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REVIEW

A Narrative Review of Diabetic Kidney Disease: Previous and Current Evidence-Based Therapeutic Approaches

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ABSTRACT

Diabetic kidney disease (DKD) is one of the most important diabetic complications. DKD is also the most common cause of chronic kidney disease (CKD) and end-stage renal disease. This review focused on potential therapeutic drugs for which there is established evidence of treatment for DKD. The earliest evidence for DKD treatment was established with renin–angiotensin system (RAS) inhibitors; however, their efficacy was partial. Recently, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, including empagliflozin (EMPA-REG Outcome), canagliflozin (CREDENCE trial), and dapagliflozin (DAPA-CKD), demonstrated a significant and clinically relevant reduction in the risks of albuminuria and progression of nephropathy, doubling of serum creatinine levels, and initiation of renal replacement therapy. Additionally, incretin-based therapeutic agents, such as glucagon-like peptide 1, liraglutide (LEADER), and dipeptidyl peptidase 4 inhibitors, linagliptin (CARMERINA) have elicited vasotropic actions, suggesting a potential for reducing the risk of DKD. Until recently, mineralocorticoid receptor antagonists (MRAs) have not been suitable for DKD treatment because of their adverse effect of hyperkalemia. In contrast, finerenone, a non-steroidal MRA, significantly reduced renal composite endpoint without severe hyperkalemia that would force its discontinuation (FIDELIO-DKD). Thus, the mainstay treatments of DKD are RAS inhibitors, SGLT2 inhibitors, incretin-based therapeutic agents, and non-steroidal MRA, or in other words, the DKD "fantastic four".

Keywords: Diabetic kidney disease; Dipeptidyl peptidase 4 inhibitors; End-stage kidney disease; Glucagon-like peptide 1; Mineralocorticoid receptor antagonists; Renin–angiotensin system inhibitors; Sodium-glucose co-transporter 2 inhibitors

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Key Summary Points

The incidence of diabetes is rapidly increasing in the population; therefore, therapeutic agents that meet the medical needs of its complications (such as diabetic kidney disease) must be identified.

The combination of ACEIs and ARBs did not improve outcomes and was linked to an increased risk of serious adverse events; thus, it is not recommended in DKD.

SGLT2 inhibitors have a protective effect on renal outcomes in DKD, including decreased albuminuria, increased serum creatinine levels, and induced renal replacement therapy.

Beyond their effects on glycemic control, incretin-based therapeutic agents have potent pleiotropic effects in patients with DKD.

Non-steroidal mineralocorticoid receptor antagonists (MRAs) have been developed to selectively increase benefits and decrease adverse effects via changes in receptor affinity and tissue tropism.

INTRODUCTION

The number of patients with diabetes worldwide is rapidly increasing. Additionally, type 2 diabetes is reported as the seventh leading cause of mortality in the USA (http://www.cdc.gov). According to the recent report published by International Diabetes Foundation, the number of patients with diabetes worldwide is approximately 380 million, and the total number of patients will reach 590 million by 2035. Moreover, most new patients with diabetes will emerge from Southeast Asia and West Pacific regions (http://www.idf.org/). Two large clinical trials, the Diabetes Control and Complications Trial in type 1 diabetes and the United Kingdom Prospective Diabetes Study in type 2 diabetes, clearly indicated that intensive glycemic control slows the progression of diabetic complications, including diabetic kidney disease (DKD). These clinical studies suggest that hyperglycemia is a major factor in developing DKD [1, 2]. In addition to hyperglycemia, activation of the renin–angiotensin system (RAS) plays a significant role in the pathogenesis of DKD [3–5].

Many studies have reported that the blockade of RAS using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin I receptor blockers (ARBs) slows the progression of DKD [6–10]. However, recent studies suggest that ACEIs and ARBs could not stop the progression of DKD.

The Empagliflozin and Progression of Kidney Disease in type 2 diabetes (EMPA-REG Renal outcome) trial, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, and the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial revealed that sodium-glucose cotransporter 2 (SGLT2) inhibitors have a protective effect on renal outcomes in DKD, including decreased albuminuria, doubled serum creatinine levels, and induction of renal replacement therapy [11–13].

