banki NF, Ver A, Wagner LJ, et al. Aldosterone antagonists in monotherapy are protective against streptozotocin-induced diabetic nephropathy in rats. *PLoS ONE*. 2012;7(6):e39938.
69. Lian M, Hewitson TD, Wigg B, Samuel CS, Chow F, Becker GJ. Long-term mineralocorticoid receptor blockade ameliorates progression of experimental diabetic renal disease. *Nephrol Dial Transplant*. 2012;27(3):906-912.
70. Lachaux M, Barrera-Chimal J, Nicol L, et al. Short- and long-term administration of the non-steroidal mineralocorticoid receptor antagonist finerenone opposes metabolic syndrome-related cardio-renal dysfunction. *Diabetes Obes Metab*. 2018;20(10):2399-2407.
71. Kolkhof P, Delbeck M, Kretschmer A, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol*. 2014;64(1):69-78.
72. Lattenist L, Lechner SM, Messaoudi S, et al. Nonsteroidal mineralocorticoid receptor antagonist Finerenone protects against acute kidney injury-mediated chronic kidney disease: role of oxidative stress. *Hypertension*. 2017;69(5):870-878.
73. Grune J, Beyhoff N, Smeir E, et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. *Hypertension*. 2018;71(4):599-608.
74. Michea L, Villagran A, Urzua A, et al. Mineralocorticoid receptor antagonism attenuates cardiac hypertrophy and prevents oxidative stress in uremic rats. *Hypertension*. 2008;52(2):295-300.
75. Fraccarollo D, Berger S, Galuppo P, et al. Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction. *Circulation*. 2011;123(4):400-408.
76. Rickard AJ, Morgan J, Tesch G, Funder JW, Fuller PJ, Young MJ. Deletion of mineralocorticoid receptors from macrophages protects against deoxycorticosterone/salt-induced cardiac fibrosis and increased blood pressure. *Hypertension*. 2009;54(3):537-543.
77. Usher MG, Duan SZ, Ivaschenko CY, et al. Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. *J Clin Invest*. 2010;120(9):3350-3364.
78. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the Management of Blood Pressure in chronic kidney disease. *Kidney Int*. 2021;99(3S):S1-S87.
79. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892-1903.
80. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015;372(3):222-231.
81. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211-221.

82. Norton L, Shannon CE, Fourcaudot M, et al. Sodium-glucose co-transporter (SGLT) and glucose transporter (GLUT) expression in the kidney of type 2 diabetic subjects. *Diabetes Obes Metab*. 2017;19(9):1322-1326.
83. Solini A, Rossi C, Mazzanti CM, Proietti A, Koepsell H, Ferrannini E. Sodium-glucose co-transporter (SGLT)2 and SGLT1 renal expression in patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19(9):1289-1294.
84. Kolkhof P, Hartmann E, Freyberger A, et al. Effects of finerenone combined with empagliflozin in a model of hypertension-induced end-organ damage. *Am J Nephrol*. 2021;52(8):642-652.
85. Agarwal R, Joseph A, Anker SD, et al. Hyperkalemia risk with Finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol*. 2022;33(1):225-237.
86. Thompson S, James M, Wiebe N, et al. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol*. 2015;26(10):2504-2511.
87. Tuttle KR, Alicic RZ, Duru OK, et al. Clinical characteristics of and risk factors for chronic kidney disease among adults and children: an analysis of the CURE-CKD registry. *JAMA Netw Open*. 2019;2(12):e1918169.
88. Chu CD, McCulloch CE, Banerjee T, et al. CKD awareness among US adults by future risk of kidney failure. *Am J Kidney Dis*. 2020;76(2):174-183.
89. Filippatos G, Anker SD, Agarwal R, et al. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. *Circulation*. 2021;143(6):540-552.

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