Abstract

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

Methods: A narrative review of primary and/or secondary renal outcomes from randomized, controlled trials is summarized in this article. The main objective was to provide the most up-to-date information regarding existing and new pharmacotherapy for the management of CKD amongst people with diabetes, specifically type 2 diabetes (T2D).

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 approval by the FDA for the management of CKD such as dapagliflozin, with a role in reducing intraglomerular pressure. Evidence with sodium–glucose cotransporter 2 inhibitors show a potential class effect on improving renal outcomes, independent on their effect on glycaemic parameters. Recently, finerenone was approved for people with T2D and CKD based on clinical evidence as a non-steroidal mineralocorticoid receptor antagonist. Overall, 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 management and achievement of glycaemic targets for people with diabetes and CKD, following adequate screening of glomerular filtration rate and/or severity of albuminuria.

Conclusion: Due to more robust evidence, clinical practice guidelines have been modified to reflect high-level recommendations for the management of CKD in people with diabetes, specifically T2D. Additional evidence is needed amongst people with lower glomerular filtration rates and in comparison with the standard of care.

Keywords: chronic kidney disease, clinical practice guidelines, diabetes, pharmacotherapy, renal outcomes, type 2 diabetes.

Citation

Overview of CKD

There are several risk factors for CKD that could impact the projected prevalence of 37.8% in the United States amongst individuals 65 years or 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 appropriately screen individuals for CKD.5 Some risk factors, such as smoking and obesity, are independent but associated with CKD.5 Diabetes is the leading cause of end-stage kidney disease amongst adults in the United States compared to 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, can increase the progression to CKD in people with diabetes, whereas promoters could be genetics, inflammation and oxidative stress.6,7 Some associations have been identified with CKD and diabetes, including albuminuria and eGFR.8 These factors can promote the progression of CKD with the duration of diabetes being one of the strongest predictors for nephropathy.9 Hence, people with T2D do not know the risk of developing CKD later in life.

There are pathophysiological changes from the presence of glomerular injury, impacting filtration area, blood flow and capillary pressure.9,10 When an injury occurs in the kidney, there can be a reduction in nephrons, leading to adaptive hyperfiltration. Due to hyperfiltration, proteinuria can occur from an increased glomerular permeability. In addition, the renin–angiotensin–aldosterone system is activated and can promote inflammation and remodelling. If CKD is untreated, fibrosis and sclerosis within the kidney can occur, reducing eGFR and urinary output. Systemic complications can develop and persist over time.9,10 Therefore, albuminuria is one of the earliest signs of CKD, whereas other symptoms could include oedema, fatigue, itching and/or nausea.11 People with diabetes and CKD can be at an increased risk of cardiovascular (CV) events. Regardless of the risk factor for a person with T2D progressing to a diagnosis of CKD, there is damage that can happen to the kidneys through different pathways such as metabolic, haemodynamic, inflammatory and oxidative stress pathways. Complications from CKD can be detrimental for a person with diabetes, further increasing the risk of CV disease.11

CKD can be an undiagnosed condition; therefore, it is important to identify individuals at risk particularly by evaluating comorbid conditions, eGFR and albuminuria in order to make appropriate referrals or start appropriate treatment.12 The classification of CKD is based on the cause of kidney injury, eGFR, and/or the presence or severity of albuminuria.12 Refer to Tables 1 and 2 for the classification of CKD based on eGFR and albuminuria, respectively.12

Table 1. Kidney function based on GFR category. Adapted from ref.12

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Kidney function</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Glycaemic targets

As indicated by landmark trials, a 1% reduction in A1C level can lead to improvement in microvascular complications such as nephropathy by 37%. The original evidence supporting these findings was produced by the Diabetes Control and Complications Trial (DCCT) and the UKPDS trial, in people with type 1 diabetes (T1D) and T2D, respectively.13–16 These trials have shown improvement in microalbuminuria or the development of macroalbuminuria when A1C is less than 7% as a target following the diagnosis of diabetes.

