REVIEW

Focus on Finerenone, a Non-Steroidal MRA in Diabetic Kidney Disease. What Physicians Should Know?

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Abstract

Diabetes mellitus is not only a global concern in recent times but also has become the most common cause of chronic kidney disease which has a great impact on life expectancy, development of cardiovascular diseases, all-cause mortality, and morbidity. Despite the recent addition of SGLT2inhibitors along with ACEi and ARBs in the treatment armamentarium of diabetic kidney disease (DKD), there is still an unmet need to minimize the risk of progression to ESKD. Mineralocorticoid Receptor (MR) overactivation has proven to be a significant risk factor in CKD progression which has been targeted as a novel therapeutic modality. Finerenone as a non-steroidal MR Antagonist (MRA) has unique features of the mechanism of action in regards to inhibition of recruitment of transcriptional cofactors implicated in hypertrophic, proinflammatory, and profibrotic gene expression. Salient pharmacokinetic features like shorter half-life, insignificant drug-drug interactions, and not forming any major active metabolite have put the molecule far ahead of its other congener varieties. Pre-clinical and clinical studies have established the safety and efficacy of this molecule in the treatment of DKD. In spite of those results, issues like an appropriate time of initiation of the drug and clinical outcome as add-on therapy have to address on large-scale trial basis.

Keywords: Diabetic Kidney Disease, Mineralocorticoid Receptor Antagonist, Non-steroidal, safety, efficacy.

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INTRODUCTION

Diabetes mellitus (DM) is a global health problem that has affected an estimated 463 million persons in 2019[1]. Diabetic kidney disease (DKD) is found in up to 40% of these people, making it the most common cause of chronic kidney disease[2]. Diabetic individuals have an increased risk of morbidity, cardiovascular disease, and all-cause mortality[3,4]. The presence of chronic renal disease increases the incidence of cardiovascular and all-cause mortality up to a great extent [5-7]. Patients with DM have a 10-year reduction in life expectancy, while those with DKD have a 16-year reduction[8]. Diabetes mellitus and its complications are not only a personal but also a financial burden to society[9,10]. Albuminuria and a progressive decrease in glomerular filtration rate (GFR) characterize diabetic nephropathy (DN). Glomerulosclerosis, thickening and hypertrophy of the glomerular basement membrane, hypertrophy of renal cells, enlargement of mesangial cells, and tubulointerstitial fibrosis are the most common abnormalities seen in individuals with DN[11]. DKD is a disease that progresses from an early stage of hyperfiltration and renal hypertrophy to an incipient nephropathy stage with microalbuminuria and hypertension[12]. Patients develop overt nephropathy with proteinuria and a decrease in GFR over time, and some develop the end-stage kidney disease (ESKD)[13]. DKD is diagnosed clinically when a patient with diabetes has a reduced estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m2 and/or albuminuria (urinary albumin–creatinine ratio (UACR) of more than 30 mg/g). Albuminuria is also a significant risk factor for renal disease development, as well as the progression to end-stage kidney disease[14,15].

Unmet needs of available treatment options: - Treatments to prevent the progression of CKD in T2D have primarily focused on improving hyperglycaemia and hypertension management, as well as the use of Angiotensin-Converting Enzyme inhibitors (ACEis) or Angiotensin II Receptor Blockers(ARBs), throughout the previous two decades [16.17,18]. Since mid-2019, the American Diabetes Association has recommended sodium-glucose cotransporter-2 inhibitors (SGLT2is) in addition to an ACEi or ARB for the reduction of kidney and cardiovascular risk in patients with T2D who have albuminuria >30mg/g and an estimated glomerular filtration rate (eGFR) greater than 30mL/min/1.73m2, especially in those with albuminuria >300mg/g[19]. Despite the use of ACE inhibitors or ARBs in combination with SGLT2 inhibitors, there is still an unmet need to minimize the risk of progression to ESKD as well as CV morbidity and mortality[20]. As a result, new medicines targeting inflammation, fibrosis, oxidative stress, renal hemodynamics, glomerular hyperfiltration, the endothelin system, the Janus kinase(-JAK)-signal transducer and activator of transcription (STAT) pathway, and other factors are being developed[21,22]. N-acetyl-seryl aspartyl-lysyl-proline (AcSDKP), sirtuin 3 (SIRT3), glycolysis inhibitors, pyruvate kinase M2 type (PKM2) activators, and other possible therapeutic targets are constantly being discovered[23,24]. New information about DKD's pathogenesis is also being collected. The absence of endothelial glucocorticoid receptors, for example, has been shown to aggravate diabetic nephropathy in mice[25]. Before new treatments are used in ordinary clinical practice, more research and large-scale randomized controlled trials are required.

