

Diabetes and Chronic Kidney Disease, Joint Management of 2 Associated Conditions and their Complex Interaction, Review of the Literature

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Abstract

Background: Chronic Kidney Disease (CKD) is a prevalent and progressive condition worldwide and diabetes is a major risk factor for this kidney disorder. People with diabetes and CKD are at high risk of complications, such as cardiovascular events and death. CKD is often unrecognized and undiagnosed among people with diabetes. To control CKD, multiple existing and newer agents have been studied in trials and recommended in clinical practice guidelines.

Methods: This article summarizes a narrative review of primary and/or secondary renal outcomes from randomized controlled trials. The main objective was to provide the most up-to-date information on new and existing pharmacotherapy for the treatment of CKD among people with diabetes, specifically type 2 diabetes (DM2).

Discussion: Traditional agents, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers, have been used for 20 years to preserve kidney function. Other existing agents have received FDA approval for the treatment of CKD, such as dapagliflozin, with a role in reducing intraglomerular pressure. Evidence with sodium-glucose cotransporter 2 inhibitors shows a possible class effect in improving renal outcomes, independent of their effect on glycemic parameters. Finerenone was recently approved for people with DM2 and CKD based on clinical evidence as an antagonist of non-steroidal mineralocorticoid receptors. In general, primary and secondary prevention trials have influenced changes in clinical practice guidelines regarding the use of existing and new pharmacotherapy for CKD. Additional considerations include lifestyle modifications, blood pressure control and achievement of glycemic goals for people with diabetes and CKD, following appropriate screening for glomerular filtration rate and/or albuminuria severity.

Conclusion: Due to stronger evidence, clinical practice guidelines have been modified to reflect high-level recommendations for the management of CKD in people with diabetes, specifically DM2. Further evidence is needed among people with lower glomerular filtration rates and in comparison with standard of care.

Keywords: Chronic kidney disease; Clinical practice guidelines; Diabetes; Drug therapy; Renal outcomes; Type 2 diabetes

Introduction

Chronic Kidney Disease (CKD) is defined as a decrease in estimated Glomerular Filtration Rate (eGFR) below 60 mL/min/1.73 m² or detection of kidney damage from laboratory tests for at least 3 months [1]. Specifically, this condition is defined as the presence of persistently elevated albuminuria >30 mg/24 hrs or Urine Albumin Creatinine Ratio (UACR) >30 mg/g creatinine. These abnormalities need to be confirmed in two out of three samples. This condition is not adequately recognized according to a meta-analysis that assessed the worldwide prevalence of CKD, the prevalence varied greatly by eGFR category. It was estimated that 13.4% of people worldwide have stages 1 to 5 of CKD [2]. Evaluating only stages 3 to 5 of CKD, the prevalence was estimated to be 10.6% worldwide. According to the National Kidney Foundation, approximately 37 million people in the United States have CKD (15% of the population), with 1 in 3 adults at risk of developing CKD [3]. High CKD-related morbidity and mortality is impacting the cost and burden on hospitalizations, dialysis centers and healthcare systems. This article is a narrative review on CKD management with a primary focus among people with diabetes, specifically type 2 diabetes (DM2). Provide a brief overview of CKD and summarize new evidence and pharmacotherapy for CKD with recommendations from clinical practice guidelines.

CKD Overview

There are several risk factors for CKD that could affect the projected prevalence of 37.8% in the United States among people 65 years and older by the year 2030 [4]. These risk factors include family history, age, race, obesity, Atherosclerotic Cardiovascular Disease (ASCVD), hypertension and diabetes. Sociodemographic risk factors (e.g. ethnicity, family history, socioeconomic status) can be identified to properly screen individuals for CKD. Some risk factors, such as smoking and obesity, are independent but associated with CKD. Diabetes is

the leading cause of end-stage renal disease among adults in the United States compared with other causes (e.g. glomerulonephritis, cystic kidney) and is a predictor of progressive CKD [5].

Related to diabetes, additional risk factors such as metabolic syndrome and elevated blood pressure may increase progression to CKD in people with diabetes, while genetics, inflammation and oxidative stress could be driving factors [6,7]. Some associations with CKD and diabetes have been identified, including albuminuria and eGFR. These factors can promote the progression of CKD, with the duration of diabetes being one of the strongest predictors of nephropathy [8].

