Slowing Diabetic Kidney Disease Progression: Where Do We Stand Today?

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Despite increasing awareness and great strides in treatment options, diabetes continues to be a global epidemic currently affecting well above 400 million individuals worldwide. This figure is expected to reach 600 million by 2035, affecting one in 10 individuals (269). Diabetes is the chief contributor to chronic kidney disease (CKD), followed by hypertension and prediabetic hyperglycemia (1), which, when taken together, capture close to 75% of CKD causes (138). Defined by the presence of diabetes and reduced estimated glomerular filtration rate (eGFR) to <60/mL/min/1.73 m^2, increased albuminuria (>300 mg/24 hours) or both, diabetic kidney disease (DKD) is a progressive disease that affects one in seven individuals worldwide eventuating renal replacement therapy (RRT) and premature death secondary to cardiovascular causes (2,270).

In 2010, the number of RRT recipients worldwide was 2.618 million, 78% of whom were on dialysis. This figure is expected to burgeon by more than twofold by 2030, reaching 5.435 million, based on demographic projections of "unhealthy" aging populations (271). Although lifesaving, RRT expansion is not economically sustainable for health care systems in developed nations and remains largely inaccessible to many low- to middle-income countries. Thus, several organizations launched by a U.S. government executive order have called for the development of novel approaches to identify therapeutic options to prevent or slow DKD progression, with the overarching goal of reducing the incidence of end-stage renal disease (ESRD) by 25% by 2030 (272). This article aims to provide an overview of the major clinical trials conducted within the past 20 years, addressing this critical clinical need. Specifically, we will review several therapeutic drug classes that have demonstrated renoprotective potential by halting the progression of DKD.

Angiotensin II Receptor Blockers

Albuminuria levels >30 mg/day are an established continuous variable associated with adverse cardiovascular outcomes, while levels >300 mg/day indicate established kidney disease associated with faster DKD progression (273,274). Two early randomized trials—RENAAL (Reduction of End Points in Non-insulin Dependent Diabetes With the Angiotensin II Antagonist Losartan) (3) and IDNT (Irbesartan Diabetic Nephropathy Trial) (4)—support the renoprotective effects of the angiotensin receptor blockers (ARBs) losartan and irbesartan in people with type 2 diabetes who have albuminuria >300 mg/day. In comparison to placebo, losartan achieved a 25% relative risk reduction in time to doubling of serum creatinine, a 28% risk reduction in time to ESRD, and a 35% decline in proteinuria. In a trial using the same endpoints, irbesartan showed a similar benefit pattern, with a 33% lower risk of doubling of creatinine and a 23% lower relative risk of glomerulopathy progression relative to the comparator groups. Notably, the renoprotective effects conferred by both ARBs in these separate trials were not attributable to any blood pressure differences observed between the active and control arms. This conclusion was confirmed by statistically correcting for any small blood pressure differences (275). The beneficial effects of ARBs on the kidney seem to extend to individuals with diabetes without overt proteinuria, as shown in the MARVAL (Microalbuminuria Reduction with Valsartan) trial (276), which showed a significant protein-lowering effect of valsartan, again independent of blood pressure effects.

Because ARBs curtailed CKD progression to some degree via mechanisms apart from significant blood pressure-lowering, they were integrated into the standard of care (277). Although these ARB trials reduced DKD progression to about a 4–5 mL/min/year loss, we still did not have a way to normalize the rate of decline to normality (i.e., 0.8 mL/min/year), as shown in **Figure 1** (3,4,9,53,236,278–281). Thus, the significant residual risk that remained in DKD patients drove the development of a spectrum of agents, all of which unfortunately failed to further slow nephropathy progression (**Figure 2**) (237,282–287).

The subsequent renal outcomes trials examined agents addressing mechanisms such protein kinase C (PKC)-ß inhibition, dual ACE inhibition/ARB blockade, transforming growth factor (TGF)-ß production inhibition, renin inhibition, and activation of the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway while inhibiting the nuclear factor-κB pathway; however, none of them successfully further slowed DKD progression, and

FIGURE 1 Historical perspective on slowing CKD progression associated with type 2 diabetes (3,4,9,53,236,278–281).

