Protecting the Kidneys: Update on Therapies to Treat Diabetic Nephropathy

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This article provides an update on pharmacotherapy for diabetic nephropathy. ACE inhibitor or angiotensin 2 receptor blocker therapy is a standard of care for hypertension management in people with diabetes and albuminuria. Additionally, recent trials have elucidated the roles of additional therapeutic agents, including the sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, and the recently approved mineralocorticoid receptor antagonist finerenone, in the treatment of chronic kidney disease in people with type 2 diabetes. This article provides an evidence-based review of therapies that may delay the progression of kidney disease in this population, including discussion of recent outcomes trials.

Diabetes is a major public health concern with increasing prevalence worldwide. The two most common presentations of the disease are type 1 and type 2 diabetes. Type 1 diabetes typically develops over a short period of time and is often more difficult to manage but is less common, accounting for only 7–12% of the global diabetes burden (1). In contrast, type 2 diabetes accounts for nearly 90% of diabetes worldwide and tends to evolve unnoticeably over a prolonged period of time, often resulting in the development of serious complications by the time it is diagnosed (1). Complications of diabetes, which can be debilitating and potentially life-threatening, include cardiovascular disease (CVD), chronic kidney disease (CKD), retinopathy, neuropathy, and lower-limb amputations (1).

CKD is one of the most common complications of diabetes, occurring in ∼20–40% of people with diabetes (2). CKD is defined by the presence of persistent elevated urinary albumin excretion (albuminuria), with a urine albumin-to-creatinine ratio (UACR) ≥30 mg/g and/or decreased estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for at least 3 months (1,2).

Although CKD is not always preventable, several modifiable risk factors can be targeted to delay its progression. Among these modifiable risk factors are poor glycemic control, hypertension, lipid abnormalities, smoking, and obesity (1). CKD can ultimately progress to end-stage renal disease (ESRD), which affects about 2 of every 1,000 people in the United States, leading to the need for dialysis or renal transplant (3). Approximately 80% of ESRD cases around the world are caused by either hypertension, diabetes, or both. The incidence of ESRD is up to 10 times higher in people with diabetes than in those without diabetes (1). Additionally, caring for patients with ESRD is very expensive, with total annual Medicare-related expenditures for beneficiaries diagnosed with ESRD reaching $49.2 billion in 2018 (4). Thus, it is imperative that people with diabetes and their health care teams address modifiable risk factors to prevent the progression of CKD.

Very few therapies are currently approved or recommended to slow the progression of CKD. ACE inhibitors and angiotensin 2 receptor blockers (ARBs) are considered first-line choices for the management of hypertension in people with diabetes and albuminuria (5). These agents belong to a broad class of drugs called renin-angiotensin-aldosterone system (RAAS) inhibitors, which are effective because they address the dysregulation of the RAAS that is found in CKD (6). CKD causes continuous overstimulation of the RAAS, leading to increased glomerular capillary pressure and activation of proinflammatory pathways that can cause glomerular hypertrophy (6). ACE inhibitors and ARBs work to decrease the intraglomerular pressure and therefore can slow the development of kidney damage and disease. As a result, the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (5) recommends initiating an ACE inhibitor or

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ARB in people with diabetes, hypertension, and albuminuria and titrating this therapy to the maximum tolerated dose.

In addition to the use of antihypertensive agents such as ACE inhibitors and ARBs, other potential agents have been investigated for their use in delaying the progression of CKD, including antihyperglycemic therapies such as sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. Recent research has also identified finerenone, a mineralocorticoid receptor antagonist (MRA), as an agent that may be used to delay progression of CKD. This article reviews recent major landmark clinical trials that have provided evidence for slowing the progression of CKD in people with type 2 diabetes and resulting drug indication approvals by the U.S. Food and Drug Administration (FDA). The landmark trials described below are summarized in Table 1.