There are pathophysiological changes from the presence of glomerular lesion, impacting the filtration area, blood flow and capillary pressure [9,10]. When kidney injury occurs, there may be a reduction in nephrons, leading to adaptive hyperfiltration. Due to hyperfiltration, proteinuria may result from increased glomerular permeability. In addition, the renin-angiotensin-aldosterone system is activated and can promote inflammation

and remodeling. If CKD is not treated, fibrosis and sclerosis can occur within the kidney, reducing eGFR and urine output. Systemic complications can develop and persist over time. Therefore, albuminuria is one of the first signs of CKD, while other symptoms may include edema, fatigue, itching and/or nausea. People with diabetes and CKD may be at increased risk of Cardiovascular (CV) events. Regardless of the risk factor for a person with DM2 to progress to a CKD diagnosis, the kidneys can be damaged through different pathways, such as metabolic, hemodynamic, inflammatory and oxidative stress pathways. The complications of CKD can be detrimental to a person with diabetes, further increasing the risk of CV disease [11].

CKD can be an undiagnosed condition; therefore, it is important to identify people at risk, particularly by assessing comorbid conditions, eGFR and albuminuria in order to make appropriate referrals or initiate appropriate treatment. CKD classification is based on the cause of renal injury, eGFR and/or the presence or severity of albuminuria (**Tables 1 and 2**) [12].

Table 1: Renal function based on GFR category [12].

TFG category	GFR (ml/min/1.73 m ²)	Kidney function
G1	≥ 90	Normal or high
G2	60-89	Slightly diminished
G3a	45-59	Mild to moderate decrease
G3b	30-44	Moderate to severe decrease
G4	15-29	Severe decline
G5	<15	Severe kidney failure

Table 2: Classification of renal function based on the category of albuminuria [12].

Albuminuria category	Albumin/Creatinine ratio (mg/g)	Urine albumin
A1	<30	Normal to slightly maintained
A2	30-300	Moderately established
A3	>300	Severely established

Glycemic goals

As indicated by historical trials, a 1% reduction in A1C level can lead to a 37% improvement in microvascular complications, such as nephropathy. The original evidence supporting these trials was produced by the Diabetes Control and Complications Trial (DCCT) and the UKPDS trial, in people with Type 1 Diabetes (T1D) and Type 2 Diabetes (T2DM), respectively [13-16]. These trials have shown an improvement in microalbuminuria or the development of macroalbuminuria when the A1C is below 7% on target after diagnosis of diabetes.

The purpose of the DCCT was to determine the risk of microvascular and macrovascular complications among people with T1D. In the DCCT, there were two treatment groups: Intensive treatment group (n=378) with a preprandial target of 70-120 mg/dL, postprandial target of <180 mg/dL and A1C <6.05% versus a conventional treatment group (n=348). The primary outcome was the development of long-term complications of diabetes. Intensive treatment resulted in a 43% reduction in the risk of nephropathy, particularly microalbuminuria [13]. People with T1D who receive intensive treatment with more stringent glycemic targets may obtain long-term benefits, specifically in reducing microvascular complications (e.g. nephropathy) and

these long-term benefits may extend beyond 10 years after treatment diagnosis.

In the UKPDS trials, the risk of microvascular and macrovascular complications was investigated among people with newly diagnosed T2DM after intensive or conventional treatment for a specific A1C target [14,15]. In the intensive treatment group, a more stringent A1C goal was met with sulfonylureas or insulin, as the median A1C was 7% after 10 years of treatment. As of the UKPDS 33, there was a 12% risk reduction in the diabetes-related endpoint, which was a combination of microvascular and macrovascular complications as the primary endpoint [14]. Evaluating intensive treatment particularly with metformin will improve a median A1C of 7.4%, resulting in a 32% risk reduction on the composite endpoint of microvascular and macrovascular complications [15]. From the UKPDS trials, it was concluded that blood pressure control was essential as a control of risk factors to decrease the possibility of developing microvascular and macrovascular complications in people with DM2 [16]. This conclusion is important as blood pressure management will be part of overall management among people with diabetes and CKD.