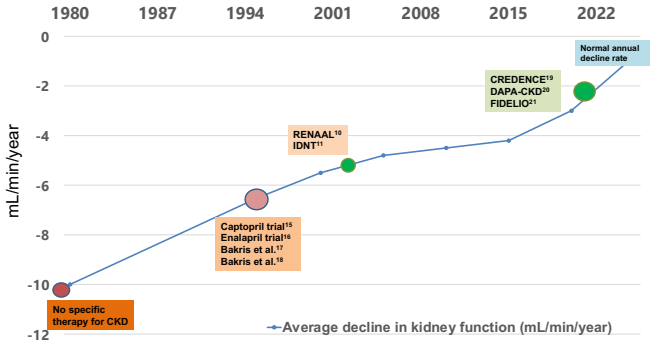
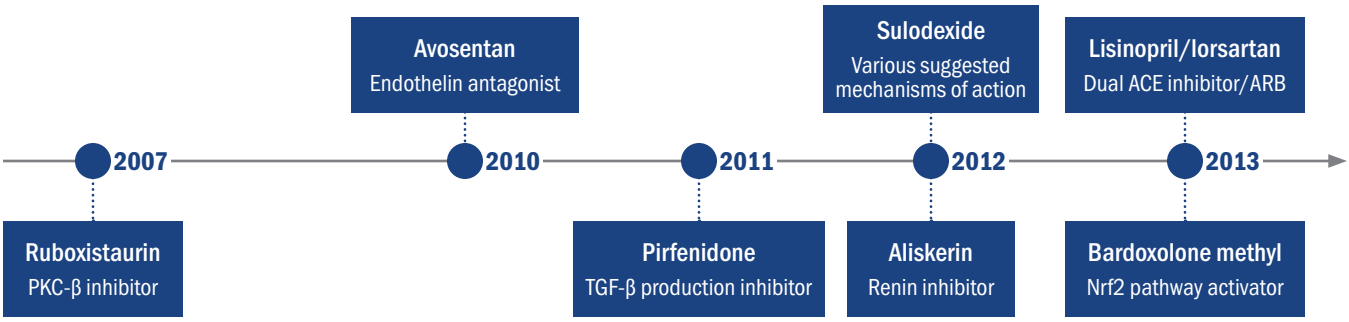


FIGURE 2 Summary of clinical outcomes trials focused on slowing DKD progression after the RENAAL and IDNT trials (237,282–287). These new therapeutic strategies largely failed to further slow nephropathy progression.



some were associated with even higher morbidity and mortality (237,285,288). The development of sodium–glucose cotransporter 2 (SGLT2) inhibitors for hyperglycemia management and the subsequent results of their cardiovascular outcomes trials (CVOTs) led to a marked paradigm shift in DKD management from a cardiorenal perspective.

SGLT2 Inhibitors

Although initially designed to manage hyperglycemia, SGLT2 inhibitors proved to possess pleiotropic effects that extend well beyond their glucose-lowering effects. They have been clearly shown to be cardiorenal risk–reducing agents irrespective of glycemic control and level of kidney function down to an eGFR of 25 mL/min/1.73 m^2 (53,281,289). In people with relatively healthy kidneys (i.e., an eGFR >60 mL/min/1.73 m^2), they aid in glycemic control by blocking SGLT2 receptors in the proximal tubule. Hence, renal absorption of glucose is withheld independent of insulin action. This mechanism results in osmotic diuresis, natriuresis, and reduction in intraglomerular pressure, often observed as a rapid decline in eGFR during the first weeks of treatment, followed by a slight increase toward baseline, then stabilization reflecting long-term renoprotection (290,291). Also, note that this initial reduction in eGFR does not occur among individuals with an eGFR well below 40 mL/min/1.73 m^2, yet renal and cardiovascular benefits are still seen (281,292). Moreover, the magnitude of blood pressure reduction is independent of glucose-lowering and eGFR, as similar levels of reduction are seen throughout the eGFR range of 25–80 mL/min/1.73 m^2 (293).