Several studies have reported that glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP4) inhibitors exhibit potent pleiotropic effects against DKD beyond their effects on glycemic control. The pre-specified secondary analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial revealed that the rates of the development and progression of DKD were lower in the liraglutide-treated group than in the placebo group [14]. Furthermore, the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) trial indicated that linagliptin, a DPP4 inhibitor, decreased the risk of progression of microvascular diseases, including albuminuria, in patients with DKD [15].

Recently, third-generation mineralocorticoid receptor antagonists (MRAs) using non-steroidal molecules have been developed to selectively

increase benefits and decrease adverse effects through changes in receptor affinity and tissue tropism; The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial revealed favorable properties of renal protection [16, 17]. Thus, finerenone may be a promising drug for the unmet medical need of DKD. This review aims to discuss the latest DKD treatment using four types of drugs, which can be called the "fantastic four". This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

EFFECTS OF ACEIS AND ARBS ON DKD

The RAS plays a significant role in the development of DKD. The angiotensin-converting enzyme converts angiotensin I to angiotensin II, which increases aldosterone secretion, antidiuretic hormone (vasopressin) secretion, microvascular vasoconstriction, and sympathetic nerve activity, leading to inflammation and activation of fibrosis signaling. Activation of the angiotensin II–protein kinase C (PKC) pathway in the glomeruli is associated with processes that increase the extracellular matrix, thicken the basement membrane, increase endothelial dysfunction, and activate cytokines or transforming growth factor-β (TGFβ) [18, 19]. Furthermore, we have reported that the angiotensin II-activated TGFβ/Smad1 pathway increases the extracellular matrix in mesangial cells. Olmesartan, an ARB, directly inhibits Smad1 expression, thereby decreasing mesangial expansion in DKD [3, 5].

The Reduction of Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial is a randomized comparison of the losartan-treated group (50–100 mg/day) versus the placebo group. The primary endpoints of the study were creatinine doubling, end-stage kidney disease (ESKD), or death. Administration of losartan decreased the risk of creatinine doubling and ESKD by 25% and 28%, respectively [9] (Table 1). The Irbesartan Diabetic Nephropathy Trial (IDNT) had three arms: irbesartan, amlodipine, and placebo, and the primary endpoints were creatinine doubling, ESKD development, and death. The primary endpoints, particularly creatinine doubling, demonstrated a relatively lower risk with the irbesartan group than with the placebo group [10] (Table 1). However, despite this promising progress, DKD still exhibits residual cardiorenal morbidity and mortality. Thus, the next obvious question was whether the combination of ACEIs and ARBs would provide additional benefits. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared telmisartan, ramipril, or both in patients at high risk for vascular events and RAS inhibition. The combination of ACEIs and ARBs did not improve outcomes and was associated with an increased risk of serious adverse events such as acute kidney injury, hyperkalemia, or syncope, and therefore cannot be recommended in DKD [20].

EFFECTS OF SGLT2 INHIBITORS ON DKD

The EMPA-REG Outcome trial compared empagliflozin with placebo in patients with type 2 diabetes who were at high risk for cardiovascular events. The primary composite outcomes were death from cardiovascular diseases, nonfatal myocardial infarction, or nonfatal stroke. The pre-specified secondary analysis of the EMPA-REG Renal outcome trial revealed that empagliflozin decreased the risk of incident or worsening DKD by 39% (hazard ratio (HR) in the empagliflozin group, 0.61; 95% confidence interval (CI) 0.53–0.70; $P < 0.001$); the risk of creatinine doubling reduced significantly by 44%. Moreover, the risk of renal replacement therapy, including hemodialysis initiation, was significantly decreased by 55% in the study [11]. The subgroup findings of the EMPA-REG Renal outcome trial, including the patients with overt DKD (defined as a urinary albumin-to-creatinine ratio greater than