SGLT2 Inhibitors

SGLT2 inhibitors are antihyperglycemic medications that were developed to lower glucose levels in people with type 2 diabetes. These medications work by inhibiting SGLT2 proteins on the luminal surface of proximal tubular cells in the kidneys to prevent the reabsorption of sodium and glucose from the renal tubule (7). As a result, sodium and glucose are excreted in the urine, and blood glucose levels decrease. It is also hypothesized that these agents decrease intraglomerular pressure and, as a result, slow the progression of CKD, which has ultimately been the focus of several recently published clinical trials. SGLT2 inhibitors that have published data for CKD as a primary outcome include canagliflozin and dapagliflozin.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial investigated the benefits of canagliflozin on the risk of kidney failure and cardiovascular events in people with type 2 diabetes. Overall, the trial found that canagliflozin safely reduced composite renal and cardiovascular events in the study population (8). A secondary analysis of the CREDENCE trial was performed to examine whether the benefit expanded across all eGFR levels. The secondary analysis showed that relative benefits were consistent across all eGFR groups, but there were greater absolute benefits among people with a lower eGFR (7). Canagliflozin reduced the chronic decline in eGFR by 60% in those with an initial eGFR of 30 to <45 mL/min/1.73 m^2 and by 65% in those with an initial eGFR of 45 to <60 mL/min/1.73 m^2 (7).

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial examined the effects of dapagliflozin on kidney and cardiovascular events; however, this trial included participants with CKD both with and without type 2 diabetes, which made the study population uniquely different from that in the CREDENCE trial (9). The results of the study showed that dapagliflozin reduced the risk of the primary composite outcome, which included worsening of kidney function, occurrence of ESRD, death from cardiovascular events, hospitalization for heart failure, and death from any cause in both people with and without diabetes (10). The findings of this study were consistent with results from prior smaller studies that demonstrated a reversible reduction in eGFR, reduced body weight, and increased hematocrit (10). These physiological changes support the idea that dapagliflozin reduces intraglomerular pressure and enhances glycosuria and natriuresis, which are believed to preserve long-term kidney function in people with CKD regardless of diabetes status (10).

The CREDENCE and DAPA-CKD trials provide substantial evidence for delaying the progression of CKD in people with and without diabetes. Although the kidney-protective effects of SGLT2 inhibitors were reflected in both trials, the DAPA-CKD trial showed that dapagliflozin was also effective for people without diabetes and with an eGFR <30 mL/min/1.73 m^2 (10). Not only do SGLT2 inhibitors control hyperglycemia, which is a major risk factor for CKD progression, but they also have consistently shown to reduce CKD progression by 30–40% independent of their glucose-lowering effects (2,10). As a result of these trials, it is recommended to initiate SGLT2 inhibitor therapy at an eGFR ≥30 mL/min/1.73 m^2 (or ≥25 mL/min/1.73 m^2 with dapagliflozin specifically) in people with diabetes and albuminuria and to continue it until initiation of kidney replacement therapy (5,11).

GLP-1 Receptor Agonists

GLP-1 receptor agonists are antihyperglycemic medications that have potential use in the prevention of CKD progression. These medications treat diabetes by mimicking the action of GLP-1, which stimulates glucose-dependent insulin release from pancreatic islet cells, slows gastric emptying, and decreases appetite stimulation (5). Several GLP-1 receptor agonists are currently available on the U.S. market, including exenatide,

TABLE 1 Renal Outcomes Trials for SGLT2 Inhibitors, GLP-1 Receptor Agonists, and the MRA Finerenone