Despite the fact that intensive treatment led to better glycemic outcomes, there was long-term progression of kidney disease from the UKPDS findings for people with T2DM. Participants with normoalbuminuria at the start of the trial progressed to microalbuminuria at a rate of 2% per year; comparatively, participants with microalbuminuria at the start of the trial progressed to macroalbuminuria at a rate of 2.8% per year. In addition, 38% and 28% of the participants, respectively, developed albuminuria and had an eGFR of <60 mL/min/1.73 m² 15 years after T2DM diagnosis [17]. Overall, it is estimated that 37% of people with diabetes have CKD [18]. In addition, there are individuals at risk of progression to renal dysfunction, leading to complications and adverse cardiorenal consequences.

Other studies have evaluated the benefit of intensive control of microvascular complications in a different patient population: People with established diabetes and a history of microvascular and/or macrovascular complications [19-21]. According to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive treatment among those with established type 2 diabetes and a prior history of complications is not appropriate and therefore the preference would be to individualize A1C based on duration of treatment diabetes and other comorbid conditions. In terms of microvascular events, there was a 21% reduction in new or worsening kidney disease in the Action in Diabetes and Vascular Disease Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, indicating a benefit for those with type 2 diabetes established and average A1C of 6.4% [20]. Similar to the ADVANCE trial, the Veteran Affairs Diabetes Trial (VADT) showed no impact on glycemic control (intensive therapy and standard therapy with mean A1C 6.9% and 8.4%, respectively) [21]. In general, the ACCORD, ADVANCE and VADT trials suggested that there is a benefit to the patient with intensive therapy where this is not correct. In relation to CKD, intensive therapy may be indicated for a person with diabetes and no history of CV disease or microvascular

disease taking into account other factors (*e.g.* age, baseline A1C, risk of hypoglycemia).

Pharmacotherapy

Clinical practice guidelines have been updated to incorporate recent evidence in the management of CKD among people with diabetes, as it is essential to understand the evidence and change the culture within clinical practice in the management of CKD [22-25]. Before reviewing the evidence with Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors and a third-generation mineralocorticoid receptor antagonist, it is important to mention that renin-angiotensin system blockers have been and continue to be part of the treatment of CKD in people with diabetes over the past 20 years. In the American Diabetes Association's 2022 Standards of Medical Care in Diabetes, Angiotensin-Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARBs) remain highly recommended for people with moderate to severe albuminuria increased in the presence of diabetes and hypertension. However, these agents are not recommended for people with normal blood pressure or eGFR in the absence of albuminuria [25]. Although this review article summarizes new evidence on SGLT2 inhibitors and third-generation mineralocorticoid receptor antagonists, ACE inhibitors or ARBs were the mainstay therapy within clinical trials, generally prescribed for at least 4 weeks at a stable or maximum tolerated dose prior to randomization.

When evaluating pharmacotherapy for CKD, it is essential to evaluate the definition of renal outcomes. There have been a wide range of renal outcomes investigated in randomized controlled trials as primary or secondary endpoints. Primary outcomes may have focused on treatment (*e.g.* specific agent) while secondary outcomes focused on follow-up (*e.g.* safety). Post hoc data or analysis provide exploratory information. Renal outcomes range from a doubling of serum creatinine to the rate of decline in renal function (*e.g.* specific percentage) to the onset or worsening of renal disease. When reviewing the literature on major adverse renal endpoints, there were also surrogate endpoints, such as decreased eGFR [26]. In cardiovascular outcome trials with T2DM agents since 2008, renal outcomes have often been composite and/or exploratory outcomes. There was a lack of standardization between trials of CV outcomes in people with T2DM and ASCVD or at high risk of CV disease. The International Society of Nephrology has published consensus definitions of clinical and eGFR-based outcomes. After evaluating randomized controlled trials and a variety of definitions, The International Society of Nephrology defined a clinical outcome as kidney transplantation, initiation of dialysis, or death from kidney failure. Results based on eGFR would include a sustained reduction in GFR by a specified percentage or a sustained eGFR at a low rating [27].