Table 1 Clinical trials of four drugs for diabetic kidney disease

Type of drug	Abbreviated trial title	Full trial title	Year of publication	Number of subjects enrolled	Interventions	Primary composite kidney outcome	Renal outcomes
RAS inhibitors	RENAAL [9]	Reduction of endpoints in non-insulin-dependent diabetes mellitus with the angiotensin II antagonist losartan	2001	1513	Losartan 50–100 mg vs. placebo	Doubling of serum creatinine, ESKD, or death	Risk reduction; 16%
	IDNT [10]	Irbesartan diabetic nephropathy trial	2001	1715	Irbesartan 20 mg vs. amlodipine 10 mg vs. placebo	Doubling of serum creatinine, ESKD, or death	Risk reduction; 20% vs. placebo, 23% vs. amlodipine
SGLT2 inhibitors	EMPA-REG OUTCOME [11]	Empagliflozin and progression of kidney disease in type 2 diabetes	2016	7020	Empagliflozin 10 mg vs. placebo	Doubling of serum creatinine, initiation of kidney replacement therapy, or death from renal disease	Risk reduction by 39% in the risk of incident or worsening DKD (HR 0.61; 95% CI 0.53–0.70)
	CREDENCE [12]	Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation	2019	4401	Canagliflozin 100 mg vs. placebo	Doubling of serum creatinine, ESKD, or death from renal or cardiovascular disease	Risk reduction; 30% vs. placebo (HR 0.70; 95% CI 0.59–0.82)
	DAPA-CKD [13]	Dapagliflozin and prevention of adverse outcomes in chronic kidney disease	2020	4304	Dapagliflozin 5 mg or 10 mg vs. placebo	Sustained $\geq$ 50% decline in eGFR, ESKD, or death from renal disease	Risk reduction; 50% vs. placebo (HR 0.50; 95% CI 0.35–0.72)

Table 1 continued

Type of drug	Abbreviated trial title	Full trial title	Year of publication	Number of subjects enrolled	Interventions	Primary composite kidney outcome	Renal outcomes
Incretin-based therapeutic agents	LEADER [14]	Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results	2017	9340	Liraglutide 1.8 mg vs. placebo	New-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, ESKD, or death due to renal disease	Risk reduction; 22% vs. placebo (HR 0.78; 95% CI 0.67–0.92)
	CARMELINA [15]	Cardiovascular and renal microvascular outcome study with linagliptin	2019	6979		Sustained $\geq$ 40% decline in eGFR, ESKD, or renal death (secondary endpoint) Progression of microalbuminuria in overt proteinuria (another evaluation value)	Risk reduction in progression of microalbuminuria; 14% vs. placebo (HR 0.86; 95% CI 0.78–0.95)

Table 1 continued

Type of drug	Abbreviated trial title	Full trial title	Year of publication	Number of subjects enrolled	Interventions	Primary composite kidney outcome	Renal outcomes
MRAs	ARTS-DN [54]	Mineralocorticoid receptor antagonist tolerability study-diabetic nephropathy	2013	1501	Finerenone 1–25 mg vs. placebo	Change in urinary albumin-to-creatinine ratio	Finerenone reduced urinary albumin-to-creatinine ratio compared to placebo as follows; 0.76 (90% CI 0.65–0.88; 10 mg/day), and 0.62 (90% CI 0.54–0.72; 20 mg/day)
	FIDELIO-DKD [16]	Finerenone in reducing kidney failure and disease progression in diabetic kidney disease	2020	5674	Finerenone 10 mg or 20 mg vs. placebo	Sustained ≥ 40% decline in eGFR, ESKD, or death from kidney cause (primary endpoint)	HR 0.82; 95% CI 0.73–0.93
	FIGARO-DKD (17)	Finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease	2021	7352	Finerenone 10 mg or 20 mg vs. placebo	Sustained ≥ 40% decline in eGFR, ESKD, or death from kidney cause (secondary endpoint)	HR 0.87; 95% CI 0.76–1.01

RAS renin–angiotensin system, *ESKD* end-stage kidney disease, *SGLT2* sodium-glucose co-transporter 2, *HR* hazard ratio, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *MRAs* mineralocorticoid receptor antagonists

300 mg/g creatinine), revealed that empagliflozin significantly decreased the risk of the hard renal composite endpoint (defined as an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m^2, sustained creatinine doubling from baseline levels, induction of renal replacement therapy, or renal death (HR in the empagliflozin group, 0.40; 95% CI 0.21–0.77) [21] (Table 1).