The purpose of the DCCT was to determine the risk of microvascular and macrovascular complications amongst people with T1D.13 In the DCCT, there were two interventions – intensive treatment group (n=378) with a preprandial goal of 70–120 mg/dL, postprandial goal 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% risk reduction in nephropathy, particularly microalbuminuria.13 People with T1D who receive intensive treatment with more stringent glycaemic targets can gain benefit long term, specifically in the reduction of

Table 2. Classification of kidney function based on albuminuria category. Adapted from ref.12

<table>
<thead>
<tr>
<th>Albuminuria category</th>
<th>Albumin to creatinine ratio (mg/g)</th>
<th>Albumin in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>30–300</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>A3</td>
<td>&gt;300</td>
<td>Severely increased</td>
</tr>
</tbody>
</table>
microvascular complications (e.g. nephropathy), and these long-term benefits can span over 10 years after diagnosis.

In the UKPDS trials, the risk of microvascular and macrovascular complications was investigated amongst people with newly diagnosed T2D following intensive or conventional treatment for a specific A1C target.\textsuperscript{14,15} In the intensive treatment group, a more stringent A1C goal was achieved with sulfonylureas or insulin as the median A1C was 7% after 10 years of therapy. From UKPDS 33, there was a 12% risk reduction in the diabetes-related endpoint, which was a composite of microvascular and macrovascular complications as the primary endpoint.\textsuperscript{16} When evaluating intensive treatment particularly with metformin, a median A1C of 7.4% was achieved, resulting in a 32% risk reduction in the composite endpoint of microvascular and macrovascular complications.\textsuperscript{15} From the UKPDS trials, it was concluded that blood pressure management was essential as a risk factor control to lessen the chance of developing microvascular and macrovascular complications in people with T2D.\textsuperscript{16} This conclusion is important as blood pressure treatment will be part of the overall management amongst people with diabetes and CKD.

Despite intensive treatment leading to improved glycaemic outcomes, there was a long-term progression of kidney disease from UKPDS findings for those with T2D. Participants with normoalbuminuria at the beginning of the trial progressed to microalbuminuria at a rate of 2% per year; comparatively, participants with microalbuminuria at the beginning of the trial progressed to macroalbuminuria at a rate of 2.8% per year.\textsuperscript{17} In addition, 38% and 28% of participants respectively developed albuminuria and had eGFR of <60 ml/min/1.73 m\textsuperscript{2} 15 years after the diagnosis of T2D.\textsuperscript{17} Overall, it is estimated that 37% of people with diabetes have CKD.\textsuperscript{18} In addition, there are individuals at risk of progression to renal dysfunction, leading to cardio renal complications and consequences.

Other studies have evaluated the benefit of intensive control on microvascular complications in a different patient population – people with established diabetes and a history of microvascular and/or macrovascular complications.\textsuperscript{19–21} From the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive treatment amongst those with established T2D and prior history of complications is not appropriate and, therefore, the preference would be to individualize A1C based on the duration of diabetes and other comorbid conditions. In terms of microvascular events, there was a 21% reduction amongst new or worsening nephropathy in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, indicating benefit for those with established T2D and average A1C of 6.4%.\textsuperscript{20} Similar to the ADVANCE trial, the Veteran Affairs Diabetes Trial (VADT) showed no impact of glycaemic control (intensive treatment and standard treatment with average A1C of 6.9% and 8.4%, respectively).\textsuperscript{21} Overall, the ACCORD, ADVANCE and VADT trials indicated that there is a benefit with intensive therapy for the right patient.\textsuperscript{19–21} Related to CKD, intensive therapy may be indicated for a person with diabetes and no history of CV disease or microvascular disease with consideration for other factors (e.g. age, baseline A1C, risk of hypoglycaemia).

**Pharmacotherapy**

Clinical practice guidelines have been updated to incorporate recent evidence in the management of CKD amongst people with diabetes as it is essential to gain an understanding of evidence and change the culture within clinical practice in the management of CKD.\textsuperscript{22–25} Prior to 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 remain a part of the management of CKD for people with diabetes for the past 20 years. In the 2022 Standards of Medical Care in Diabetes from the American Diabetes Association, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) remain highly recommended for individuals with moderately or severely increased albuminuria in the presence of diabetes and hypertension.\textsuperscript{23} However, these agents are not recommended for those with a normal blood pressure or eGFR in the absence of albuminuria.\textsuperscript{25} Whilst this review article summarizes new evidence on SGLT2 inhibitors and third-generation mineralocorticoid receptor antagonists, ACE inhibitors or ARBs were background therapy within the clinical trials, typically prescribed for at least 4 weeks at a stable or maximally tolerated dose prior to randomization.