There is no unifying mechanism for how SGLT2 inhibitors reduce cardiovascular risk and preserve kidney and cardiac function; however, potential mechanisms have been reviewed (294–296). For example, blood pressure reduction occurs irrespective of sodium loss with glucose or eGFR level (293) and may relate to sympathetic inhibition of this class, as SGLT2 inhibition has been nicely shown to have effects such as renal denervation in an animal model (297). Extrarenal metabolic effects include reductions in body weight (specifically, in visceral fat); lower systolic and diastolic blood pressure, serum uric acid, and albuminuria; and either neutral or favorable effects on lipid fractions (292,298,299). **Figure 3** summarizes the panoply of mechanisms found to relate to changes seen with SGLT2 inhibitors.

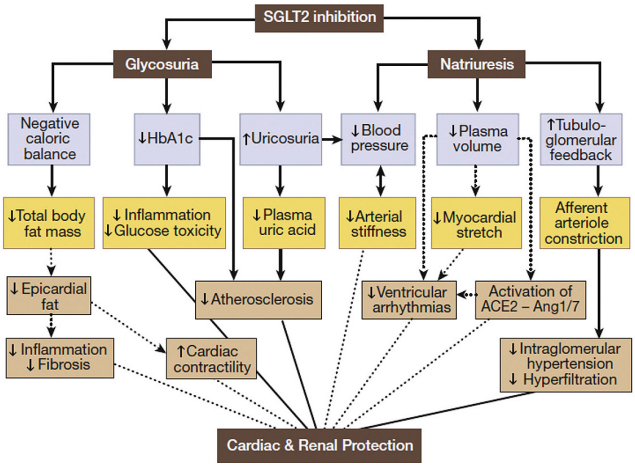
There are currently four U.S. Food and Drug Administration (FDA)–approved SGLT2 inhibitors that have been studied in large and appropriately statistically powered CVOTs and two renal outcomes trials. All have converged on favorable cardiovascular and renal outcomes. The most recent meta-analysis, by McGuire et al. (156) included the six trials that, despite heterogeneity across the different SGLT2 inhibitor agents concerning cardiovascular outcomes, found consistent reduction of hospitalization for heart failure (HHF) and progression of kidney disease. On closer examination of the individual trials included in this meta-analysis, patients in four of the six trials had baseline eGFRs between 60 and 90 mL/min/1.73 m^2, with high or moderately increased albuminuria (<300 mg/day). This argues for a relatively healthier subgroup of patients at lower risk for kidney failure. Moreover, these trials looked at kidney disease progression through secondary data analyses that were generally limited by smaller numbers of patients with ESRD (160,300–302).

These shortcomings were addressed in two dedicated trials examining renal outcomes with canagliflozin and dapagliflozin in patients with stage 3 CKD with macroalbuminuria at study entry (293,294).

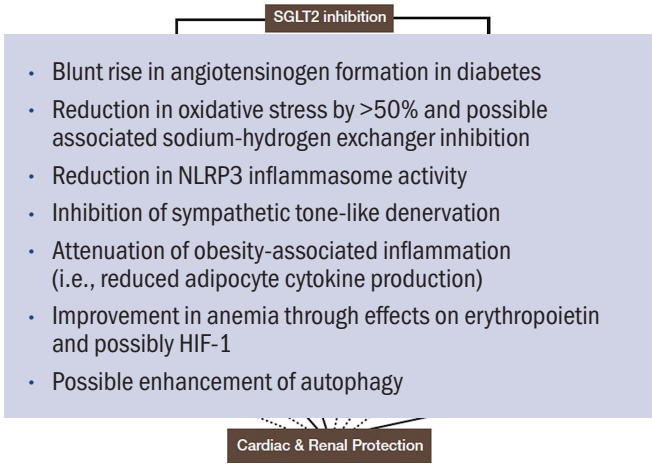
In the landmark CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (8), canagliflozin was compared to placebo in patients with type 2 diabetes, with the primary endpoint encompassing ESRD or a sustained eGFR of <15 mL/min/1.73 m^2), doubling of creatinine level, or death from renal or cardiovascular causes. The trial was terminated early due to clear renal benefits of canagliflozin. It showed a 30% lower relative risk of reaching the primary endpoint, a 32% lower relative risk of progressing to ESRD, and a significantly lower risk of cardiovascular death and HHF. Importantly, amputation and fracture risks were similar between canagliflozin and placebo. This result led to the FDA lifting its "black box" warning labeling requirement regarding these risks.