In the CREDENCE trial in DKD, long-term treatment with canagliflozin demonstrated renal protection effects in patients with eGFR between 30 and 90 mL/min/1.73 m^2 (mean eGFR 56 mL/min/1.73 m^2), urinary albumin-to-creatinine ratio between 300 and 5000 mg/g, and receiving the maximum dose of RAS inhibitors. Canagliflozin decreased the risk of a primary outcome, which was defined as ESKD (initiation of dialysis, renal transplantation, or sustained eGFR of less than 15 mL/min/1.73 m^2), creatinine doubling, or death from renal or cardiovascular causes by 30% (HR in the canagliflozin group, 0.70; 95% CI 0.59–0.82; $P = 0.00001$) [12] (Table 1). Furthermore, the DAPA-CKD trial has recently evaluated dapagliflozin in patients with CKD, regardless of the presence or absence of diabetes. In this study, dapagliflozin significantly reduced the risk of the composite endpoint by a 50% reduction in eGFR, ESKD, and renal or cardiovascular death in patients with or without diabetes (HR in the dapagliflozin group, 0.50; 95% CI 0.35–0.72) [13] (Table 1).

Several reno-protective mechanisms by SGLT2 inhibitors have been proposed. The regulation of tubuloglomerular feedback, which maintains the eGFR by adjusting the preglomerular arteriole tone; a high concentration of sodium chloride constricts afferent arterioles, thereby decreasing the eGFR [22]. Administration of SGLT2 inhibitors increases sodium supply to the macula densa. Subsequently, tubuloglomerular feedback modulates arteriolar tone and decreases glomerular flow, thereby normalizing glomerular hyperfiltration [23–25].

Inflammation and oxidative stress play a significant role in the development and progression of CKD [19, 26, 27]. Additionally, they can increase mesangial expansion and interstitial fibrosis. The nuclear factor, NF-kappa-B has been reported to stimulate cytokine expression via reactive oxygen species and PKCβ [18, 28]. Furthermore, we have reported that tumor necrosis factor-α has a crucial role in the development of microvascular complications including DKD [29, 30]. Treatment with empagliflozin reduced inflammation and subsequently decreased glomerular extracellular matrix accumulation-related signaling pathway, TGFβ, and connective tissue growth factor [31]. However, the precise mechanism underlying the anti-inflammatory effect of SGLT2 inhibitors is unclear. One possible explanation is that SGLT2 inhibitors increase mild ketosis; β-hydroxybutyrate, a type of ketone body, interacts with G-protein-coupled receptors or activates other signaling pathways [32]. Interestingly, intravenously administered β-hydroxybutyrate significantly increases the expression of catalase, FOXO3a, and manganese dioxide, which are anti-inflammatory and anti-oxidative stress molecules in rodents' kidneys [33].

EFFECTS OF INCRETIN-BASED THERAPEUTIC AGENTS ON DKD

GLP-1, a type of intestinal incretin hormone, stimulates a glucose-dependent insulin response [34]. GLP-1 acts via GLP-1 receptors, which are abundant in the gastrointestinal tract and in many other tissues, including glomerular endothelial cells [18, 35–37]. We reported that exendin-4, a GLP-1 receptor agonist, activates the cyclic adenosine monophosphate/protein kinase A pathway, increases phosphor-c-Raf (Ser259) levels, and potentially inhibits phosphor-c-Raf (Ser338)/phosphor-Erk1/2/plasminogen activator inhibitor-1 signaling activated by angiotensin II and PKCβ. Furthermore, PKCβ increases levels of ubiquitinated GLP-1 receptor and decreases protein levels of GLP-1 receptor in the glomeruli [18]. Additionally, we revealed that GLP-1 receptor agonists decreased inflammatory markers such as CD68 and CXCL2 in the renal cortex of diabetic mice. GLP-1 decreases albuminuria and ameliorates mesangial expansion, which is a typical pathological feature of DKD [18, 38]. GLP-1 also inhibits TGFβ signaling, which is related to