When evaluating pharmacotherapy for CKD, it is essential to evaluate the definition of renal outcomes. There has been a wide range of renal outcomes investigated in randomized controlled trials as primary or secondary endpoints.\textsuperscript{26} Primary outcomes may have focused on the treatment (e.g. specific agent) whereas secondary outcomes focused on monitoring (e.g. safety). Post hoc data or analyses provided exploratory information. Renal outcomes have ranged from doubling of serum creatinine to rate of decline in kidney function (e.g. specific percentage) to onset or worsening of nephropathy. When evaluating the literature on major adverse renal endpoints, there were also surrogate endpoints, such as the decline of eGFR and UACR.\textsuperscript{26} In CV outcome trials with agents for T2D since 2008, renal outcomes have often been composite and/or exploratory outcomes. There was a lack of standardization amongst CV outcome trials in people with T2D and ASCVD or at high risk of CV disease. The International Society of Nephrology has published consensus definitions of clinical and eGFR-based outcomes.\textsuperscript{27} After evaluating randomized controlled trials and a variety of definitions, the International Society of Nephrology defined a clinical kidney outcome as transplantation, initiation of dialysis, or death from kidney failure. The eGFR-based outcomes would include sustained lowering of GFR by a specific percent or sustained eGFR at a low classification.\textsuperscript{27}
SGLT2 inhibitors

SGLT2 inhibitors have emerged with strong evidence to support their role in CV and renal conditions beyond effects on glucose levels and independent of glucose-lowering effects. Whilst the mechanism of action for CV and renal benefit is still being defined and studied, it is suspected that there are short-term and long-term effects from this class of agents on slowing the progression of CKD. Short term, the class can promote diuresis and natriuresis and promote afferent arteriole vasoconstriction and reduction in intraglomerular pressure. Long term, they can have an effect on reducing inflammation and fibrosis whilst increasing haematocrit for hypoxia in tubular cells. The mechanism of action is extensive and multifactorial – beyond the classification of promoting glucose excretion.

Secondary analyses have concluded favourable outcomes on renal endpoints with SGLT2 inhibitors. Empagliflozin resulted in a 46% reduction in its exploratory renal outcome, whereas canagliflozin showed a 40% reduction in eGFR, renal replacement or renal death.28,29 Dapagliflozin showed a 47% reduction in decrease in eGFR to 60 mL/min/1.73 m², end-stage renal disease (ESRD) or renal death.30 Ertugliflozin improved renal outcomes but results were not statistically significant.31 From these CV outcome trials, the patient population had a history of T2D and ASCVD or was at high risk of CV disease. In addition, the studied populations were generally healthy and at low risk of kidney disease.28–31 Lastly, renal outcomes were not the main purpose of the studies as the focus was a reduction on 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, the class resulted in a 45% reduction in the composite of new-onset macroalbuminuria, sustained doubling of serum creatinine or 40% decline in eGFR, ESRD, or death from renal causes.32 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 benefit for CKD management in people with T2D.33,34 Canagliflozin was investigated amongst people with T2D and CKD in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.33 Participants had a diagnosis of T2D 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 of 923 mg/g). Canagliflozin 100 mg orally once daily was compared to placebo, with canagliflozin reducing major adverse renal events by 30% as a composite primary endpoint. The reduction was mainly driven by a 40% reduction in doubling of serum creatinine and a 32% reduction in end-stage kidney disease.32 Dapagliflozin was investigated in a randomized, placebo-controlled trial in the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD).33 Dapagliflozin 10 mg orally once daily was compared to 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 of 949 mg/g). Dapagliflozin reduced the major adverse renal primary outcome by 39% whereas secondary outcomes indicated further benefit with dapagliflozin with a 29% and 31% reduction in CV death or hospitalization for heart failure and death, respectively.33 There are several questions remaining amongst these clinical trials with primary endpoints for renal outcomes. The degree of improvement in renal outcomes amongst people 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. Lastly, most participants from the CREDENCE and DAPA-CKD trials were middle-aged and non-Hispanic White; the generalizability of the trials is lacking amongst populations at high risk of CKD such as non-Hispanic Black individuals.32,33