SGLT2 inhibitors

SGLT2 inhibitors have emerged with strong evidence supporting their role in cardiovascular and renal disease beyond effects on glucose levels and independently of hypoglycemic effects. Although the mechanism of action for cardiovascular and renal benefit is still being defined and studied, it is

suspected that there are short and long-term effects of this class of agents in delaying the progression of CKD. In the short term, the class can promote diuresis and natriuresis and promote vasoconstriction of afferent arterioles and reduction of intraglomerular pressure. In the long term, it may have an effect in reducing inflammation and fibrosis while increasing hypoxic hematocrit in tubular cells. The mechanism of action is extensive and multifactorial, beyond classification to promote glucose excretion.

Secondary analyzes have concluded favorable results in renal endpoints with SGLT2 inhibitors. Empagliflozin resulted in a 46% reduction in their exploratory renal outcome, while canagliflozin showed a 40% reduction in eGFR, renal replacement, or renal death [28,29]. Dapagliflozin showed a 47% reduction in eGFR decline at 60 mL/min/1.73 m², End-Stage Renal Disease (ESRD), or renal death [30]. Ertugliflozin improved renal outcomes, but the results were not statistically significant [31]. Of these CV outcome trials, the patient population either had a history of T2DM and ASCVD or was at high risk for CV disease. In addition, the populations studied were generally healthy and at low risk of kidney disease [28-31]. Finally, renal outcomes were not the primary objective of the studies, as the aim was to reduce major adverse cardiovascular events; therefore, these renal outcomes were explored as secondary endpoints or in post hoc analyses. In a meta-analysis including empagliflozin, canagliflozin and dapagliflozin, class resulted in a 45% reduction in new-onset macroalbuminuria compound, a sustained doubling of serum creatinine, or a 40% decrease in eGFR or death from renal causes. Empagliflozin, canagliflozin and dapagliflozin reduced the composite endpoint by 46%, 40% and 47%, respectively [32].

In specifically designed renal outcome trials, canagliflozin and dapagliflozin have shown benefits for the treatment of CKD in people with T2DM [33,34]. Canagliflozin was investigated in people with T2DM and CKD in the Canagliflozin and Renal Events in Diabetes with Clinical Evaluation of Established Renal Disease (CREDENCE) trial. Participants had a diagnosis of T2DM with an A1C of 6.5%-12%, along with eGFR between 30 and 90 mL/min/1.73 m² (mean eGFR, 56.3 mL/min/1.73 m²) and albuminuria (median 923 mg/g). Canagliflozin 100 mg orally once daily is compared with placebo; canagliflozin reduced major adverse renal events by 30% as the primary composite endpoint. The

reduction is primarily due to a 40% reduction in serum creatinine doubling and a 32% reduction in end-stage renal disease [32]. Dapagliflozin was investigated in a randomized placebo-controlled trial on Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD). Dapagliflozin 10 mg orally once daily was compared with placebo in people with CKD regardless of diabetes status; participants were included if eGFR was between 25 and 75 mL/min/1.73 m² (mean eGFR, 43.1 mL/min/1.73 m²) and albuminuria between 200 and 5000 mg/g (median 949 mg/g). Dapagliflozin reduced the primary adverse renal outcome by 39%, while secondary outcomes indicated greater benefit with dapagliflozin with a 29% and 31% reduction in cardiovascular death or heart failure hospitalization and death, respectively [33]. There are several questions among these clinical trials with primary endpoints for renal outcomes. The degree of improvement in renal outcomes among patients with stage 1 or 2 CKD and albuminuria is unknown. In addition, all participants were taking an ACE inhibitor or ARB at baseline for at least 4 weeks prior to randomization. The efficacy of canagliflozin or dapagliflozin compared to an ACE inhibitor or ARB is unknown. Finally, most of the participants in the CREDENCE and DAPA-ERC trials were middle-aged whites and not Hispanic; the possibility of generalizing trials among populations at high risk of CKD, such as non-Hispanic black individuals, is lacking [32,33].

