BMJ Open Diabetes Research & Care

Management of type 2 diabetes in chronic kidney disease

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To cite: Triozzi JL, Parker Gregg L, Virani SS, *et al*. Management of type 2 diabetes in chronic kidney disease. *BMJ Open Diab Res Care* 2021;**9**:e002300. doi:10.1136/bmjdrc-2021-002300

Received 29 March 2021
Accepted 4 July 2021

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ABSTRACT

The management of patients with type 2 diabetes and chronic kidney disease (CKD) encompasses lifestyle modifications, glycemic control with individualized HbA1c targets, and cardiovascular disease risk reduction. Metformin and sodium-glucose cotransporter-2 inhibitors are first-line agents. Glucagon-like peptide-1 receptor agonists are second-line agents. The use of other antidiabetic agents should consider patient preferences, comorbidities, drug costs, and the risk of hypoglycemia. Renin–angiotensin–aldosterone system inhibitors are strongly recommended for patients with diabetes, hypertension, and albuminuria. Non-steroidal mineralocorticoid receptor antagonists, which pose less risk of hyperkalemia than steroidal agents, are undergoing further evaluation among patients with diabetic kidney disease. Here, we discuss important advancements in the management of patients with type 2 diabetes and CKD.

INTRODUCTION

Diabetic kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) globally.[1] DKD is characterized by albuminuria and reduced estimated glomerular filtration rate (eGFR), which are independent risk factors for end-stage kidney disease (ESKD), cardiovascular events, and death.[2 3] However, some patients with diabetes develop reduced eGFR with minimal or no albuminuria and retain the risks of microvascular and macrovascular complications.[4] Moreover, kidney biopsy data among patients with DKD indicate variability in histopathological findings and overlap with non-diabetic disease processes.[5] With advancements in diabetes care and therapeutics, the prevalence of kidney disease among patients with diabetes has stabilized around 35%,[6] and the incidence of acute cardiovascular events among patients with diabetes has decreased by over 50%.[7] Nevertheless, the absolute number of patients with diabetes is rising, with an anticipated global prevalence of 7.7% by 2030.[8] The impending burden of diabetes, in the context of the obesity epidemic, will likely affect younger patients with more time at risk to develop kidney disease and its complications.[9] In this review, we describe the management of type 2 diabetes in CKD, highlight important aspects of clinical practice guidelines, and discuss the evidence that supports modern practice.[10 11]

MANAGEMENT OF TYPE 2 DIABETES IN CKD

Overview

Glycemic control delays the development of albuminuria and improves clinical outcomes in those with diabetes and kidney disease.[12] DKD care requires a multifaceted approach, encompassing lifestyle modifications, glycemic control, cardiovascular risk mitigation, and blood pressure regulation with a renin–angiotensin–aldosterone system (RAAS) inhibitor. ACE inhibitors (ACEi) and angiotensin II receptor blockers reduce kidney disease progression and incident ESKD and are recommended in clinical practice guidelines. Metformin is recommended alongside sodium–glucose cotransporter-2 inhibitor (SGLT2i) as first-line DKD agents. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are second-line agents that may decrease albuminuria and cardiovascular risk in some patients. Evolving data regarding SGLT2i, GLP-1 RA, and their combinations will likely impact standards of DKD care. Mineralocorticoid receptor antagonists (MRAs) have potential benefits in DKD, but the use of steroidal agents is limited by the risk of hyperkalemia among patients with reduced kidney function. Emerging safety and efficacy data for non-steroidal MRAs may support their adjunctive use in certain populations.

Lifestyle modifications

Lifestyle modifications encompassing dietary changes, increased physical activity, and smoking cessation have potential cardiovascular benefits and are recommended for all adults with diabetes and CKD (table 1). Studies examining the benefits of intentional weight loss in CKD are limited. However, weight loss

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Table 1 Clinical practice guidelines from KDIGO and ADA

	KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease	ADA Standards of Medical Care in Diabetes—2021
HbA1c target	<6.5% to <8.0%	<7% for many non-pregnant adults, less stringent HbA1c goals (eg, <8%) for patients with limited life expectancy, or where harms outweigh benefits
Blood pressure	Not included	<130/80 mm Hg (existing ASCVD or 10-year ASCVD risk≥15%), <140/90 mm Hg (10-year ASCVD risk<15%)
Sodium restriction	<2 g/day	<2300 mg/day, as part of a DASH-style eating pattern for patients with blood pressure of >120/80 mm Hg
Protein intake	0.8 g/kg body weight/day for non-dialysis-dependent patients	0.8 g/kg body weight/day for non-dialysis-dependent patients; consider higher levels of dietary protein intakes for dialysis-dependent patients
Physical activity	Moderate-intensity physical activity for >150 min/week or to a level compatible with their cardiovascular and physical tolerance	≥150 min of moderate-intensity to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity
Weight loss	Not included	≥5% weight loss for most patients with type 2 diabetes who are overweight or obese and are ready to achieve weight loss
Tobacco	Cessation of tobacco products	Cessation of tobacco products
ACE inhibitor/ARB	ACE inhibitor or ARB for patients with diabetes, hypertension, and albuminuria, titrated to the highest approved dose that is tolerated	ACE inhibitor or ARB recommended for patients with diabetes and hypertension, modestly elevated UACR (30–299 mg/g creatinine), and strongly recommended for those with UACR of ≥300 mg/g and/or eGFR of <60 mL/min/1.73 m^2
Metformin	Metformin for patients with DKD and eGFR of >30 mL/min/1.73 m^2	Metformin is the preferred initial pharmacological agent for the treatment of type 2 diabetes; metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin.
SGLT2i	SGLT2i for patients with DKD and eGFR of 30 mL/min/1.73 m^2	SGLT2i for patients with DKD with eGFR of ≥30 mL/min/1.73 m^2 and UACR of >300 mg/g; SGLT2i additionally for cardiovascular risk reduction with eGFR of ≥30 mL/min/1.73 m^2 or UACR of >300 mg/g
GLP-1 RA	GLP-1 RA for patients with DKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i or who are unable to use those medications	GLP-1 RA for patients with CKD who are at increased risk of cardiovascular events to reduce renal endpoints, primarily albuminuria, progression of albuminuria, and cardiovascular events
MRA	Not included	Not included

ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DASH, Dietary Approaches to Stop Hypertension; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

through caloric restriction and exercise modifies cardiovascular risk factors and improves glycemic control in those with diabetes and hence likely benefits those with DKD. Restricting sodium intake to <2 g/day may decrease albuminuria and maximize the effects of RAAS inhibition. Sodium-sensitive hypertension is common in DKD, and thus sodium restriction may also mediate blood pressure and reduce cardiovascular events.[13] Experimental studies and clinical trials previously suggested that protein restriction reduces glomerular hyperfiltration and delays the progression of non-diabetic CKD, but there is a paucity of data in those with DKD.[14] Advanced DKD is a catabolic state associated with low muscle mass, cachexia, and malnutrition, and thus very low-protein diets are potentially harmful. Protein intake of 0.8 g/kg body weight/day is recommended for non-dialysis-dependent patients, and protein intake of >1.0–1.2 g/kg body weight/day is recommended for the hemodialysis and peritoneal dialysis population.[10 11]

Glycemic control

Assessment of glycemic control

Glycated hemoglobin (HbA1c) is the preferred laboratory measure of glycemia in DKD, with certain limitations. Changes in red blood cell turnover in advanced DKD may decrease the validity of HbA1c.[15] HbA1c reflects average blood glucose over 90 days and cannot adequately capture glycemic variability, which is associated with vascular complications, oxidative stress, and hypoglycemia.[16] In these situations, continuous blood glucose monitoring using retrospective, real-time, or intermittent techniques provides a more accurate assessment of glycemic control. Other biomarkers, such as glycated albumin and fructosamine, have not demonstrated clear or consistent

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advantages over HbA1c in CKD. Both albumin-based assessments and fructosamine may be affected by hypoalbuminemia, a common finding among patients with advanced kidney disease.[17] For most patients with DKD, HbA1c monitoring every 3–6 months is adequate to guide therapy.

Glycemic target

Individualized HbA1c targets balance the benefits (eg, reducing microvascular complications) and risks (eg, hypoglycemia) of glycemic control in those with CKD. Glycemic control decreases the incidence of kidney disease and other microvascular complications among patients with diabetes.[18] This benefit is supported by clinical trial data using albuminuria and eGFR as outcome measures of DKD. The Diabetes Control and Complications Trial and the corresponding observational follow-up study, Epidemiology of Diabetes Interventions and Complications, enrolled patients with type 1 diabetes and reported a significant and durable reduction in microalbuminuria and albuminuria in the intensive glycemic control group, along with a reduction in the development of stage 3 CKD.[19] The United Kingdom Prospective Diabetes Study (UKPDS) enrolled patients with type 2 diabetes and demonstrated a 33% risk reduction of incident microalbuminuria in the intensive glycemic control group.[20] Other studies show that intensive glycemic control is associated with a lower risk of incident ESKD. Post-trial analysis by the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation study group reported a 65% reduction of ESKD in the intensive glycemic control group.[21] A post hoc analysis of the Steno-2 study suggested that intensive glycemic control, as part of a multifactorial behavioral and pharmacological intervention, slows eGFR decline and reduces ESKD and death.[22] However, aggressive glycemic control is associated with increased mortality in CKD. In a secondary analysis of the Action to Control Cardiovascular Risk in Diabetes trial, intensive blood glucose control in patients with CKD increased mortality.[23] Hypoglycemia is the most important limiting factor for intensive glycemic control, as insulin clearance and gluconeogenesis are impaired in patients with reduced kidney function. Intensive glycemic control poses greater risks for patients receiving medications that cause hypoglycemia, such as insulin or insulin secretagogues. Other factors that support a less aggressive approach to glycemic control in CKD include shorter life expectancy, pre-existing macrovascular complications, greater comorbid conditions, hypoglycemic unawareness, and limited resources for self-care.