The evidence is overwhelming for SGLT2 inhibitors, solidifying 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 T2D and CKD to slow the progression of CKD; the role of these agents can extend to stage 4 CKD and severely increased albuminuria.25 SGLT2 inhibitors can also be considered amongst those with T2D and CKD at risk of CV disease as canagliflozin and dapagliflozin reduced CV outcomes in the CREDENCE and DAPA-CKD trials.25,32,33 In the update from 2020, the KDIGO clinical practice guidelines suggest metformin and an SGLT2 inhibitor as first-line therapy for T2D and CKD, specifically with an SGLT2 inhibitor amongst those with eGFR above 30 mL/min/1.73 m².22 Table 3 summarizes the indications and renal adjustments for the approved SGLT2 inhibitors.35–38

Mineralocorticoid receptor antagonist

On July 9, 2021, finerenone was approved as a third-generation or non-steroidal, selective mineralocorticoid receptor antagonist for risk reduction in sustained eGFR decline, ESRD and CV death and events in people with T2D and CKD.39 Its approval was based on large randomized, controlled trials in this specific patient population. As a more selective mineralocorticoid receptor antagonist, finerenone has a higher affinity and potency, leading to a reduction in inflammation and fibrotic markers.39,40 Through this targeted mechanism of action, it has a lack of affinity for sex and glucocorticoid receptors, as compared to spironolactone and eplererone.39,40

In a phase IIb trial, various doses of finerenone were compared to eplerenone in people with heart failure with reduced ejection fraction with diabetes and/or CKD.41 Whilst the primary outcome was focused on finerenone with guideline-based...
medical therapy for heart failure, there were safety observations related to eGFR changes. The doses of 2.5 and 5 mg improved eGFR from baseline to day 30, whereas other doses had a slight decrease in eGFR.\textsuperscript{41} The study was not powered or designed to show statistical significance in the heart-related primary outcome but did find that people with T2DM, CKD and heart failure could gain benefit with finerenone as the medication reduced CV hospitalization by 44%.\textsuperscript{41} In another trial, finerenone was investigated with the standard of care (e.g. ACE inhibitors, ARB) amongst people with T2D and albuminuria (36.7% of participants with ≥300 mg/g); it should be noted that a majority of the participants had an eGFR >60 mL/min/1.73 m\textsuperscript{2}.\textsuperscript{42} From baseline to 90 days, finerenone reduced the primary outcome of UACR in a dose-dependent manner with 7.5, 10, 15 and 20 mg per day.\textsuperscript{42} This trial showed no difference between finerenone and placebo in eGFR decline of 30% or more, but did add to the evidence of supporting UACR as a surrogate endpoint for CKD.\textsuperscript{42}

In an event-driven, randomized, controlled trial (known as the FIGARO trial), the efficacy of finerenone was determined in people with T2D and CKD who were already receiving an ACE inhibitor or ARB.\textsuperscript{43} Finerenone reduced the primary composite outcome of kidney failure, sustained 40% reduction in eGFR from baseline, or death from renal cause by 18%. The primary outcome was mainly driven by the 19% lowered risk of sustained decrease of >40% in eGFR from baseline; it is important to note that the patient population had lower baseline eGFR than in previous finerenone trials (52.5% with 25–45 mL/min/1.73 m\textsuperscript{2}). Amongst people with T2D and CKD, finerenone also reduced major adverse cardiovascular events by 14%; however, 5% of the participants were taking SGLT2 inhibitors at baseline.\textsuperscript{43} In another event-driven, randomized, controlled trial, finerenone was compared to placebo amongst people with T2D and CKD with background ACE inhibitor of ARB therapy.\textsuperscript{44} In this trial, known as the FIGARO trial, participants could have had stage 2 CKD at baseline. Finerenone reduced the same renal outcome from the FIDELIO trial by 24%. Additional outcomes showed a reduction in the incidence of new-onset heart failure; however, there was no difference between finerenone and placebo for a reduction in hospitalization for heart failure and CV death.\textsuperscript{44} These trials were pooled for further analysis to determine the cardiorenal benefit of finerenone. Amongst over 13,000 participants with T2D and CKD, finerenone 10 or 20 mg can reduce time to kidney failure, sustained reduction in eGFR of 57%, or renal death by 23%, whilst providing CV benefit in terms of major events and hospitalization for heart failure.\textsuperscript{45} Similar to SGLT2 inhibitors, there remain questions on the clinical application of