The evidence is overwhelming for SGLT2 inhibitors, cementing their role as first-line therapy for people with CKD, regardless of diabetes status. The American Diabetes Association recommends an SGLT2 inhibitor for people with T2DM and CKD to slow the progression of CKD; the role of these agents may extend to stage 4 CKD and severe increase in albuminuria [25]. SGLT2 inhibitors may also be considered among those with T2DM and CKD at risk for CV disease, as canagliflozin and dapagliflozin reduced CV outcomes in the CREDENCE and DAPA-CKD trials [25,32,33]. In the 2020 update, the KDIGO clinical practice guidelines suggest metformin and an SGLT2 inhibitor as first-line therapy for T2DM and CKD, specifically with an SGLT2 inhibitor among those with eGFR greater than 30 mL/min/1.73 m² [22]. **Table 3** summarizes the indications and renal settings of the approved SGLT2 inhibitors [35-38].

Table 3: Comparison of SGLT2 inhibitors [35-38].

Name	Approval	CV indication	Renal indications	Kidney adjustments
Canagliflozin (Invokana®)	2013	Reduced risk of MACE in people with DM2 and established CVD	Reduced risk of ESKD, Scr doubling, CV death and HHF in people with T2DM and albuminuric nephropathy	eGFR (mL/min/1.73 m ²) ≥ 60: 100 mg per day, up to 300 mg per day 45-59: 100 mg per day 30-44: 100 mg per day (with albuminuria) <30: Contraindicated
Dapagliflozin (Farxiga®)	2014	Reduced risk of HHF in people with T2DM and established CVD or multiple CV risk factors reduced risk of CV death	Reduced risk of decreased eGFR, ESKD, CV death, and HHF for people with CKD	eGFR ≥ 25: 10 mg per day for HF rEF or CKD <25: No start dialysis: Contraindicated

		and HHF for people with HFrEF		
Empagliflozin (Jardiance®)	2014	Reduced risk of CV death for people with DM2 and established CVD	No	eGFR \geq 25: 10 mg per day for HFrEF dialysis: Contraindicated
Ertugliflozin (Steglatro®)	2017	No	No	eGFR \geq 60: 5 mg per day, titrated to 15 mg per day for DM2

Note: CKD: Chronic Kidney Disease; CV: Cardiovascular; CVD: Cardiovascular Disease; eGFR: estimated Glomerular Filtration Rate; ESKD: End-Stage Renal Disease; HFrEF: Heart Failure with reduced Ejection Fraction; HHF: Hospitalization for Heart Failure; MACE: Major Adverse Cardiovascular Events; SCr: Serum Creatinine; SGLT2: Sodium-Glucose Cotransporter 2; DM2: Type 2 Diabetes.

Mineralocorticoid receptor antagonist

On July 9, 2021, finerenone was found to be a selective third-generation or non-steroidal mineralocorticoid receptor antagonist for reduction of the risk of sustained decline in eGFR, ESRD and CV death and events in people with T2DM and CER. Its approval was based on large randomized controlled trials in this specific patient population. As an antagonist of the more selective mineralocorticoid receptors, finerenone has higher affinity and potency, leading to a reduction in inflammation and fibrotic markers. Through this targeted mechanism of action, it has a lack of affinity for sex and glucocorticoid receptors, compared to spironolactone and eplerenone [39,40].

In a phase IIb trial, various doses of finerenone were compared with eplerenone in people with heart failure with reduced ejection fraction with diabetes and/or CKD. Although the main outcome focused on finerenone with guideline-based medical treatment for heart failure, there were safety observations related to changes in eGFR. The 2.5 mg and 5 mg doses improved eGFR from baseline to day 30, while other doses had a slight decrease in eGFR. The study was not powered or designed to show statistical significance in the primary heart-related outcome, but found that people with T2DM, CKD and heart failure might benefit from finerenone, as the drug reduced hospitalization for CV causes in 44% [41]. In another trial, finerenone with standard of care (*e.g.* ACE inhibitors, ARBs) was investigated among people with type 2 diabetes and albuminuria (36.7% of participants \geq 300 mg/g): It should be noted that most of the participants had an eGFR >60 ml/min/1.73 m². From baseline to 90 days, finerenone reduced the primary outcome in a dose-dependent manner at 7.5, 10, 15 and 20 mg per day. This trial showed no difference between finerenone and placebo in decreasing eGFR of 30% or more, but added to the evidence supporting UACR as an alternative endpoint for CKD [42].