Clinical practice guidelines emphasize individualized HbA1c targets (table 1). The Kidney Disease: Improving Global Outcomes Diabetes Work Group recommends a target HbA1c range from <6.5% to <8% in non-dialysis-dependent DKD. The American Diabetes Association does not make a specific HbA1c recommendation for patients with kidney disease but recommends a target of <7% for most patients and <8% for patients with a limited life expectancy or high risk of complications. For example, an intensive HbA1c target would benefit a younger patient with early-stage CKD and no cardiovascular complications. Whereas an intensive HbA1c target would pose greater risk than benefit for an elderly patient with advanced-stage CKD, cardiovascular complications, and risk of hypoglycemia.

Pharmacological agents

Metformin

Metformin is a first-line antidiabetic agent that can be safely administered in most patients with baseline eGFR of >30 mL/min/1.73 m^2. Metformin is a biguanide medication with multiple mechanisms of action, including insulin sensitization in peripheral tissues and the reduction of hepatic gluconeogenesis. In the UKPDS study, patients treated with metformin demonstrated decreased diabetes-related, cardiovascular-related, and all-cause mortality when compared with insulin and sulfonylureas.[24] Metformin is associated with a reduction in ESKD and adverse cardiovascular outcomes among patients with DKD when compared with other antihyperglycemic agents.[25] Kwon *et al* reported lower all-cause mortality and ESKD progression in patients with eGFR OF >30 mL/min/1.73 m^2 prescribed metformin, with no increased incidence in all-cause lactic acidosis events.[26] In separate studies, metformin was associated with decreased risk of cardiovascular events and heart failure readmissions among patients with DKD.[27 28]

Metformin is often underprescribed or prematurely discontinued among patients with reduced eGFR due to a perceived risk of lactic acidosis. Early biguanide medications were recalled due to life-threatening risks of lactic acidosis, but clinically significant lactic acidosis due to metformin is rare and often attributable to other acute illnesses (table 2). In a large retrospective cohort using national-level data, Lazarus *et al* reported no difference between hospitalization for lactic acidosis among patients with reduced kidney function taking metformin versus sulfonylureas.[29] An analogous study using data from the Veteran's Health Administration found no difference in lactic acidosis hospitalizations between metformin and sulfonylurea users who developed reduced kidney function.[30] In a cohort study using national-level data from Sweden, metformin demonstrated less risk of a composite endpoint of acidosis, serious infection, and all-cause mortality compared with insulin and other oral antihyperglycemic agents in the subgroup of patients with eGFR of 45–60 mL/min/1.73 m^2.[31] It is recommended to continue metformin in those with eGFR of ≥45 mL/min/1.73 m^2, titrate cautiously or halve the dose with eGFR of 30–44 mL/min/1.73 m^2, and to discontinue with eGFR of <30 mL/min/1.73 m^2 and the dialysis population. Holding metformin during acute illness or acute kidney injury is reasonable.

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Table 2 Selected observational studies reporting the risk of acidosis among metformin users with reduced kidney function

Author	Year of publication	Country	N	Age	HR (95% CI) of acidosis outcome	Key findings
Ekström *et al*[31]	2012	Swedish National Diabetes Register (Sweden)	51 675	Mean 65.3 years	0.85 (0.74 to 0.97) (eGFR 45–60 mL/min/1.73 m^2); 0.98 (0.79 to 1.21) (eGFR 30–45 mL/min/1.73 m^2)	Compared with other oral antihyperglycemic agents and insulin, metformin use was associated with reduced risk of acidosis and serious infection and all-cause mortality in patients with eGFR of 45–60 mL/min/1.73 m^2. Metformin use was not associated with increased risk of acidosis and serious infection and all-cause mortality in patients with eGFR of 30–45 mL/min/1.73 m^2.
Lazarus *et al*[29]	2018	Geisinger Health System (USA)	75 413	Mean 60.4 years	1.16 (0.95 to 1.41)(eGFR 45–59 mL/min/1.73 m^2); 1.09 (0.83 to 1.44) (eGFR 30–44 mL/min/1.73 m^2); 2.07 (1.33 to 3.22) (eGFR <30 mL/min/1.73 m^2)	Metformin use was not associated with incident acidosis among patients with eGFR of >30 mL/min/1.73 m^2. Metformin use was associated with increased incident acidosis among patients with eGFR of <30 mL/min/1.73 m^2.
Chu *et al*[30]	2020	National Veterans Health Administration, Medicare, Medicaid, National Death Index (USA)	49 204	Median 70 years	1.21 (0.99 to 1.50) (eGFR <60 mL/min/1.73 m^2)	Among patients who developed reduced kidney function, the rate of lactic acidosis hospitalization was not statistically different between metformin users and sulfonylurea users.

eGFR, estimated glomerular filtration rate.