mesangial expansion or interstitial fibrosis in DKD [18, 38]. Interestingly, we have confirmed that protein levels of GLP-1 receptor were significantly decreased in the renal cortex of patients with long-term type 1 diabetes (The Joslin medalist Program at Harvard University; Mima A and King GL, unpublished observation). The LEADER trial is a large clinical study that assesses the long-term effects of liraglutide on renal outcomes in patients with type 2 diabetes, and this supports the results of the basic experiments in this study. The renal outcome was a composite of new-onset persistent macroalbuminuria, persistent serum creatinine doubling, ESKD, or death due to renal disease. Changes in the eGFR and albuminuria were also analyzed. Renal outcomes occurred in fewer patients in the liraglutide group than in the placebo group (268 of 4668 versus 337 of 4672, HR 0.78; 95% CI 0.67–0.92; $P = 0.003$). This was mainly due to new onset of persistent macroalbuminuria, which occurred in fewer patients in the liraglutide group than in the placebo group (161 versus 215 patients, HR 0.74; 95% CI 0.60–0.91; $P = 0.004$) [14] (Table 1).

We reported that inhibition of insulin/insulin receptor substrate-1 signaling was recognized in the glomeruli of patients with DKD [26, 39]. In our previous study, diabetes increased podocyte apoptosis in DKD through the activation of the Src homology-2 domain containing phosphatase-1, resulting in vascular endothelial growth factor (VEGF) resistance [40]. Insulin enhances VEGFA expression; thus, the loss of insulin signaling on glomeruli may contribute to the development of DKD. It is reported that several DPP4 inhibitors improved renal pathology in DKD. However, as GLP-1 is rapidly degraded by DPP4, DPP4 inhibitor-induced reno-protective effects could be a function of their pleiotropic actions. Interestingly, a DPP4 inhibitor, linagliptin, improved insulin-induced phosphorylation of insulin/insulin receptor substrate-1 and Akt, which was inhibited in the glomeruli of DKD, improving both renal pathology and function. The Kelch-like ECH-associated protein 1 or nuclear factor

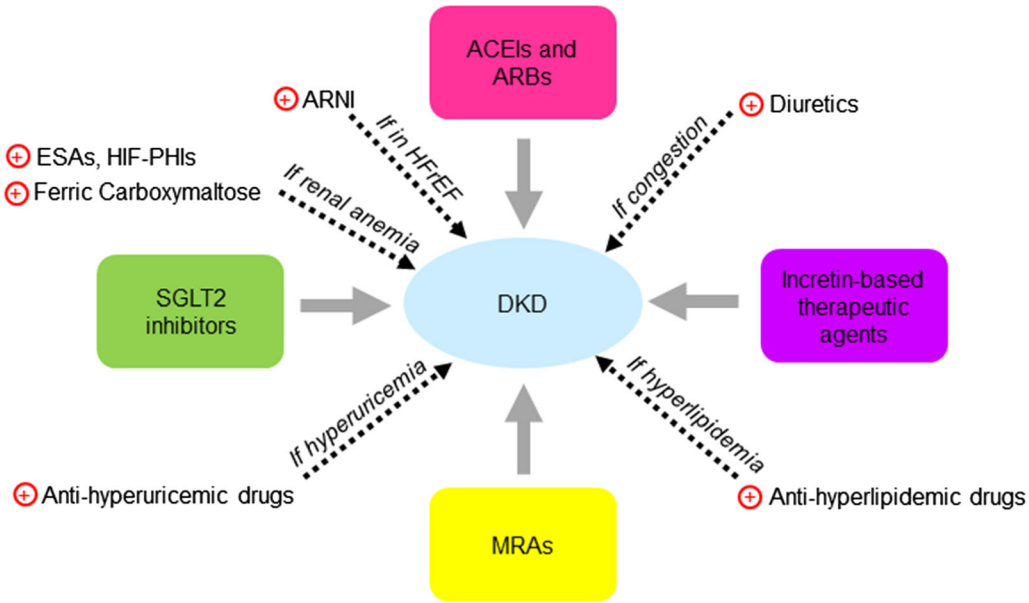

Fig. 1 Recommended drug combinations for DKD treatment. *ARNI* angiotensin receptor–neprilysin inhibitor, *ESAs* erythropoiesis-stimulating agents, *HIF-PHIs* hypoxia-inducible factor–prolyl hydroxylase domain inhibitors, *HFrEF* heart failure with reduced ejection fraction, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin I receptor blockers, *SGLT2* sodium-glucose co-transporter 2, *DKD* diabetic kidney disease, *MRAs* mineralocorticoid receptor antagonists