In short-term investigations in patients with DM with micro- or macroalbuminuria treated with ACE-Is or ARBs, further inhibition of the renin-angiotensin system with Mineralocorticoid Receptor Antagonists (MRAs) has been demonstrated to reduce albuminuria[26]. Indeed, MR overactivation accelerates DKD progression by increasing intraglomerular pressure and by non-hemodynamic consequences such as direct proinflammatory and profibrotic effects, as well as Klotho deficiency[27]. Combining MRAs with ACE-Is or ARBs, on the other hand, raises the risk of serious side effects, particularly hyperkalaemia, which is a major limitation of MRA use.

Role of Mineralocorticoid Receptor (MR) Blockade in Chronic Kidney Disease: - There is growing evidence that pathologic overactivation of the mineralocorticoid receptor (MR) causes inflammation and fibrosis, as well as is a critical factor of CKD development. As a result, MR blocking is being studied as a novel therapeutic strategy for slowing the course of CKD[28,29]. Early CKD interventions [KDIGO stages G1A2, G2A1 or G2A2] are more successful in slowing CKD progression and CKD-related morbidity and mortality[30,31]. Reducing inflammation and fibrosis as early as feasible may thus prove to be the most effective treatment. Although most clinicians are familiar with the steroidal hormones that activate the MR—aldosterone, and cortisol; MR antagonists (MRAs) are not

approved for use in patients with CKD or T2D and so are not routinely used[32-35]. Spironolactone and eplerenone, two of the available steroidal MRAs, are both beneficial in lowering mortality and hospitalization in the management of heart failure[36,37]. Their significance in slowing the progression of kidney disease to ESKD, however, is uncertain. Although a meta-analysis found that treatment with a steroidal mineralocorticoid receptor antagonist reduced urine protein or albumin excretion by 31% in individuals with CKD, but the data on objective clinical outcomes are missing[38].

Pharmacology of Finerenone: The nonsteroidal MRA Finerenone, formerly known as BAY 94-8862, has a high binding potential for the mineralocorticoid receptor[39]. It is a complete antagonist of the MR that is highly selective[40]. Finerenone, unlike spironolactone and eplerenone, which bind to the MR's ligand domain, causes a conformational change inside the MR complex, altering the receptor's stability and nuclear translocation[41]. Structurally it is a dihydropyridine derivative, although it has little action at the L-type calcium channel[42]. It has no active metabolites and it has a half-life of 2 hours[40]. Finerenone is highly polar and is less lipophilic than steroidal MRA[43]. According to quantitative whole-body autoradiography in rodents, it reaches at the same concentration in the kidneys and the heart[40]. Even though CYP3A4 is responsible for 90% of finerenone metabolism, renal function and serum albumin levels have an impact on the drug's serum levels[44]. It does not appear to interact clinically with cytochrome P450 [45] substrates and does not require dose adjustment in patients with mild or moderate hepatic impairment[46]. Finerenone has been shown to have good selectivity for the mineralocorticoid receptor, with an Half-maximal inhibitory concentration (IC50) of only 17.8 nmol/L (compared to 24.2 nmol/L for spironolactone and 990 nmol/L for eplerenone)[47]. Finerenone selectivity for the mineralocorticoid receptor is therefore substantially higher (>500-fold) than for the glucocorticoid, androgen, and progesterone receptors[48]. Finerenone exposure is higher in moderate and severe renal impairment patients, but not in mild renal impairment individuals[49].