FIGURE 3 Contributing mechanisms to the panoply of effects of SGLT2 inhibitors. NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; HIF-1, hypoxia-inducible factor. Adapted from Rajasekeran H, Lytvyn Y, Cherney DZI. Kidney Int 2016;89:524–526 and Packer M. Am J Nephrol 2020;51:289–293.

Multidimensional effects with **eGFR >45 mL/min/1.73 m²**



Multidimensional effects that persist at **eGFR >45 mL/min/1.73 m²**



In another landmark study, DAPA-CKD (Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease) (303), participants, of whom about two-thirds had type 2 diabetes and about one-third did not, were randomized to receive either dapagliflozin or placebo against a background ACE inhibition/ARB treatment. Dapagliflozin resulted in a significant reduction in risk of a sustained decline in eGFR, progression to ESRD, or death from renal or cardiovascular causes and a 29% reduction in risk of death from cardiovascular causes or HHF irrespective of diabetes status. As a result, dapagliflozin is now also indicated to reduce the risk of sustained eGFR decline, ESRD, cardiovascular death, and HHF in adults with CKD at risk of progression, with or without type 2 diabetes, including initiation with an eGFR ≥25 and continuation even if eGFR drops below 25 mL/min/1.73 m² (162a). Additionally, dapagliflozin is the only SGLT2 inhibitor to demonstrate a reduction in all-cause mortality (31% relative risk reduction with a 2.9% absolute risk reduction, hazard ratio [HR] 0.69, 95% CI 0.53–0.88, $P = 0.0035$). Safety outcomes data and adverse events were similar across both arms, with no reports of hypoglycemia or diabetic ketoacidosis in patients without diabetes, a concern that had been raised in the literature.

Taken together, all six trials add to the unequivocal benefits of SGLT2 inhibitors in both primary and secondary kidney disease prevention, even in patients with lower eGFRs. This is reflected in the American Diabetes Association's *Standards of Medical Care in Diabetes—2021*, which supports the use of an SGLT2 inhibitor if CKD or heart failure is present irrespective of glucose level or metformin use (168,277).

Glucagon-Like Peptide 1 Receptor Agonists

Glucagon-like peptide 1 (GLP-1) receptor agonists, another novel class of injectable antidiabetics and more recently available in an oral formulation, are glucose-dependent insulinotropic medications, the mechanisms of which involve enhancing both peripheral glucose uptake and glycogen synthesis, delaying gastric emptying, and promoting satiety (304). The myriad clinical effects beyond glycemic control have placed this drug class at center stage with endocrinologists, cardiologists, and nephrologists. In addition to reductions in weight, small reductions in systolic blood pressure, and improved lipid profiles, this incretin-based drug class has proved to have a role in curtailing CKD progression and reducing cardiovascular morbidity and mortality (305).