Discussion

In an event-based, randomized, controlled trial (known as the FIDELIO trial), the efficacy of finerenone was prolonged in people with type 2 diabetes and chronic kidney disease who

were already receiving an ACE inhibitor or ARB. Finerenone reduced the primary composite outcome of renal failure, maintained a 40% reduction in eGFR from baseline, or renal-related death by 18%. The primary outcome was primarily driven by the 19% reduction in the risk of a sustained decline of $>40\%$ in eGFR from baseline; It is important to note that the patient population had a lower baseline eGFR than in previous finerenone trials (52.5% at 25–45 mL/min/1.73 m²). Among people with T2DM and CKD, finerenone also reduced major adverse cardiovascular events by 14%; however, 5% of participants took SGLT2 inhibitors at baseline [43]. In another event-based, randomized, controlled trial, finerenone was compared with placebo in people with type 2 diabetes and chronic kidney disease on ACE inhibitor-based ARB therapy. In this trial, known as the FIGARO trial, participants may have had stage 2 CKD at the start of the study. Finerenone reduced the same renal outcome in the FIDELIO trial by 24%. Additional results showed a reduction in the incidence of new-onset heart failure; however, there was no difference between finerenone and placebo in reducing hospitalization for heart failure and CV death [44]. These trials were pooled for further analysis to determine the cardiorenal benefit of finerenone. Among more than 13,000 participants with T2DM and CKD, finerenone 10 or 20 mg can reduce time to renal failure, a sustained eGFR reduction of 57%, or renal death by 23%, while providing a cardiovascular benefit in terms of major events and heart failure hospitalization [45]. As with SGLT2 inhibitors, questions remain about the clinical application of finerenone in clinical practice. The benefit of an SGLT2 inhibitor with finerenone is unknown, as 5% and 8% of participants in the FIDELIO and FIGARO trials, respectively, were taking SGLT2 inhibitors at baseline [43,44]. Furthermore, finerenone has not been compared with an SGLT2 inhibitor and therefore its role as a potential first-line option remains undefined. Lastly, there was a lack of generalisability as study participants were similar to other renal trials in terms of age and ethnicity.

The American Diabetes Association guidelines are the only clinical practice guidelines that have recommendations for finerenone for people with T2DM and CKD. Finerenone can be considered among those with intolerance or contraindication to SGLT2 inhibitors [25]. This new drug has a clinical niche in

practice for people with DM2 and CKD; however, utilization will be determined over time and will be based on insurance

coverage. **Table 4** summarizes general drug-specific information regarding finerenone.

Table 4: General summary of finerenone [39].

Indication	Lower risk of sustained decline in eGFR, ESRD, CV death, non-fatal myocardial infarction and HHF for those with CKD associated with DM2
Contraindications	Strong CYP3A4 inhibitors; suprarrenal insufficiency
Interaction	Weak to strong CYP3A4 inhibitors; grapefruit and grapefruit juice
Dosage	10 mg or 20 mg PO QD (initial) 20 mg PO QD (target)
eGFR dosing	≤ 60 mL/min/1.73 m ² =20 mg VO QD ≥ 25 to <60 mL/min/1.73 m ² =10 mg VO QD ≥ 25 to <60 mL/min/1.73 m ² =10 mg VO QD <25 mL/min/1.73 m ² =Do not use <25 mL/min/1.73 m ² =Do not use
Note: CKD: Chronic Kidney Disease; CV: Cardiovascular; CYP: Cytochrome; eGFR: estimated Glomerular Filtration Rate; ESRD: End-Stage Renal Disease; HHF: Hospitalization for Heart Failure; MI: Myocardial Infarction; PO: by mouth; QD: daily; DM2: Type 2 Diabetes.	