Mechanism of action: Finerenone causes an MR blockage that is at least as effective as spironolactone and more selective than eplerenone[50]. Finerenone, unlike spironolactone and eplerenone, has a nonsteroidal structure that permits it to bind to the MR via a unique method that prevents recruitment of transcriptional cofactors implicated in hypertrophic, proinflammatory, and profibrotic gene expression[51,52]. Finerenone's mechanism of action is represented in Figure 1. Renal benefits of this MRA are demonstrated in preclinical

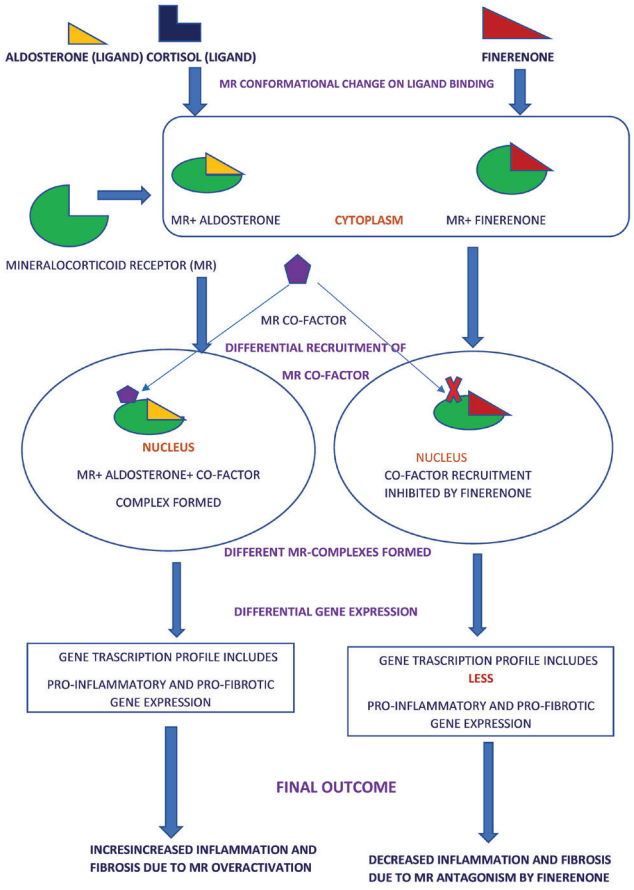

Figure 1. Mechanism of action of Finerenone[76]

animal models by decreased expression of proinflammatory and profibrotic markers in the kidney, protection from glomerular, tubular, and renal vascular damage, and an improvement in proteinuria[53-55]. Finerenone also showed a more effective reduction in cardiac hypertrophy, proteinuria, inflammation, and kidney fibrosis in mouse models when compared to an equi-natriuretic dose of the steroidal MRA eplerenone[56,57]. Salient Pharmacological differentiating features between Finerenone and other available MRAs (steroidal and non-steroidal) are mentioned in Table 1 and 2[68,69].

Table 1. Key differential pharmacological features with other MRAs (Spironolactone and Eplerenone) 66,67

Feature	Finerenone (Non-steroidal)	Spironolactone (Steroidal)	Eplerenone (Steroidal)
Mode of MR antagonism	Potent and selective[70]	Potent and non-selective	Less potent and more selective than Spironolactone
Tissue distribution pattern	Equally in kidney and heart[71]	6 times higher concentration in the kidneys than in the heart [72]	3 times higher concentration in the kidneys than in the heart [73]
Half-life	2hrs	1-2hrs	4-6hrs
Major metabolite(s)	None	7Alpha-thiomethylspironolactone Canrenone (half-life: 18–24 h)	None
Effect on cofactor recruitment in absence of aldosterone in vitro	Inverse agonist (inhibits cofactor binding in the absence of aldosterone)[75]	Partial agonistic cofactor recruitment[75]	Partial agonistic cofactor recruitment[75]
Effect on cofactor recruitment in the presence of aldosterone in vitro	More potent and efficacious than eplerenone in blocking MR cofactor binding and inducing corepressor binding[73]	Inhibition of cofactor recruitment	Inhibition of cofactor recruitment
Effect on mutated (S810L) MR in vitro	Antagonist	Agonist	Agonist
Effect on inflammation and fibrosis in mouse model of cardiac fibrosis	Finerenone (at,equi-natriuretic dose to eplerenone): strong inhibition of inflammation and fibrosis[73]	Less significant effects on inflammation and fibrosis[73]	Less significant effects on inflammation and fibrosis[73]
Effect on renal inflammation and fibrosis in a DOCA–salt rat model of CKD	Finerenone (at equi-natriuretic dose to eplerenone): significant systolic BP reduction only at highest dosage; greater protection from cardiac and renal injury and structural remodelling; stronger inhibition of renal expression of pro-inflammatory and pro-fibrotic markers[69]	Significant BP reduction; less efficacious proteinuria and renal injury reduction[69]	Significant BP reduction; less efficacious proteinuria and renal injury reduction[69]