An analysis of renal outcomes of CVOTs showing a slowing of CKD progression was published recently (306); however, no specific primary renal outcomes trials with GLP-1 receptor agonists have been published. There are data from post hoc analyses and a recent meta-analysis suggesting that drugs in this class slow CKD progression (307–309). The ongoing FLOW (Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease) trial (263) is a randomized controlled trial examining the efficacy of semaglutide compared to placebo in people with type 2 diabetes and CKD that has sufficient statistical power for a primary renal endpoint. Its results are expected in 2024. Nonetheless, the impact of GLP-1 receptor agonists can be readily inferred from several important cardiovascular trials enrolling mixed patient populations with either CKD, coronary artery disease, or a combination of the two, which will be reviewed here.

The first trial to examine the efficacy of dulaglutide, a long-acting GLP-1 receptor agonist, in patients with type 2 diabetes and moderate to severe CKD was AWARD-7 (Dulagulide Versus Insulin Glargine in Patients with Type 2 Diabetes and CKD) (305). At baseline, the average mean eGFR was 38 mL/min/1.73 m², with one-third of patients at stage 4 CKD (eGFR 16–29 mL/min/1.73 m²). Over 1 year, insulin was associated with a steeper decline in eGFR (−3.3mL/min/1.73 m² compared to dulaglutide, which evidenced an eGFR decline of −0.7mL/min/1.73 m² for both low-dose (0.75 mg weekly)

and high-dose (1.5 mg weekly) groups. Notably, the gradients of eGFR decline between dulaglutide and insulin were maintained even among patients with a urine albumin-to-creatinine ratio >300 mg/g creatinine, who are at higher risk of CKD progression, with eGFR declines of −0.7 and −0.5 mL/min/1.73 m^2 for dulaglutide 1.5 mg and 0.75 mg, respectively, compared to −5.5 mL/min/1.73 m^2 for insulin. Compared to patients in the insulin group, fewer patients who received high-dose dulaglutide reached the composite renal endpoint of ESRD or >40% decline in eGFR (10.8 vs. 5.2%, P <0.038).

Similar trends were reported in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) (310), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) (7), and REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) (52) trials, in which, compared to placebo, liraglutide, semaglutide, and dulaglutide achieved significant risk reductions of 22, 36 and 15%, respectively, in secondary composite renal endpoints (new onset of macroalbuminuria, doubling of serum creatinine, sustained 45% reduction in eGFR, RRT, or renal death), findings that were largely driven by macroalbuminuria reduction (7,52,310). In the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial (311), although secondary renal endpoints were not prespecified, post hoc analyses demonstrated a risk reduction of 40% associated with exenatide in combined renal endpoints, defined similarly to the above studies. The proportion of patients with an eGFR <60 mL/min/1.73 m^2 ranged from 17 to 28% in these four trials. The similarity in outcomes across the different medications argues persuasively for a class effect on DKD.

Collectively, these studies suggest that GLP-1 receptor agonists may be as efficacious as SGLT2 inhibitors for cardiorenal risk reduction, particularly for patients with lower renal reserve who are at higher risk for DKD progression. It would seem intuitive to consider combining GLP-1 receptor agonist and SGLT2 inhibitor regimens, given the absence of overlapping mechanisms of action and side effect profiles, to determine whether they work synergistically to optimize renal outcomes. This is a question being investigated by the EMPA-SEMA (Renal Effects of Treatment With Empagliflozin Alone or in Combination With Semaglutide in Patients With Type 2 Diabetes and Albuminuria) trial (312).