Study	Main Inclusion Criteria	Renal Outcomes	Adverse Events	NNT
CREDENCE (8)	• ≥30 years old • Type 2 diabetes • A1C 6.5–12% • UACR >300–5,000 mg/g • eGFR 30–90 mL/min/1.73 m^2 • Maximum tolerated dose of ACE inhibitor or ARB therapy for ≥4 weeks	Primary composite of ESRD outcomes, doubling of serum creatinine, and death from renal or cardiovascular causes	• Genital mycotic infections • Diabetic ketoacidosis	23
DAPA-CKD (10)	• ≥18 years old • eGFR 25–75 mL/min/1.73 m^2 • UACR 200–5,000 mg/g • Maximum tolerated dose of ACE inhibitor or ARB therapy for ≥4 weeks	Primary composite of worsening kidney function, defined as sustained ≥50% decline in eGFR, occurrence of ESRD, or death due to kidney disease and cardiovascular death	• Diabetic ketoacidosis • Volume depletion	19
LEADER (12)	• ≥50 years of age and at least one existing cardiovascular condition (CHD, PVD, CKD, or chronic HF) • ≥60 years of age with at least one cardiovascular risk factor (microalbuminuria, proteinuria, HTN, LVH, or LVD) • Type 2 diabetes • A1C ≥7% • eGFR ≥15 mL/min/1.73 m^2	Composite renal outcome including new onset of macroalbuminuria or doubling of serum creatinine and an eGFR <45 mL/min/1.73 m^2, need for CRRT, and death from renal cause	• Nausea • Vomiting • Diarrhea • Abdominal discomfort • Acute gallstone disease	67
SUSTAIN-6 (13)	• ≥50 years of age and at least one existing cardiovascular condition (CHD, PVD, CKD, or chronic HF) • ≥60 years of age with at least one cardiovascular risk factor (microalbuminuria, proteinuria, HTN, LVH, or LVD) • Type 2 diabetes • A1C ≥7% • eGFR ≥30 mL/min/1.73 m^2	Secondary outcome of new or worsening nephropathy	• Nausea • Vomiting • Diarrhea	44
REWIND (14)	• ≥50 years of age and history of vascular disease • ≥55 years of age with history of MI; coronary, carotid, or lower-extremity artery stenosis >50%; LVH; eGFR <60 mL/min/1.73 m^2; or albuminuria • ≥60 years of age with at least two of the following: tobacco smoking, dyslipidemia, HTN, or abdominal obesity • Type 2 diabetes with A1C ≤9.5% and on stable doses of up to two oral antihyperglycemic drugs with or without basal insulin	Composite secondary outcome including renal disease defined as UACR >33.9 mg/mmol in those with a lower baseline concentration, sustained 30% decline in eGFR, and CRRT	• Gastrointestinal upset • Acute pancreatitis	40
AWARD-7 (15)	• ≥18 years of age • Type 2 diabetes • Moderate to severe CKD (stage 3–4) • A1C 7.5–10.5% • Treatment with insulin plus oral antihyperglycemic drug or only insulin • Maximum tolerated dose of ACE inhibitor or ARB therapy	Secondary outcomes including change in eGFR and UACR	• Diarrhea • Nausea • Vomiting	NA

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TABLE 1 Renal Outcomes Trials for SGLT2 Inhibitors, GLP-1 Receptor Agonists, and the MRA Finerenone *(Continued)*

Study	Main Inclusion Criteria	Renal Outcomes	Adverse Events	NNT
FIDELIO-DKD (16)	• ≥18 years of age • Type 2 diabetes • UACR 30 to <300 mg/g and eGFR 25 to <60 mL/min/1.73 m^2, plus retinopathy • UACR 300–5,000 mg/g and eGFR 25 to <75 mL/min/1.73 m^2 • Maximum tolerated dose of ACE inhibitor or ARB therapy	Primary composite outcome of kidney failure, sustained decrease of ≥40% in eGFR from baseline, and death from renal causes	• Hyperkalemia	29

CHD, coronary heart disease; CRRT, continuous renal replacement therapy; HF, heart failure; HTN, hypertension; LVD, left ventricular dysfunction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NA, not applicable; NNT, number needed to treat; PVD, peripheral vascular disease.

lixisenatide, dulaglutide, liraglutide, and semaglutide. All are available as injectable therapies, and semaglutide is also available as an oral tablet. Most of the research involving the use of these agents outside of glycemic control has focused on their ability to reduce cardiovascular events, but many secondary study outcomes have examined renal outcomes and their potential use in slowing eGFR decline and reducing albuminuria.

Several studies have been conducted on GLP-1 receptor agonists to determine whether they are efficacious in reducing cardiovascular events in people with type 2 diabetes who have a history of atherosclerotic CVD, which could include a prior myocardial infarction, peripheral vascular disease, or stroke. In addition to assessing cardiovascular outcomes, many of these studies had secondary outcomes focused on microvascular complications such as retinopathy and nephropathy. The Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) trial (12) was one of the first trials that studied these outcomes in GLP-1 receptor agonists by comparing liraglutide to placebo. This trial determined that liraglutide significantly lowered the risk of cardiovascular events, as well as the risk of nephropathy events such as new-onset macroalbuminuria, doubling of serum creatinine, the need for continuous renal replacement therapy, or death from renal causes. Similarly, the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) study (13) compared injectable semaglutide and placebo to assess cardiovascular safety in people with type 2 diabetes. SUSTAIN-6 also examined microvascular complications as a secondary outcome of the study and found that new or worsening nephropathy occurred significantly less often in the semaglutide group compared with placebo. A third study investigating the use of GLP-1 receptor agonists in reducing cardiovascular outcomes in people with diabetes was the Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND) trial (14), which compared dulaglutide to placebo. Similar to the previous studies, REWIND analyzed the incidence of microvascular complications in participants and found that there were fewer composite renal outcomes in the dulaglutide group compared with placebo. Despite microvascular complications such as nephropathy not being the primary outcome in these studies, all three studies produced similar results, identifying that GLP-1 receptor agonists have a potential protective effect on renal outcomes (14).