MR: Mineralocorticoid receptor, DOCA: Deoxycorticosterone Acetate, CKD: Chronic Kidney Disease, BP: Blood Pressure

Efficacy evaluation in animal models: Finerenone has been found in animal experiments to minimize albuminuria and improve endothelial function and arterial elasticity by increasing nitric oxide bioavailability[58,59]. Finerenone has also been shown to slow the progression of acute kidney injury to chronic kidney disease by acting as an anti-inflammatory and antioxidant molecule[60-62]. Finerenone also appears to enhance glucose tolerance in obese rats fed with a high-fat diet[63]. Finerenone was found to be more effective than eplerenone in avoiding glomerular, tubular, and vascular damage in rats with deoxycorticosterone acetate/salt-induced renal injury, inhibiting renal expression of pro-inflammatory and profibrotic genes, and lowering proteinuria[64]. Huang et al.[65] found that reducing myeloid MR signalling protects the kidney without changing urine potassium levels in knockout mice. Preclinical investigations with BR-4628, a precursor of finerenone, have shown that it improves kidney structure and function without having a significant impact on urine sodium and potassium levels[66].

Table 2. Comparison of Finerenone with other Non-steroidal MRA in regards to Pharmacological features and trials done in Diabetic Kidney Disease100.

	Apararenone	Esaxerenone	Finerenone
Type of MRA	Non-steroidal (benzoxazinone derivative)	Non-steroidal (dihydropyridine derivative)	Non-steroidal (dihydropyridine derivative)
Selectivity	+++	+++	+++
Potency	+	+++	+++
Half-life	Long (approximately 250–300 h	20-30 hrs	2hrs
Major metabolite(s)	1118174	M4, M11, M1	None
Tissue distribution	Unknown	Same concentration in the kidneys and the heart, low concentration in the CNS	Same concentration in the kidneys and the heart
Dosing	5 mg or 10 mg/day	2.5-5 mg/day	10 mg or 20 mg/day
Side effects	Unknown	Hyperkalemia	Hyperkalemia
Important clinical studies in diabetic kidney disease	Wada et al.[96]	Itoh et al. [97] Ito et al. [98] ESAX-DN[99]	ARTS-DN FIDELIO-DKD FIGARO-DKD

Safety and efficacy of Finerenone in Diabetic Kidney Disease (DKD): The miner Alocorticoid Receptor antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) was a phase 2b randomized, double-blind, placebo-controlled study on 823 type 2 DM patients with albuminuria (UACR30mg/g), with an eGFR greater than 30mL/min/1.73m2, and a serum potassium concentration of 4.8mmol/L[77]. For 90 days, they were given varied doses of oral finerenone once daily or a placebo. Finerenone reduced UACR in a dose-dependent manner. Hyperkalaemia and subsequent finerenone discontinuation occurred in 1.8 percent of patients, compared to none in the placebo group. Between the placebo and finerenone groups, there were no differences in the occurrence of a 30% drop in eGFR or the incidence of severe and serious adverse events. Finerenone also had no effect on glycated haemoglobin (HbA1c) levels[78]. Due to the short duration of the previous study and the fact that UACR is not a surrogate marker of renal outcome, the FIDELIO-DKD (FInerenone in decreasing Kidney Failure and Disease Progression in Diabetic Kidney Disease) study was upgraded. A total of 5734 individuals with chronic renal disease and type 2 diabetes were enrolled in this phase 3 trial, which followed them for a median of 2.6 years[79]. Chronic kidney disease was classified using one of two sets of criteria: UACR 30–300 mg/g, eGFR 25–60 mL/min/1.73 m2, and a history of diabetic retinopathy, or UACR 300–5000 mg/gm. GFR25–75 mL/min/1.73 m2 GFR25–75 mL/min/1.73 m2 All patients were given a RAS inhibitor at the maximum recommended dose on the manufacturer's label that did not induce unacceptable side effects. Finerenone was found to reduce the risk of both primary (kidney failure, a sustained decrease of 40% in eGFR from baseline, or death from renal causes) and secondary (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) outcome events when compared to placebo. Hyperkalaemia was more common in the finerenone group, but discontinuation of the trial due to it was uncommon (2.3%). Finerenone reduced the incidence of the composite cardiovascular outcome independent of pre-existing cardiovascular illnesses, according to a subgroup analysis of these data. Finerenone decreased blood pressure by 2.1/0/9 mmHg more than placebo, however, there was no difference in body weight or HbA1c between the two groups[80]. FIGARO-DKD (FInerenone in Lowering Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) was another large phase 3 clinical research that investigated the effect of finerenone in reducing severe cardiovascular events and slowing DKD development[81]. It was a placebo-controlled, randomized,