Sodium–glucose cotransporter-2 inhibitor

SGLT2i blocks the reabsorption of glucose and sodium in the proximal convoluted tubule, producing natriuresis and glucosuria. There is substantial evidence to support a reduced risk of ESKD, cardiovascular death, and hospitalization for heart failure. The cardiovascular and kidney benefits of SGLT2i are independent of the antihyperglycemic effect, which attenuates with lower eGFR. SGLT2i may improve glomerular hemodynamics, reduce oxidative stress, and optimize tissue energetics.[32]

SGLT2i efficacy for kidney and cardiovascular outcomes

Large cardiovascular safety trials of SGLT2i demonstrated favorable secondary kidney outcomes among patients with type 2 diabetes and variable baseline kidney function (table 3). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) enrolled patients with eGFR of ≥30 mL/min/1.73 m^2 and demonstrated a 46% risk reduction of the composite secondary kidney outcome of doubling of serum creatinine, initiation of kidney replacement therapy, or renal death.[33] In a post hoc analysis of EMPA-REG OUTCOME, empagliflozin demonstrated improved kidney function regardless of the baseline eGFR or degree of albuminuria.[34] Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) enrolled patients with eGFR of ≥30 mL/min/1.73 m^2 and reported a 40% reduction in the composite secondary kidney outcome.[35] Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) enrolled patients with eGFR of ≥60 mL/min/1.73 m^2 and reported a 47% risk reduction in the composite secondary kidney outcome.[36] However, in the Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes (VERTIS CV) study, the reduction in the secondary composite kidney outcome was not statistically significant. EMPA-REG OUTCOME and CANVAS both demonstrated a significant reduction in the primary cardiovascular safety outcome, and DECLARE-TIMI 58 and VERTIS CV reached cardiovascular non-inferiority. These data argued for dedicated SGLT2i trials in the DKD population.

The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial was a seminal study of SGLT2i in DKD with a dedicated primary composite kidney outcome.[37] CREDENCE enrolled patients with type 2 diabetes, eGFR of 30–90 mL/min/1.73 m^2, and a urine albumin-to-creatinine ratio of 300–5000 mg/g. The prespecified enrollment strategy aimed to include at least 60% of patients with eGFR of <60 mL/min/1.73 m^2, a population at higher risk of ESKD than previously studied. In this double-blind, placebo-controlled trial, canagliflozin reduced the primary composite kidney endpoint by 31%, with a noteworthy benefit in a secondary heart failure outcome. The trial was prematurely discontinued after 2.6 years due to overwhelming efficacy. CREDENCE demonstrated kidney benefits independent of baseline HbA1c, extent of HbA1c reduction, and stage of CKD, leading to the first kidney-related indication for SGLT2i by the US FDA in 2019.

There is evolving information about the use of SGLT2i among patients with eGFR of <30 mL/min/1.73 m^2 and non-DKD. Dapagliflozin in Patients with Chronic Kidney Disease included 4304 participants, two-thirds with diabetes, with eGFR of 25–75 mL/min/1.73 m^2. Dapagliflozin reduced the composite risk of ≥50% eGFR decline, ESKD, and renal or cardiovascular death by

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Table 3 Selected clinical trials of SGLT2i and SGLT1/2i, empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin

SGLT2i or SGLT1/2i	Trial	Intervention	N	Mean baseline eGFR (mL/min/1.73 m^2)	Median follow-up (years)	Primary composite outcome (HR (95% CI))	Kidney outcome (HR (95% CI))
Empagliflozin	EMPA-REG OUTCOME	Empagliflozin 10 mg once per day, empagliflozin 25 mg once per day, or placebo	7020	74	3.1	Death from cardiovascular causes, non-fatal myocardial infarction (excluding silent myocardial infarction), or non-fatal stroke (0.86 (0.74 to 0.99))	Doubling of serum creatinine with eGFR of ≤45 mL/min/1.73 m^2, renal replacement therapy, or renal death (0.54 (0.40 to 0.75))
Canagliflozin	CANVAS	Canagliflozin 100 mg once per day, with an optional increase to 300 mg once per day, or placebo	10 142	76.5	2.4	Death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (0.86 (0.75 to 0.97))	≥40% reduction in eGFR, renal replacement therapy (transplant, chronic dialysis, or sustained eGFR<15 mL/min/1.73 m^2), or renal death (0.53 (0.33 to 0.84))
	CREDENCE	Canagliflozin 100 mg once per day or placebo	4401	56.2	2.62	ESKD (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes (0.70 (0.59 to 0.82))	See primary composite outcome.
Dapagliflozin	DECLARE-TIMI 58	Dapagliflozin 10 mg once per day or placebo	17 160	85.1	4.2	Cardiovascular death, myocardial infarction, or ischemic stroke (0.93 (0.84 to 1.03))	≥40% reduction in eGFR to <60 mL/min/1.73 m^2, ESKD (dialysis≥90 days, transplant or sustained eGFR 15 mL/min/1.73 m^2), or renal or cardiovascular death (0.53 (0.43 to 0.66))
	DAPA-CKD	Dapagliflozin 10 mg once per day or placebo	4304	43.1	2.4	Sustained decline in the eGFR of at least 50%, ESKD, or death from renal or cardiovascular causes (0.61 (0.51 to 0.72))	See primary composite outcome.
Ertugliflozin	VERTIS CV	Ertugliflozin 5 mg once per day, ertugliflozin 15 mg once per day, or placebo	8246	76.1	3.0	Death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (0.97 (0.85 to 1.11))	Death from renal causes, renal replacement therapy, or doubling of the serum creatinine level (0.81 (0.63 to 1.04))
Sotagliflozin	SCORED	Sotagliflozin 200 mg once per day, with an optional increase to 400 mg once per day, or placebo	10 584	44.4	1.3	Total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure (0.74 (0.63 to 0.88))	Sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 mL/min/1.73 m^2 for ≥30 days (0.71 (0.46 to 1.08))