In comparison with the previously described trials, the Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease (AWARD-7) trial (15), published in 2018, was one of the first trials to study the use of GLP-1 receptor agonists—specifically dulaglutide—in people with moderate to severe CKD. This study compared the effects of once-weekly dulaglutide versus insulin glargine primarily in reducing A1C, but included as secondary outcomes changes in eGFR and UACR. Despite similar levels of glycemic control between the dulaglutide and insulin glargine groups, there were significant differences with regard to the renal outcomes. Over the 52-week study period, dulaglutide significantly slowed the decline in eGFR compared with insulin glargine, having the strongest benefit in patients with macroalbuminuria (UACR >300 mg/g) (15). Additionally, the AWARD-7 trial showed that dulaglutide significantly decreased UACR in a dose-dependent manner, with the greatest benefit seen in those who received dulaglutide 1.5 mg compared with dulaglutide 0.75 mg once weekly (15). The results of this study support using

GLP-1 receptor agonists in people with diabetes and CKD to slow the progression of CKD through tighter glycemic control, reducing the decline in eGFR and improving UACR.

Finerenone

A newer study published in 2020 presented the potential use of an MRA as a therapy to reduce albuminuria in people with CKD and type 2 diabetes. Finerenone is a nonsteroidal, selective MRA with potent anti-inflammatory and antifibrotic effects (16). The potential use of this agent in slowing the progression of CKD stems from evidence showing overactivation of mineralocorticoid receptors in cardiorenal diseases such as CKD and diabetes (16). Overactivation of these receptors often leads to inflammation and fibrosis, ultimately resulting in progression to kidney failure and cardiovascular events. The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study (16) was designed to further investigate this theory and to determine whether there is a potential place for finerenone in the CKD treatment armamentarium.

The FIDELIO-DKD study enrolled adults with type 2 diabetes and CKD who were currently on a maximum tolerated dose of an ACE inhibitor or ARB. Similar to other clinical trials investigating the prevention of CKD progression, the study's primary composite outcome focused on development of kidney failure or cardiovascular events. Enrolled patients were assigned to either finerenone or placebo throughout the study's duration of 2.6 years, and starting doses of finerenone were adjusted based on patients' eGFRs and titrated as necessary (16).

At the conclusion of the study, the primary composite outcome of kidney failure, which included a sustained decrease of ≥40% in eGFR from baseline or death from renal causes, was significantly lower in the finerenone group compared with placebo (16). The study determined that the number of patients needed to treat to prevent one primary outcome event was 29 in the finerenone group (16). The study also evaluated additional outcomes, including UACR, and the finerenone group was found to have a 31% greater reduction from baseline than placebo (16).

The results of the FIDELIO-DKD trial provided evidence that finerenone may be effective in reducing CKD progression in people with type 2 diabetes and advanced CKD. As a result, on 9 July 2021, finerenone was approved by the FDA to "reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adult patients with CKD associated with type 2 diabetes" (17).

Prescribing Considerations

The KDIGO 2020 guideline (5) provides excellent information on medication therapy recommendations for people with diabetes and CKD. An ACE inhibitor or ARB is recommended as first-line therapy for people with diabetes, hypertension, and albuminuria and should be titrated to a maximum tolerated dose. Both ACE inhibitors and ARBs can be associated with adverse events such as angioedema, cough, hypotension, hyperkalemia, and increased serum creatinine (5). Patients taking either type of medication should have their blood pressure, serum potassium, and serum creatinine monitored regularly, and if an adverse event occurs, either the medication should be discontinued or the dose should be decreased to safely resolve the event (18).