double-blind study. They assigned 7437 individuals with an eGFR of 25 mL/min/1.73 m2 and a UACR of 30–5000 mg/g to finerenone or placebo therapy. The composite of time to cardiovascular death or non-fatal cardiovascular event was the primary objective (myocardial infarction, stroke, or hospitalization for heart failure). The composite of time to kidney failure, a sustained drop in eGFR of 40%, or renal death was a key secondary goal. Time to all-cause mortality, all-cause hospitalization, UACR change from baseline to month 4, and a composite outcome of time to the first occurrence of kidney failure or sustained fall in eGFR57 percent from baseline over at least 4 weeks or renal death were the other secondary endpoints. There was no significant difference in the overall frequency of adverse events across groups. Finerenone (1.2 percent) had a greater rate of hyperkalaemia-related trial discontinuation than placebo (0.4 percent) [82]. Only a special press release in May 2021 announced that the study's primary endpoint had been met[83]. Finerenone reduced albuminuria more than placebo at day 90 in a multicentre, randomized, double-blind, placebo-controlled phase 2b study among 96 Japanese patients with type 2 DM and DN who were treated with ACE-Is or ARBs; however, the change in serum potassium levels was similar in the two groups; no patient developed hyperkalemia[84]. In a recent meta-analysis, finerenone with ACE-Is or ARBs was not linked to hyperkalaemia, however, spironolactone and eplerenone, when taken with ACE-Is or ARBs, elevated the risk of hyperkalemia by 4.58 and 2.81 times, respectively[85]. On June 2021, the most recent meta-analysis of finerenone's efficacy and safety in patients with chronic kidney disease (CKD) was published. Finerenone appears to have a significant antiproteinuric impact in individuals with CKD, with a less negative effect on eGFR, according to this study. Although finerenone has a higher risk of hyperkalemia than placebo, it is associated with a decreased incidence of cardiovascular problems in people with CKD[86]. Summary of important clinical trials on Finerenone in Diabetic Kidney Disease is tabulated in Table 3.

Finerenone was approved by the FDA on July 9th, 2021, for the treatment of adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Finerenone is a first-in-class nonsteroidal mineralocorticoid receptor antagonist (MRA) that is used to minimize the risk of kidney failure, cardiovascular death, non-fatal myocardial infarction, and heart failure hospitalization. It's also the first and only nonsteroidal MRA approved for this patient group. The FDA granted the approval based on the findings of the phase 3 FIDELIO-DKD trial, which showed improved renal and cardiovascular outcomes in individuals with CKD and T2D[87].

CONCLUSION

Finerenone appears to slow the progression of DKD and may lower the risk of cardiovascular events in this high-risk group of people. Finerenone appears to be safer than other MRAs, despite the fact that it causes hyperkalaemia. Patients on a combination of finerenone and ACE-Is or ARBs, on the other hand, must be closely monitored. The FIDELIO-DKD and FIGARO-DKD investigations will examine the impact of a unique way to treating CKD in T2D that tackles the underlying disease processes, making them the largest CKD trial to date. The trials are also large enough to show efficacy and safety in this high-risk cohort for the major kidney and cardiovascular outcomes. Finally, the FIDELIO-DKD and FIGARO-DKD trials are superiority studies rather than safety trials, and they examine a medication that does not lower blood sugar. Future studies should be conducted based on the success of the FIDELIO-DKD trial to explore the notion that overactivation of the MR modulates a wide range of non-diabetic CKD clinical groups, many of which are underserved. As a result, these nondiabetic CKD groups may be responsive to nonsteroidal MRA therapy. In preclinical studies, the novel, nonsteroidal, selective MRA finerenone displays several promising differences from steroidal MRAs, with a mechanism of action separate from other developing cardiorenal medicine treatments in CKD and T2D.