### Table 3. Comparison of SGLT2 inhibitors. Adapted from ref.\textsuperscript{35–38}

<table>
<thead>
<tr>
<th>Name</th>
<th>Approval</th>
<th>CV indication</th>
<th>Renal indication</th>
<th>Renal adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>3/2013</td>
<td>Risk reduction of MACE in people with T2D and established CVD</td>
<td>Risk reduction of ESKD, doubling of Scr, CV death and HHF in people with T2D and nephropathy with albuminuria</td>
<td>eGFR (mL/min/1.73 m\textsuperscript{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) &lt;30: contraindicated</td>
</tr>
<tr>
<td>(Invokana\textsuperscript{®})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>1/2014</td>
<td>Risk reduction of HHF in people with T2D and established CVD or multiple CV risk factors</td>
<td>Risk reduction eGFR decline, ESKD, CV death and HHF for people with CKD</td>
<td>eGFR ≥25: 10 mg per day for HFrEF or CKD &lt;25: no initiation Dialysis: contraindicated</td>
</tr>
<tr>
<td>(Farxiga\textsuperscript{®})</td>
<td></td>
<td>Risk reduction of CV death and HHF for people with HFrEF</td>
<td>No</td>
<td>eGFR ≥25: 10 mg per day for HFrEF Dialysis: contraindicated</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>8/2014</td>
<td>Risk reduction of CV death for people with T2D and established CVD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>(Jardiance\textsuperscript{®})</td>
<td></td>
<td>Risk reduction in CV death and HHF for people with HFrEF</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>12/2017</td>
<td>No</td>
<td>No</td>
<td>eGFR ≥60: 5 mg per day, titrated to 15 mg per day for T2D</td>
</tr>
<tr>
<td>(Steglatro\textsuperscript{®})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Approval date and indications based upon review by the Food and Drug Administration. CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney 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; T2D, type 2 diabetes.
Table 4. General summary of finerenone. Adapted from ref.39

| Indication | Reduced risk of sustained eGFR decline, ESRD, CV death, non-fatal MI and HHF for those with CKD associated with T2D |
| Contraindications | Strong CYP3A4 inhibitors; adrenal insufficiency |
| Interaction | Weak to strong CYP3A4 inhibitors; grapefruit and grapefruit juice |
| Dosing | 10 or 20 mg PO QD (initial) |
| | 20 mg PO QD (target) |
| Dosing per eGFR | ≤60 mL/min/1.73 m² = 20 mg PO QD |
| | ≥25 to <50 mL/min/1.73 m² = 10 mg PO QD |
| | <25 mL/min/1.73 m² = do not use |

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, orally; QD, daily; T2D, type 2 diabetes.

Figure 1. Guidance on finerenone per potassium level. Adapted from ref.39

![Figure 1](https://example.com/figure1.png)

PO, orally; QD, daily (once daily).

finerenone in clinical practice. The benefit of an SGLT2 inhibitor with finerenone is unknown as 5% and 8% of participants from the FIDELIO and FIGARO trials, respectively, were taking SGLT2 inhibitors at baseline.43,44 In addition, finerenone has not been compared to an SGLT2 inhibitor and, therefore, its role as a possible first-line option remains undefined. Lastly, there was a lack of generalizability as the 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 to have recommendations for finerenone for people with T2D and CKD. Finerenone can be considered amongst those with intolerance or contraindication to SGLT2 inhibitors.25 This new medication has a clinical niche in practice for people with T2D and CKD; however, utilization will be determined over time and based on insurance coverage. Table 4 summarizes general drug-specific information regarding finerenone, whereas Figure 1 is an algorithm for managing hyperkalaemia with finerenone as it was the most common adverse event in clinical trials.