In addition to the use of an ACE inhibitor or ARB in people with diabetes and CKD, it is also recommended that an SGLT2 inhibitor should be started as a first-line antihyperglycemic therapy alongside metformin in people with type 2 diabetes. The KDIGO guideline recommends initiating an SGLT2 inhibitor in people with an eGFR ≥30 mL/min/1.73 m^2 (eGFR ≥25 mL/min/1.73 m^2 for dapagliflozin) even if they have achieved their glycemic target on metformin alone (5,19). Using both of these antihyperglycemic medications together has been deemed safe because of their different mechanisms of action and the low risk of hypoglycemia with both medications. Unfortunately, SGLT2 inhibitors can cause several adverse events that may lead to their discontinuation, including an increased risk of diabetic ketoacidosis (<1%), increased risk of genital mycotic infections (2–12%), increased risk of urinary tract infections (6–9%), and an increased risk of lower-limb amputations with canagliflozin (2–4%) (19–21). It is important to continuously monitor patients for a decline in renal function as well as adverse events during their use of an SGLT2 inhibitor. Current guidelines recommend not initiating therapy with a SGLT2 inhibitor when eGFR is <30 mL/min/1.73 m^2 (<25 mL/min/1.73 m^2 for dapagliflozin); however, if a patient's eGFR declines below that threshold while on the medication, it is safe to continue until initiation of renal replacement therapy (5,19).

GLP-1 receptor agonists are considered to be an excellent add-on therapy to metformin and an SGLT2

inhibitor to achieve glycemic goals or serve as an alternative for people who are unable to take those medications. Patients may be unable to take metformin or an SGLT2 inhibitor because of intolerable adverse events or insufficient renal function. GLP-1 receptor agonists are also considered to be the preferred therapy in people with type 2 diabetes and CKD who desire weight loss and tighter glycemic control (10). Because most of these agents are injectable with the exception of the more recently formulated semaglutide oral tablet, it is important to ensure that patients are receptive to taking an injection before prescribing. GLP-1 receptor agonists can cause adverse events such as injection site reactions or dose-dependent gastrointestinal upset (nausea, vomiting, diarrhea) that can vary across formulations and should be monitored routinely (5). Their use should be avoided in people with a personal or family history of medullary thyroid tumors or a history of acute pancreatitis (5).

Based on its FDA indication, finerenone may be an appropriate add-on therapy for people with type 2 diabetes and CKD who are already on maximally tolerated ACE inhibitor or ARB therapy. However, its exact place in therapy has not yet been clearly defined in guidelines. Finerenone can be given once daily, with a recommended starting dose of 20 mg/day for people with an eGFR >60 mL/min/1.73 m^2 and 10 mg/day for those with an eGFR of 25–60 mL/min/1.73 m^2 (22). Because of a risk of hyperkalemia seen in the FIDELIO-DKD trial, it is important to measure serum potassium before and 4 weeks after finerenone initiation (16,22).

Conclusion

As the prevalence of diabetes, and particularly type 2 diabetes, continues to increase around the world, using therapies that can delay the progression of CKD in this patient population is imperative. Historically, ACE inhibitors and ARBs were the only medication classes with evidence of slowing the progression of CKD in people with diabetes. Based on the outcomes of the SGLT2 inhibitor and GLP-1 receptor agonist trials described above, the International Society of Nephrology KDIGO 2020 guideline now recommends the use of SGLT2 inhibitors and GLP-1 receptor agonists in addition to metformin (5). There are also several future considerations for the treatment of CKD in people with type 2 diabetes that will be elucidated as research in this area continues. The FDA's approval of finerenone in July 2021 adds an additional therapy that could be used to slow the progression of CKD. There is also an ongoing phase 3 clinical trial examining the GLP-1 receptor agonist semaglutide specifically for its use in slowing the worsening of CKD that is scheduled to be completed by August 2024 (23). This ongoing trial using semaglutide is significantly different from the SUSTAIN-6 trial, in which cardiovascular outcomes were the primary focus.

CKD is a major complication of diabetes that can be delayed with the use of appropriate therapies. The availability of new agents with strong evidence of renoprotective effects, and the expectation of more on the horizon, make this an exciting time for health care professionals treating people with type 2 diabetes and CKD. It is not yet known where finerenone will fit into clinical practice recommendations. Still, implementing existing evidence-based recommendations for ACE inhibitors, ARBs, SGLT2 inhibitors, and GLP-1 receptor agonists can delay progression of CKD and improve the lives of people with type 2 diabetes and CKD.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

K.N.D. wrote the manuscript and researched data. A.E.H. researched data and reviewed/edited the manuscript. M.C.S. reviewed/edited the manuscript. K.W.N. wrote the abstract, researched data, and reviewed/edited the manuscript. K.W.N. is the guarantor of this work and, as such, takes responsibility for the integrity and accuracy of data analysis and research.

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