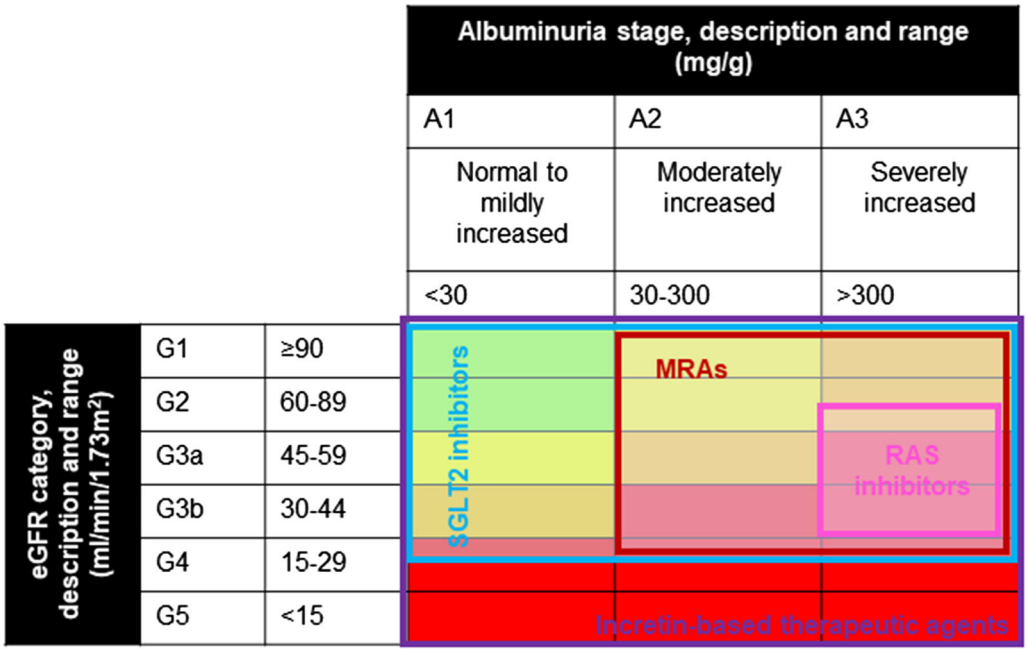

Fig. 2 Evidence supporting use of RAS inhibitors, SGLT2 inhibitors, incretin-based therapeutic agents, and MRAs for DKD treatment as represented on the KDIGO heat map. The color code indicates risk category according to KDIGO [55]: green "low risk", yellow "moderate risk", orange "high risk", and red "very high risk". *RAS* renin–angiotensin system, *SGLT2* sodium-glucose co-transporter 2, *MRAs* mineralocorticoid receptor antagonists, *KDIGO* Kidney Disease: Improving Global Outcomes

erythroid 2-related factor 2 (Nrf2) pathway is one of the most important intrinsic anti-oxidative systems [39]. Furthermore, our previous study revealed that linagliptin increased Nrf2 levels in podocytes, partially contributing to the reduction of podocyte apoptosis [39]. Another important mechanism of developing DKD is the endothelial-to-mesenchymal transition (End-MT) in glomerular endothelial cells [41, 42]. Linagliptin has been reported to decrease renal fibrosis following DKD-induced End-MT through an effect mediated by microRNA [41]. A recently published large clinical trial, CARMELINA, established that renal endpoints using linagliptin revealed that linagliptin administration prevented the progression of microalbuminuria in overt proteinuria in patients with type 2 diabetes; the linagliptin group (763/2162; 21.4 per 100 person-years) versus the placebo group (819/2129; 24.5 per 100 person-years; HR 0.86; 95% CI 0.78–0.95; $P = 0.003$) [15] (Table 1).