CANVAS, Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes; CREDENCE, Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy; DAPA-CKD, Dapagliflozin in Patients with Chronic Kidney Disease; DECLARE-TIMI 58, Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; ESKD, end-stage kidney disease; SCORED, Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease; SGLT2i, sodium–glucose cotransporter-2 inhibitors; SGLT1/2i, combined sodium–glucose cotransporter-1 and -2 inhibitors; VERTIS CV, Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes.

39%. In subgroup analyses, the benefit of dapagliflozin was consistent regardless of HbA1c, eGFR, or presence of diabetes. The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) is an ongoing study that will report the effect of empagliflozin on kidney progression or cardiovascular (CV) death.[38] EMPA-KIDNEY will deliver important information among patients with or without diabetes, with or without albuminuria, and eGFR as low as 20 mL/min/1.73 m^2.

Dual SGLT1 and SGLT2 inhibition

Sotagliflozin is a dual SGLT1 and SGLT2 inhibitor with antihyperglycemic efficacy in both type 1 and type 2 diabetes.[39] The SGLT1 cotransporter is also present in the gastrointestinal lumen, where it delays glucose absorption and reduces postprandial blood glucose levels.[40] In the Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease (SCORED) trial, sotagliflozin decreased a composite outcome of cardiovascular death, hospitalization for heart failure, and urgent heart failure among patients with DKD with or without albuminuria.[41] Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure (SOLOIST-WHF) enrolled patients with diabetes during acute heart failure hospitalization and demonstrated improved heart failure outcomes among a

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population with mean eGFR 50 mL/min/1.73 m^2.[42] Both SCORED and SOLOIST-WHF reported several adverse events and prominent gastrointestinal upset with sotagliflozin, which may hinder its widespread use.

SGLT2i safety

SGLT2i safety data are extrapolated from trials that were not powered to detect individual adverse events. In a large meta-analysis, SGLT2i was associated with increased genital mycotic infections but not bacterial urinary tract infections.[43] Genital mycotic infections are more common in women and manageable with antifungal therapy. Studies suggesting risks of Fournier's gangrene are limited by low event rates.[44] SGLT2i decreases available carbohydrate and drives metabolism towards more efficient ketone-based energy sources, leading to weight loss, decreased tissue adiposity, and increased serum concentrations of β-hydroxybutyrate.[45] Diabetic ketoacidosis, including euglycemic ketoacidosis, is more likely to develop among patients with certain risk factors, such as insulin dependence or acute stress states.[46] A cohort study in the USA identified a twofold increase in ketoacidosis among new users of SGLT2i compared with dipeptidyl peptidase-4 inhibitors (DPP4i).[47] Amputation, fracture, and acute kidney injury have also been reported. A risk of leg and foot amputation reported in CANVAS (amputation event rate of 6.3 per 1000 patient-years, p<0.001) was ultimately not observed in CREDENCE.[35 37] The US FDA subsequently recalled a black box amputation warning for canagliflozin. Similarly, a risk of fracture reported in CANVAS (15.4 fracture events per 1000 patient-years, p<0.001) was not observed in other SGLT2i trials.[33 35 36] Finally, pooled analyses suggest SGLT2i is indeed associated with decreased risk of acute kidney injury.[48] Volume depletion was proposed as a mechanism for amputation, fracture, and acute kidney injury, although the relative increase in urinary volume related to SGLT2i is transient.[49]

Clinical practice guidelines now recommend SGLT2i for patients with type 2 diabetes with DKD and eGFR of ≥30 mL/min/1.73 m^2. It is reasonable to temporarily hold SGLT2i when predisposed to volume depletion or ketoacidosis, such as surgery, fasting states, or acute illnesses. History of urinary tract infection is not a contraindication to SGLT2i. In the absence of clear risk factors, the potential cardiovascular and kidney benefits justify SGLT2i therapy for most patients with DKD.

Glucagon-like peptide-1 receptor agonist

Incretin-based therapies stimulate postprandial neuroendocrine pathways to increase pancreatic insulin secretion, suppress glucagon release, increase satiety, and delay gastric emptying. In addition to an antihyperglycemic effect, incretin-based therapies improve risk factors for cardiovascular and kidney disease by improving blood pressure, body weight, and lipid profile. Other anti-inflammatory properties are proposed.[50] Whereas DPP4i transiently reduces the breakdown of physiological incretin hormones, GLP-1 RA with prolonged half-lives resists degradation by DPP4 and stimulate incretin receptors at supraphysiological levels. As a possible consequence, GLP-1 RA has a greater effect in DKD.