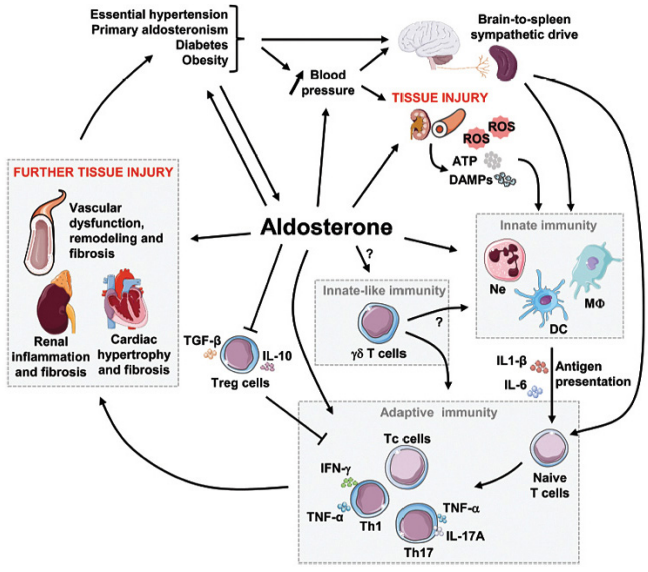
Mineralocorticoid Receptor Antagonists

Early studies establishing the renoprotective effects of renin-angiotensin system (RAS) blockade spurred the investigation of whether maximal inhibition of angiotensin II signaling would further slow DKD progression over either class alone. However, dual inhibition with combined ACE inhibitor and ARB therapy was unsuccessful in improving renal outcomes, as shown in the VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) trial (237) and ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) (288), and there was a notable increase in risk for acute kidney injury and hyperkalemia (237,288). Moreover, this was also seen when renin inhibition was used with an ARB in ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) (286).

Attention then shifted to a downstream target of the RAS, the mineralocorticoid receptor (MR), activated by aldosterone. This was the result of aldosterone's recognized deleterious effects on the heart and kidney and role in CKD pathophysiology (313). Aldosterone is a vital ligand of the MR, the activation of which mediates inflammation and fibrosis beyond blood pressure and sodium retention effects (313). Moreover, patients on long-term ACE inhibitor/ARB therapy evidence increased plasma aldosterone due to incomplete suppression of aldosterone, also known as "aldosterone escape," which is an important contributor to MR activation (314). MR antagonism exerts anti-inflammatory and anti-fibrotic effects on the kidney (313,315), heart, and vasculature that, when combined with ACE inhibitor/ARB therapy can exert sustained declines in proteinuria and blood pressure and better preservation of renal function (316,317), as shown in **Figure 4**.

The use of MR antagonists outside of heart failure has generally been limited because of a lack of data in DKD and important side effects such as hyperkalemia and gynecomastia associated with earlier-generation agents. With finerenone, a third-generation MR

FIGURE 4 Summary schematic of aldosterone's contribution to fibrosis and inflammation in diabetes over time. Excess aldosterone production occurring in diseases such as essential hypertension, primary aldosteronism, diabetes, and obesity contributes to increased blood pressure. Over time, elevated blood pressure and/or aldosterone cause renal and vascular injury, which activates the innate and adaptive immune systems, causing further tissue injury and thereafter exacerbating the detrimental effects of the initial disease. ATP, adenosine triphosphate; DAMP, damage-associated molecular pattern; DC, dendritic cell; IFN, interferon; IL, interleukin; MΦ, macrophage; Ne, neutrophil; ROS, reactive oxygen species; Tc, cytotoxic T cells; TGF, transforming growth factor; Th, T-helper cells; TNF, tumor necrosis factor; Treg, T regulatory cells. Reprinted with permission from Ferreira NS, Tostes RC, Paradis P, Schiffrin E. Am J Hypertens 2021;34:15–27.



antagonist that is a selective nonsteroidal agent with higher MR affinity and potency than eplerenone and spironolactone, respectively (312,313), strong inhibition of renal pro-inflammatory and pro-fibrotic markers has emerged as a promising option.

ARTS-DN (Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy) (239) was an initial tolerability study including patients with diabetes, macroalbuminuria, and an eGFR <60mL/min/1.73 m^2 that demonstrated significant dose-dependent albuminuria-reducing effects of finerenone despite modest nonsignificant blood pressure–lowering.