EXPERT OPINION

Even with the widespread use of SGLT2 inhibitors and GLP-1 receptor agonists, DKD development remains a significant matter of concern. Nonsteroidal MRAs may help to mitigate this risk. However, there are a few clinical issues that must be addressed. First, it must be determined at which step of the DKD the process MRA should begin. Second, it's unknown whether nonsteroidal MRA monotherapy is useful for DKD. Third, because a subgroup analysis of FIDELIO-DKD revealed that finerenone reduced UACR

Table 3. Summary of Trials on Finerenone in Diabetic Kidney Disease (DKD)94,95

Trial name	Phase	Sample size	Patient Characteristics	Intervention	Follow up	Primary outcome	Key result	Safety
ARTS-DN	II	823	Type2DM with albuminuria (UACR $30mg/g) and eGFR of >30ml/min/1.73m2undertreatment with at least the minimum recommended of a RAS-blocker	Finerenone (1.25, 2.5, 5, 7.5, 10, w15, or 20mg daily) vs. placebo	90 days	Change in albuminuria	Finerenone provoked a dose-dependent reduction in UACR.	Drug discontinuation due to hyperkalemia was not observed with placebo and finerenone10mg/d, but occurred in 2.1%,3.2%, and 1.7%of patients in the finerenone7.5-,15-and 20-mg/d groups.
FIDELIO -DKD	III	5.734	T2D patients with advanced CKS (UACR 30–300 mg/ g eGFR 25–60 ml/min/1.73 m2 and a history of diabeticretinopathyorUACR300–5,000 mg/gandan eGFR of 25–75 ml/min/1.73 m2)	Finerenone (10 or 20 mg) vs Placebo	2.6 years	kidney failure, sustained decrease in eGFR 40% in the eGFR, or death from renal causes	The incidence of the primary outcome was 18% lower in the finerenone group The incidence of the key secondary outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) was 14% lower in the finerenone group Finerenone reduced albuminuria by 31% more than placebo	Incidence of hyperkalemia leading to treatment discontinuation in the finerenone and placebo groups: 2.3% and 0.9%, respectively Incidence of serum potassium levels[5.5 mmol/l in the finerenone and placebo groups: 21.7% and 9.8%, respectively
FIGARO -DKD	III	7,437)	T2D patients with UACR 30–300 mg/g and eGFR 25–90 ml/min/1.73 m2 (stage 2–4 CKD) or UACR 300–5,000 mg/g and an eGFR of at least 60 ml/min/1.73 m2 (stage 1 or 2 CKD	Finerenone (10 or 20 mg) vs Placebo	3.4 years	Cardiovascular death nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure	The primary outcome was significantly reduced by finerenone (HR 0.87; 95%CI: 076–0.98	The overall frequency of adverse events did not differ substantially between groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%).

ARTS, Mineralocorticoid Receptor Antagonist Tolerability Study; ARTS-DN, ARTS Diabetic Nephropathy study DM= Diabetes Mellitus, UACR= urinary albumin-to-creatinine ratio, eGFR =estimated glomerular filtration rate, RAS= renin-angiotensin system, 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, CKD= chronic kidney disease

with or without baseline GLP-1 receptor agonists use, it will be required to determine which anti-diabetic medications and nonsteroidal MRAs are efficacious in combination[88]. The position of nonsteroidal MRAs in DKD treatment will be determined by elucidating these topics. Novel treatment medicines for DKD that target inflammation and fibrosis are currently being developed[89]. JAK/STAT drugs, for example, have been demonstrated to have reno protective benefits in DKD patients[90]. It's critical to note that finerenone has clinically significant renal and cardiovascular protective effects that have yet to be determined with these new medicines. It is also possible that the combined impact of these medicines and nonsteroidal MRA will occur.

Nonsteroidal MRAs, unlike SGLT2 inhibitors and incretin-based drugs, can be adjusted for renoprotection without taking into account glucose-lowering effects in patients with DKD, which may be an advantage. Nonsteroidal MRAs are also expected to provide benefits other than cardiorenal protection. Endothelial cell MR has been demonstrated to mediate hypertensive remodelling in cerebral arteries, resulting in decreased cerebral perfusion, which can lead to stroke and dementia[91]. Furthermore, cortical thickness in the brain has been demonstrated to be adversely linked with MR expression in humans[92]. Finally, MR has been implicated in the progression of sarcopenia[93]. Because of its powerful anti-inflammatory characteristics, nonsteroidal MRAs may be effective for geriatric syndromes in diabetic individuals, according to these findings. It will be fascinating to see how nonsteroidal MRAs affect diabetic complications and related illnesses in future investigations.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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