EFFECTS OF MRAS ON DKD

Overactivation of mineralocorticoid receptors causes inflammation and fibrosis in DKD [43]. Furthermore, long-term administration of ACEIs and ARBs paradoxically increases aldosterone levels. This phenomenon is termed aldosterone breakthrough, leading to renal injury. Thus, combination therapy using ACEIs and ARBs with MRAs seems to be promising for DKD treatment [44]. Previous meta-analyses have revealed that the addition of MRAs to RAS inhibitors significantly decreased blood pressure and proteinuria in DKD. However, there was an increased risk of hyperkalemia [45, 46]. In contrast to steroidal MRAs such as spironolactone or eplerenone, selective non-steroidal MRAs such as finerenone act as an inverse agonist, inhibiting cofactor mobilization to the mineralocorticoid receptor in the absence of aldosterone [47]. In addition, the gene regulation profile by finerenone is different from that of

steroid-based MRAs; finerenone has more potent antifibrotic effects than eplerenone [48].

Finerenone prevents heart and renal damage in hypertensive or chronic heart failure after coronary artery ligation in rodent models. Furthermore, these cardiorenal protective effects were independent of finerenone's ability to reduce blood pressure [49]. An increase in oxidative stress plays a significant role in the development of DKD [19, 50, 51]. Importantly, finerenone significantly reduced oxidative stress and TGFβ expression and suppressed tubulointerstitial fibrosis in an ischemia–reperfusion rodent model [52]. Finerenone reduces oxidative stress by inhibiting Rac1 activation and subsequent mineralocorticoid receptor signaling pathway in vascular smooth muscle cells [53]. Several clinical studies indicate favorable results for DKD treatment, supporting the results of basic research. The Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) enrolled 823 patients with type 2 diabetes with a urinary albumin-to-creatinine ratio greater than 30 mg/g creatinine, eGFR of more than 30 mL/min/1.73 m^2, and treated with RAS inhibitors [54]. These patients were randomly assigned to the finerenone (1–-25 mg/day) or placebo groups and were followed up for 90 days. Finerenone significantly reduced the urinary albumin-to-creatinine ratio compared to placebo as follows: 0.76 (90% CI 0.65–0.88; $P = 0.001$; 10 mg/day) and 0.62 (90% CI 0.54–0.72; $P < 0.001$; 20 mg/day) (Table 1). Additionally, the decrease in albuminuria was not associated with eGFR and blood pressure [54]. Thus, finerenone-induced reno-protective effects may be independent of its hemodynamic effects. The FIDELIO-DKD trial assessed whether finerenone slows CKD progression or reduces cardiovascular morbidity and mortality in patients with type 2 diabetes treated with a maximal dose of ACEIs or ARBs [16].

Primary endpoints included renal failure (defined as ESKD or eGFR of less than 15 mL/min/1.73 m^2), a decrease in eGFR of more than 40% from baseline, and death due to renal causes. The primary outcome was significantly lower in the finerenone group (HR 0.82; 95% CI 0.73–0.93; $P = 0.001$). The adverse effects of hyperkalemia occurred in 11.8% of patients in the finerenone group compared to 4.8% in the placebo group [16] (Table 1).

The FIGARO-DKD trial assessed the efficacy of finerenone on cardiovascular and renal outcomes and its safety in patients with type 2 diabetes with CKD [17]. Participants in this trial were grouped into urinary albumin-to-creatinine ratio greater than 30–300 mg/g creatinine with eGFR 25–90 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio greater than 300–5000 mg/g creatinine with eGFR of more than 60 mL/min/1.73 m^2, indicating that FIGARO-DKD included more patients with early-stage CKD and type 2 diabetes than FIDELIO-DKD. The secondary composite outcome, similar to the primary composite endpoint of FIDELIO-DKD, was 9.5% and 10.8% in the finerenone and placebo groups, respectively (HR 0.87; 95% CI 0.76–1.01). These findings clearly indicate that finerenone has reno-protective effects in DKD [17] (Table 1).

CONCLUSIONS

For many years, RAS inhibitors were the only treatment for DKD. However, recent studies indicate that SGLT2 inhibitors and incretin-based therapeutic agents can provide reno-protective effects, which may complement the efficacy of RAS inhibitors. In addition, finerenone, a non-steroidal MRA, is a promising drug owing to its ability to produce anti-inflammatory and antifibrotic effects. Therefore, the treatment of DKD in the future will include four types of drugs: RAS inhibitors, SGLT2 inhibitors, incretin-based therapeutic agents, and MRAs (Fig. 1). Possible administration methods of these four drugs in view of renal function are shown in Fig. 2.

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