Evidence for GLP-1 RA in DKD

We lack dedicated DKD clinical trials of GLP-1 RA with predefined primary kidney endpoints. Nonetheless, some GLP-1 RA have demonstrated improved secondary microvascular outcomes in cardiovascular safety trials, driven by a reduction of albuminuria (table 4). Of the available GLP-1 RA, liraglutide, semaglutide, and dulaglutide have demonstrated both cardiovascular benefits and antialbuminuric effects. Exenatide and lixisenatide have demonstrated cardiovascular safety without a cardiovascular benefit. All therapies are administered as subcutaneous injection except for an oral formulation of semaglutide, which has demonstrated cardiovascular safety without a cardiovascular benefit.

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) was a placebo-controlled cardiovascular safety trial of liraglutide and included a secondary composite microvascular outcome. The reduction in the microvascular outcome, solely driven by reduced incidence of albuminuria, was independent of baseline HbA1c.[51] Similarly, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) demonstrated both cardiovascular safety and a decreased secondary microvascular outcome driven by reduced incidence of microalbuminuria. SUSTAIN-6 had a surprising increase in retinopathy events not previously reported in incretin trials.[52] An oral formulation of semaglutide was subsequently studied in the Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (PIONEER-6) trial. Oral semaglutide demonstrated cardiovascular safety without cardiovascular superiority, with no significant difference eGFR change from baseline.[53] In LEADER, greater cardiovascular benefit was seen among patients with eGFR <60 mL/min/1.73 m^2. In SUSTAIN-6 and PIONEER, however, there was no difference in cardiovascular safety stratified by stage of CKD.

Other than an apparent antialbuminuric effect, there is limited evidence that GLP-1 RA influences eGFR decline or other clinically meaningful kidney outcomes. In a prespecified kidney analysis of LEADER, there was a statistically less eGFR decline among patients receiving liraglutide versus placebo, only present in the eGFR of 30–60 mL/min/1.73 m^2 subgroup.[51] In the Dulaglutide versus Insulin Glargine in Patients with Type 2 Diabetes and Moderate-to-Severe CKD (AWARD-7) study, dulaglutide demonstrated significantly less eGFR decline (−1.1 mL/min/1.73 m^2) than daily titrated insulin glargine (−2.9 mL/min/1.73 m^2) after a 52-week follow-up period.[54] Although dulaglutide was associated with reduced albuminuria in the placebo-controlled Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes trial, there were no differences in albuminuria

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Table 4 Selected clinical trials of GLP-1 RA, liraglutide, semaglutide, and dulaglutide

GLP-1 RA	Trial	Intervention	N	Mean baseline eGFR (mL/min/1.73 m^2)	Median follow-up (years)	Primary composite outcome (HR (95% CI))	Kidney outcome (HR (95% CI))
Liraglutide	LEADER	Liraglutide 1.8 mg subcutaneous once per day or placebo	9340	80.4	3.8	Death from cardiovascular causes, non-fatal (including silent) myocardial infarction, or non-fatal stroke (0.87 (0.78 to 0.97))	New-onset albuminuria, doubling of serum creatinine and eGFR of <45 mL/min/1.73 m^2, need for continuous renal replacement therapy, or death due to renal disease (0.78 (0.67 to 0.92))
Semaglutide	SUSTAIN-6	Semaglutide 0.5 mg subcutaneous once weekly, semaglutide 1.0 mg subcutaneous once weekly, or placebo	3297	Not reported. 28% eGFR of <60 mL/min/1.73 m^2	2.1	Death from cardiovascular causes, non-fatal myocardial infarction (including silent), or non-fatal stroke (0.74 (0.58 to 0.95))	New or worsening nephropathy (0.64 (0.46 to 0.88))
	PIONEER-6	Semaglutide 14 mg oral once per day or placebo	3183	74	1.3	Death from cardiovascular causes (including undetermined causes of death), non-fatal myocardial infarction, or non-fatal stroke (0.79 (0.57 to 1.11))	None. There was no significant difference in the change in eGFR from baseline or in the rate of renal death.
Dulaglutide	REWIND	Dulaglutide 1.5 mg subcutaneous once a week or placebo	9901	77	5.4	Non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes) (0.88 (0.79 to 0.99))	UACR of >33.9 mg/mmol in those with a lower baseline concentration, sustained 30% or greater decline in eGFR based on two consecutive eGFR concentrations, or chronic renal replacement therapy (0.85 (0.77 to 0.93))
	AWARD-7	Dulaglutide 1.5 mg subcutaneous once weekly, dulaglutide 0.75 mg subcutaneous once weekly, or insulin glargine titrated daily	577	38.3	Total 52 weeks	At 26 weeks, change in HbA1c with dulaglutide 0.75 mg (LSM difference −1.1% (SE 0.1) and dulaglutide 1.5 mg (−1.2% (0.1)) was not statistically different from insulin glargine (−1.1% (0.1)).	At 52 weeks, eGFR with dulaglutide of 0.75 mg (mean 33.8 mL/min/1.73 m^2 (SE 0.7), p=0.009) and dulaglutide of 1.5 mg (34.0 mL/min/1.73 m^2 (0.7), p=0.005) were statistically different from insulin glargine (31.3 mL/min/1.73 m^2 (0.7)); UACR reduction with dulaglutide of 0.75 mg and dulaglutide 1.5 mg were not significantly different from insulin glargine.