Future directions

Efpeglenatide is a once-weekly glucagon-like peptide 1 receptor agonist (GLP1 RA) being investigated as a potential option for glycaemic management.46 It has been evaluated as an effective and safe option in a randomized, controlled fashion amongst people with T2D and a history of CV disease or renal disease (eGFR 25–59.9 mL/min/1.73 m²). Efpeglenatide lowered major adverse cardiovascular events of a composite 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 amongst participants with established diabetes beyond 10 years, eGFR less than 71.5 mL/min/1.73 m², history of CV disease and no baseline use of an SGLT2 inhibitor. Whilst the medication was well tolerated and had a similar safety profile to other GLP1 RAs, efpeglenatide demonstrated CV and renal benefit as an exendin 4 analogue and benefit was seen independent of SGLT2 inhibitor use. However, the role of this investigational agent will be forthcoming, particularly as the AMPLITUDE-O trial did not meet power based on anticipated events and has a lack of generalizability to other diverse patient populations prone to CKD.\(^{46}\) The synergistic effect of a GLP1 RA and SGLT2 inhibitor needs exploring to determine if there is an additive 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 T2D and CKD if SGLT2 inhibitors are contraindicated or intolerable.\(^{94}\) In CV outcome trials, renal benefits have been reported with long-acting GLP1 RAs (e.g. liraglutide, semaglutide, dulaglutide).\(^{47–49}\) Liraglutide, semaglutide and dulaglutide have resulted in a 22%, 36% and 15% risk reduction, respectively, in secondary composite renal outcomes, which was driven by the improvement in macroalbuminuria.\(^{47–49}\) A meta-analysis indicated an 18% reduction in a composite renal outcome; however, this meta-analysis only included lixisenatide, liraglutide, semaglutide and exenatide extended release.\(^{40}\)

Additional evidence will be forthcoming with semaglutide injection, as it is being investigated versus placebo amongst people with T2D and CKD in the FLOW trial.\(^{91}\) The primary renal endpoint is a time-to-first-occurrence composite renal endpoint with anticipated completion in 2024. As summarized earlier, evidence is limited on the role of GLP1 RA in the management of CKD for people with T2D; however, the FLOW trial will provide more insight into renal benefit for those with CKD or at risk of progression to CKD.\(^{51}\)

Overall, the class of GLP1 RA has been considered an alternative option for people with T2D and kidney disease; Table 5 summarizes relevant information for CKD of liraglutide, semaglutide and dulaglutide.\(^{52–54}\)

**Conclusion**

For the management of CKD amongst people with diabetes, it is important to achieve disease state goals through glycaemic and blood pressure management. Lifestyle modifications should be encouraged amongst this patient population. In addition, specific pharmacological agents should be utilized, such as angiotensin antagonists and SGLT2 inhibitors, to improve and prevent renal outcomes, including albuminuria. The role and clinical utilization of newly approved agents, such as finerenone, has yet to be determined within clinical practice. With additional evidence and pharmacotherapy, it is important to apply evidence-based findings with appropriate monitoring to prevent clinical and therapeutic inertia amongst a population at risk of cardiorenal events. Additionally, further research should be conducted to determine the role of existing and new agents for individuals with higher eGFR in the presence of albuminuria and within a certain ethnic group. In addition, active comparator trials are needed, including ACE inhibitors and ARBs, to determine the benefit of first-line agents. With a robust amount of evidence, clinical practice guidelines have been modified and updated to reflect high-level recommendations.

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**Table 5. Comparison of selected GLP1 RA. Adapted from ref.\(^{52–54}\)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Approval</th>
<th>CV indication</th>
<th>Renal indication</th>
<th>Renal adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide (Trulicity(^{®}))</td>
<td>9/2014</td>
<td>Risk reduction of MACE for people with T2D and established CVD or multiple CV risk factors</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Liraglutide (Victoza(^{®}))</td>
<td>1/2010</td>
<td>Risk reduction of MACE in people with T2D and established CVD</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Semaglutide (Ozempic(^{®}))</td>
<td>12/2017</td>
<td>Risk reduction of MACE in people with T2D and established CVD</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

Approval date and indications based upon review by the FDA.

CV, cardiovascular; CVD, cardiovascular disease; GLP1 RA, glucagon-like peptide 1 receptor agonist; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.
Key practice points

- Standardization of renal outcomes is needed.
- Renin–angiotensin system blockers remain standard of care and are background therapy for new and existing pharmacotherapy amongst people with chronic kidney disease with or without type 2 diabetes.
- Dapagliflozin has an expanded indication for persons with chronic kidney disease regardless of diabetes status.
- Finerenone is a new agent for the management of chronic kidney disease in people with type 2 diabetes.
- Treatment should be individualized based on drug-specific and person-specific factors to optimize clinical outcomes.

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References


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