Future directions

Efpeglenatide is a Glucagon-Like Peptide 1 Receptor Agonist (GLP1 RA) that is administered once weekly and is being investigated as a possible option for glycemic control in DM2. It has been evaluated as an effective and safe option in a randomized and controlled manner among people with DM2 and a history of cardiovascular disease or renal disease (eGFR 25-59.9 ml/min/1.73 m²). Efpeglenatide reduced the major adverse cardiovascular events of a combination of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular or other causes by 27% compared to placebo. For renal outcomes, efpeglenatide was associated with a 21% risk reduction with the composite renal outcome. Based on subgroup analysis, efpeglenatide showed benefit among participants with established diabetes greater than 10 years, eGFR less than 71.5 mL/min/1.73 m², a history of CV disease and no initial use of an inhibitor from SGLT2. Although the drug was well tolerated and had a similar safety profile to other GLP1 RAs, CV and renal benefit emerged from efpeglenatide as an exendin 4 analogue and the benefit was increased regardless of SGLT2 inhibitor use. However, the role of this investigational agent is forthcoming, particularly as the AMPLITUDE-O trial did not achieve power based on anticipated events and cannot be generalized to other patient populations with varying CKD propensities [46]. The synergistic effect of a GLP1 RA and SGLT2 inhibitor should be explored to determine if there is additional benefit with

cardiorenal outcomes for those at risk of cardiorenal events, regardless of diabetes status.

As recommended by the American Diabetes Association in the 2022 Standards of Medical Care, GLP1 RAs are an alternative option for T2DM and CKD if SGLT2 inhibitors are contraindicated or intolerable [24]. In trials of cardiovascular outcomes, renal benefits are reported with long-acting GLP1 RA (e.g. liraglutide, semaglutide, dulaglutide). Liraglutide, semaglutide and dulaglutide have resulted in a 22%, 36% and 15% risk reduction, respectively, in secondary composite renal outcomes, which was driven by improvement in macroalbuminuria [47-49]. A meta-analysis indicated an 18% reduction in a composite renal outcome; however, this meta-analysis only included extended-release lixisenatide, liraglutide, semaglutide and exenatide [50].

Additional evidence with semaglutide injection is forthcoming as it is being investigated versus placebo among people with T2DM and CKD in the FLOW trial. The primary renal endpoint is a time-to-first-occurrence composite renal endpoint with early completion in 2024. As summarized above, evidence is limited on the role of GLP1 in the treatment of CKD for people with T2DM; However, the FLOW trial provides more information on the renal benefit for people with CKD or at risk of progression to CKD [51]. In general, the GLP1 class of RA has been considered an alternative option for people with T2DM and kidney disease; **Table 5** summarizes the information relevant to CKD for liraglutide, semaglutide and dulaglutide [52-54].

Table 5: Comparison of selected GLP1 RA.

Name	Approval	CV indication	Renal indications	Kidney adjustments
Dulaglutide (Trulicity®)	Sep-14	MACE risk reduction for people with T2DM and established CVD or multiple CV risk factors	No	None
Liraglutide (Victoza®)	Jan-10	Reduced risk of MACE in people with DM2 and established CVD	No	None
Semaglutide (Ozempic®)	Dec-17	Reduced risk of MACE in people with DM2 and established CVD	No	None

Note: CV: Cardiovascular; CVD: Cardiovascular Disease; GLP1 RA: Glucagon-Like Peptide 1 Receptor Agonist; MACE: Major Adverse Cardiovascular Events; DM2: Type 2 Diabetes.

Conclusion

For the management of CKD among people with diabetes, it is important to achieve disease state goals through glycemic and blood pressure management. Lifestyle modifications should be encouraged among this patient population. In addition, specific pharmacologic agents, such as angiotensin antagonists and SGLT2 inhibitors, should be used to improve and prevent renal outcomes, including albuminuria. The role and clinical utilization of recently advanced agents, such as finerenone, has yet to be determined in clinical practice. With additional evidence and pharmacotherapy, it is important to apply evidence-based evidence with adequate follow-up to prevent clinical and therapeutic inertia among a population at risk for cardiorenal events. In addition, more research should be done to determine the role of existing and new agents for people with a higher eGFR in the presence of albuminuria and within a certain ethnic group. In addition, trials with active comparators, including ACE inhibitors and ARBs, are needed to determine the benefit of first-line agents. Based on a solid body of evidence, practice guidelines have been modified and updated to highlight high-level recommendations.

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