AWARD-7, Dulaglutide vs Insulin Glargine in Patients with Type 2 Diabetes and Moderate-to-Severe CKD; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; LEADER, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes; LSM, least squares mean; PIONEER-6, Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes; REWIND, Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes; SUSTAIN-6, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes; UACR, urine albumin-to-creatinine ratio.

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in comparison with insulin glargine in the AWARD-7 trial.[55] A dedicated kidney outcomes trial for GLP-1 RA will clarify their use in DKD. A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW) is a placebo-controlled, phase III trial of semaglutide with a primary kidney outcome set to complete in 2024 (NCT03819153). FLOW is enrolling adults with DKD and will report the effect of semaglutide on the primary renal composite outcome of eGFR decline, kidney failure, or death from kidney or cardiovascular disease.

Combination of SGLT2i and GLP-1 RA

SGLT2i and GLP-1 RA have distinct clinical effects. In a systematic review and trial-level meta-analysis, GLP-1 RA and SGLT2i reduced cardiovascular events to a similar degree among patients with established atherosclerotic cardiovascular disease, but SGLT2i had a greater impact on preventing heart failure hospitalizations and DKD progression.[56] Further supported by dedicated heart failure studies, SGLT2i is now incorporated into guideline-directed strategies for congestive heart failure.[57] GLP-1 RA has not demonstrated benefit in heart failure. GLP-1 RA have a class interaction with the sympathetic nervous system, reflected by increased heart rate, with some signal towards harm in heart failure.[58] Combination of SGLT2i and incretin-based therapies may be synergistic, as both drug classes mitigate cardiovascular risk factors through improvements in weight, lipid profile, and blood pressure. Dapagliflozin and exenatide, studied alone and in combination, demonstrated improved glycemic control and cardiovascular risk in combination. The benefits of combined dapagliflozin and exenatide persisted through the 2-year follow-up, although no long-term kidney outcomes were reported.[59]

Clinical practice guidelines recommend GLP-1 RA in DKD based on potential cardiovascular risk reduction and antialbuminuric effects of certain agents. GLP-1 RA compounds with long-half-lives will require less frequent dosing and may have better compliance. Dulaglutide, exenatide, and semaglutide have extended-release formulations. Dulaglutide, liraglutide, lixisenatide, and semaglutide are not eliminated by the kidneys. The oral formulation of semaglutide is available for patients with an aversion to needles. Dedicated safety studies of GLP-1 RA have not been performed among patients with reduced kidney function. Slow titration to the maximally indicated dose is recommended to lower the risk of hypoglycemia and to mitigate gastrointestinal upset, the most reported side effect.

Other antidiabetic agents

We have discussed the roles of metformin, SGLT2i, and GLP-1 RA in detail. There are limited head-to-head efficacy data for other antidiabetic agents among patients with DKD.[60] Selection of other antidiabetic agents should consider patient preferences, comorbidities, drug costs, and the risk of hypoglycemia. Any antidiabetic agent with a prolonged duration of action, active metabolites, and elimination by the kidneys poses greater risk of hypoglycemia among patients with reduced kidney function. Sulfonylureas stimulate endogenous insulin secretion and are predominately eliminated by the kidneys. The sulfonylureas glipizide, glicazide, and glimepiride can be prescribed in eGFR <60 mL/min/1.73m^2, but glyburide has active metabolites and should be avoided. Glinides exert similar effects as sulfonylureas but have a shorter onset and duration of action. Repaglinide is metabolized by both the liver and kidneys and can be prescribed in eGFR of <60 mL/min/1.73m^2, but nateglinide has active metabolites and should be avoided. Both sulfonylureas and glinides should be avoided in eGFR of <15 mL/min/1.73 m^2 and the dialysis population. Disaccharidase inhibitors, such as acarbose and miglitol, delay carbohydrate digestion in the gut. Although disaccharidase inhibitors pose less risk of hypoglycemia, they are generally not recommended in advanced CKD due to limited safety data. Thiazolidinediones increase insulin sensitivity in peripheral tissues, have less risk of hypoglycemia, and do not require dose adjustments for patients with reduced kidney function and the dialysis population. Thiazolidinediones may cause weight gain and fluid retention. Insulin may be required for patients with progressive insulin resistance and pancreatic dysfunction. Insulin is eliminated by the kidneys and has potent glucose lowering effects. Patient education, routine monitoring, and dose reductions based on the degree of kidney disease are important to reduce the risk of hypoglycemia.