The largest phase 3 double-blinded randomized renal outcomes trial to date, FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) (9) investigated the efficacy and safety of finerenone in >5,700 participants with type 2 diabetes and moderate to severe CKD who were on a maximally tolerated RAS blocker. Over a median duration of 2.6 years, finerenone was associated with an 18% relative risk reduction (HR 0.82, 95% CI 0.73–0.93, $P = 0.001$) in the primary renal outcome, which was a composite of time to kidney failure, sustained eGFR decrease ≥40% from baseline, or renal death. There was also a 14% relative risk reduction (HR 0.86, 95% CI 0.75–0.99, $P = 0.03$) in the secondary cardiac outcome, which was a composite of time to death from cardiac causes, nonfatal myocardial infarction, nonfatal stroke or HHF (9). Adverse effects were balanced between finerenone and placebo. Of interest was the emergence of cardiovascular benefits as early as the first month in the experimental arm compared to renal benefits, which did not emerge until 12 months but then persisted throughout the study duration. These findings are in line with known underlying mechanisms of finerenone: mild natriuresis translating into a 2.4-mmHg reduction in systolic blood pressure and presumptive anti-fibrotic and anti-inflammatory effects halting progression of renal tissue remodeling. These clinical benefits may take several months to see, and this was especially true in FIDELIO-DKD, in which specific inflammatory and fibrosis markers were not incorporated into the study.

Parallel to FIDELIO-DKD is another phase 3 trial, FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) (318), a trial involving >7,000 people that is expected to be completed in summer 2021 will provide insight into this drug's cardiorenal efficacy and safety in people with type 2 diabetes and less advanced DKD. Readers should note, however, that, as of March 2021, finerenone was under evaluation but not yet approved by the FDA.

Summary

More than 400 million people are living with diabetes worldwide, and that number is projected to continue increasing steadily (269), driven by aging population trends, expanding urbanization, sedentary lifestyles, and rising obesity rates. Diabetes is the leading cause of CKD; combined with hypertension and prediabetes, it accounts for 75% of CKD causality (138). DKD, a "disease multiplier," is associated with significant cardiorenal morbidity and mortality. Treatment of DKD, when previously limited to RAS blockade and management of traditional metabolic risk factors for cardiovascular disease and CKD, did not sufficiently halt kidney disease progression (**Figure 1**). This outlook has changed in recent years with the advent of SGLT2 inhibitors and nonsteroidal MR antagonists, as well as, potentially, GLP1 receptor agonists.

Contemporary standard management of DKD now includes the use of an SGLT2 inhibitor alone or in combination with a GLP-1 receptor agonist if atherosclerotic disease is present, on top of an RAS blocker in individuals with cardiovascular and kidney disease (277). However, even under optimal conditions, there remains residual cardiorenal risk significant enough to spur the search for other therapeutic options. In addition to these drug classes, we have strong evidence from nonsteroidal MR antagonists showing both relative safety and clear efficacy in slowing DKD progression and reducing cardiovascular events (319).

Other agents that remain to be proven but have data supporting a possible role include the endothelin receptor antagonists. For example, atrasentan still holds some promise in a subset of patients whose cardiac status can handle a small increase in volume when it is dosed carefully. With distinct mechanisms of action and non-overlapping side effect profiles, some of these drug classes may even be combined to create additive or synergistic effects. This possibility was illustrated in a post hoc analysis of the SONAR (Study of Diabetic Nephropathy With Atrasentan) trial (320), in which patients with type 2 diabetes and CKD achieved larger reductions in albuminuria and body weight, a surrogate for fluid retention, when they were given an SGLT2 inhibitor in combination with atrasentan compared to those who took atrasentan alone. Finally, praliciguat, a soluble guanylate cyclase stimulator, remains to be tested to determine whether it can offer additional slowing of renal disease beyond relaxing vascular tone and reversing tissue remodeling (321).

These data, when taken together, suggest that nephrologists can finally celebrate the availability of new agents that slow CKD progression in diabetes from eGFR reduction of ~10–12 mL/min/year in 1980 to ~3 mL/min/year today. Unfortunately, the normal rate of kidney function decline is 0.7–0.9 mL/min/year; thus, residual risk remains. Future trials should aim to examine the additive or synergistic effects that may be conferred by using combinations of the therapeutics discussed here.

See references starting on p. 34.

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