RAAS blockade

RAAS inhibitors

RAAS blockade delays DKD progression in patients with albuminuria and hypertension.[61] RAAS activation, mediated by the bioactive end products angiotensin II and aldosterone, causes increased sodium avidity and vascular tone, glomerular injury, and proteinuria. RAAS activation also contributes to systemic inflammation, the production of reactive oxygen species, and fibrosis in the kidney and cardiovascular systems. ACEi and angiotensin receptor blockers (ARBs) remain the mainstay RAAS inhibitors since their implementation at the turn of the century. Clinical practice guidelines recommend ACEi or ARB monotherapy titrated to the maximally titrated dose. Patients should be monitored for hyperkalemia or acute kidney injury (>30% elevation of serum creatinine) after initiating or increasing the dose of RAAS inhibitors.

Mineralocorticoid receptor agonists

MRAs may be an important component of RAAS blockade. MRAs reduce albuminuria and secondary markers of fibrosis and inflammation in the kidney. MRAs are also indicated for many common DKD comorbidities, including resistant hypertension and congestive heart failure. Despite these potential benefits, the use of MRAs in DKD is limited by the risk of hyperkalemia posed by

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steroidal MRAs like spironolactone and eplerenone. In a meta-analysis of 19 trials, the addition of steroidal MRAs to RAAS inhibitors resulted in a threefold risk of hyperkalemia.[62] Potassium binders, low potassium diets, or diuretics were often used to mitigate the hyperkalemia risk in these trials, although unsuccessfully. Adverse safety events precluded adequate follow-up periods to detect cardiovascular and kidney endpoints in these trials.

Finerenone

Finerenone is a non-steroidal, dihydropyridine-based MRA with high affinity for the mineralocorticoid receptor, posing less risk of hyperkalemia.[63] The Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) study assessed varied doses of finerenone versus placebo among patients with diabetes and eGFR of >30 mL/min/1.73 m^2. ARTS-DN resulted in a dose-dependent reduction in albuminuria at 90 days with no risk of hyperkalemia.[64] Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) demonstrated that those treated with finerenone had decreased CKD progression and cardiovascular events in DKD, with an 18% reduction of the primary composite outcome of kidney failure, sustained decrease of eGFR by at least 40%, or renal death.[65] This outcome was driven by the reduction in eGFR, with no difference in the rate of kidney failure. There were more hyperkalemia events in the finerenone group (15.8%) than placebo (7.8%), although the study was not powered to assess adverse events. FIGARO-DKD is an ongoing study of finerenone that will examine a primary cardiovascular outcome event with secondary kidney endpoints among a similar DKD population (NCT02545049).

CONCLUSION

There has been great progress in the management of patients with type 2 diabetes and CKD. DKD management is multifaceted and individualized. A more lenient HbA1c target is appropriate in older adults and patients with advanced DKD or increased risk of hypoglycemia. Metformin is an important first-line, cost-effective agent with significant data supporting efficacy and safety for patients with DKD. SGLT2i is a first-line agent based on substantial clinical trial data supporting a reduction in ESKD, cardiovascular death, and hospitalization for heart failure. GLP-1 RA is a second-line agent that may reduce albuminuria and cardiovascular disease risk. Other antidiabetic agents, such as sulfonylureas, glinides, disaccharidase inhibitors, thiazolidinediones, and insulin, may be used for glycemic control based on the stage of kidney disease, individual risks and benefits. ACEi or ARB monotherapy is strongly recommended for patients with diabetes, hypertension, and albuminuria. Mineralocorticoid receptor antagonism is an unmet need in DKD due to the risk of hyperkalemia with steroidal MRA agents. Non-steroidal MRAs like finerenone have better safety profiles and may prove beneficial for certain patients with DKD. Effective DKD therapies target the shared pathways of diabetes, cardiovascular disease, and kidney disease, and a comprehensive approach will improve global outcomes for patients with DKD.

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Contributors JLT and SDN planned the contents of the review. JLT and SDN drafted the review and tables. LPG and SSV critically reviewed and edited the manuscript, and all authors were involved in the revision of the manuscript.

Funding SDN is supported by research funding from the Department of Veterans Affairs Health Services Research & Development (1I01HX002917-01A1) and a grant from the National Institutes of Health (NIDDK-R01DK101500). SSV is supported by a grant from the Department of Veterans Affairs Health Services Research and Development (1I01HX002917-01A1), World Heart Federation, and Tahir and Jooma Family. This work was also supported in part by the Center for Innovations in Quality, Effectiveness and Safety (CIN 13-413), Michael E. DeBakey VA Medical Center, Houston, Texas. SDN, LPG, SSV are employees of the US Department of Veterans Affairs. The interpretation and reporting of these data are the responsibility of the authors and in no way should be viewed as official policy or interpretation of the Department of Veterans Affairs or the US government. Funding agencies did not have any role in study design, data collection, analysis, reporting, or the decision to submit for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Veterans Administration.

Competing interests SDN reports personal fees from Bayer, Boehringer-Ingelheim, REATA, Tricida, and Vifor, and grants from Keryx outside the submitted work. SSV has received honorarium from the American College of Cardiology in his role as the associate editor for Innovations, ACC.org. All remaining authors have nothing to disclose.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement No data are available. This is not a clinical trial.

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