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REVIEW ARTICLE

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Evidence-based treatment of hyperglycaemia with incretin therapies in patients with type 2 diabetes and advanced chronic kidney disease

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Abstract

Type 2 diabetes is the leading cause of chronic kidney disease (CKD). The prevalence of CKD is growing in parallel with the rising number of patients with type 2 diabetes globally. At present, the optimal approach to glycaemic control in patients with type 2 diabetes and advanced CKD (categories 4 and 5) remains uncertain, as these patients were largely excluded from clinical trials of glucose-lowering therapies. Nonetheless, clinical trial data are available for the use of incretin therapies, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, for patients with type 2 diabetes and advanced CKD. This review discusses the role of incretin therapies in the management of these patients. Because the presence of advanced CKD in patients with type 2 diabetes is associated with a markedly elevated risk of cardiovascular disease (CVD), treatment strategies must include the reduction of both CKD and CVD risks because death, particularly from cardiovascular causes, is more probable than progression to end-stage kidney disease. The management of hyperglycaemia is essential for good diabetes care even in advanced CKD. Current evidence supports an individualized approach to glycaemic management in patients with type 2 diabetes and advanced CKD, taking account of the needs of each patient, including the presence of co-morbidities and concomitant therapies. Although additional studies are needed to establish optimal strategies for glycaemic control in patients with type 2 diabetes and advanced CKD, treatment regimens with currently available pharmacotherapy can be individually tailored to meet the needs of this growing patient population.

KEYWORDS

cardiovascular disease, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, glycaemic control, hyperglycaemia

1 | INTRODUCTION

1.1 | What is the extent of the problem of chronic kidney disease in type 2 diabetes?

Diabetes is the leading cause of chronic kidney disease (CKD) worldwide, defined as a glomerular filtration rate (GFR) <60 mL/min/1.73m^2 or urine albumin-to-creatinine ratio (UACR) >30 mg/g for at least 3 months.[1] CKD secondary to either type 1 diabetes or type 2 diabetes (T2D), diabetic kidney disease (DKD), occurs in 30% to 40% of patients with diabetes.[2,3] For those patients with T2D, data from 2007–2012 show the overall age-adjusted CKD prevalence to be 38.3%.[4] With T2D and impaired kidney function, mortality rates approach nearly 20% per year, a rate comparable with many serious malignancies.[5] The major impact of CKD on clinical outcomes is further informed by the observation that most of the excess cardiovascular disease (CVD) and all-cause mortality risk in patients with diabetes occurs in those with either impaired kidney function or albuminuria.[6]

The occurrence of CKD, including end-stage kidney disease (ESKD), is expected to increase as the global prevalence of diabetes continues to rise, and hence effective patient-management strategies are of growing importance.[7,8] However, the optimal approach to glycaemic control in patients with T2D and advanced CKD remains uncertain, as most clinical trials of glucose-lowering therapies excluded those patients.[9] This review will consider the available evidence for diabetes management in this growing population of patients with T2D and advanced CKD, defined as categories 4 and 5. The Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) define category 4 CKD as eGFR 15–29 mL/min/1.73m^2, and category 5 (kidney failure) as eGFR <15 mL/min/1.73m^2.[10]

1.2 | What is the importance of glycaemic control in patients with advanced CKD and T2D?

The presence of CKD in patients with T2D is associated with a markedly elevated risk of CVD, and treatment strategies for patients with these two conditions must include the reduction of both CKD and cardiovascular disease (CVD) risks, as these patients are at a higher risk of all-cause and CVD death than ESKD.[2] Management of hyperglycaemia is foundational for good diabetes care. Intensive glycaemic control is associated with a reduced risk of DKD onset, and diabetic patients with established CKD may also benefit. A Canadian population-based cohort study found strong and independent associations between higher levels of HbA1c and adverse clinical outcomes, including mortality, CVD events, hospitalization and progression to ESKD, in patients with moderate-to-severe CKD (categories 3 and 4).[11] In observational studies, lower levels of glycaemia were also associated with reduced morbidity and mortality in diabetic patients with ESKD undergoing dialysis.[12,13] Similarly, a 6-year cohort study showed that poor glycaemic control was associated with increased all-cause and CVD mortality among patients with diabetes and ESKD treated by haemodialysis.[14] More recently, a large study of patients with advanced CKD transitioning to dialysis showed that poor glycaemic control was associated with increased mortality.[9]

The assessment of glycaemia is particularly challenging in patients with diabetes with advanced CKD, as HbA1c may not be an accurate reflection of glycaemic control because of factors such as anaemia, enhanced red blood cell turnover and malnutrition, which bias assays toward lower results, and protein modifications such as glycation and carbamylation, which bias assays toward higher results.[15] Moreover, alternative measures such as glycated albumin or fructosamine also do not correlate well with fasting plasma glucose levels in this population.[16] Self-monitoring of capillary blood glucose remains the mainstay of daily assessment of glycaemia, but glucose levels are checked intermittently and not always at times of problematic hyper- or hypoglycaemia. Continuous glucose monitoring (CGM) is recommended for patients treated with intensified insulin regimens consisting of more than three injections of insulin daily, but has not been widely adopted in patients on less intensive regimens. Guidelines from the American Diabetes Association[17] and the American Association of Clinical Endocrinologists[18] endorse the use of CGM for people at risk of hypoglycaemia, regardless of diabetes type. Thus, high-risk patients with T2D and CKD will probably benefit from CGM technology.

In addition to the difficulties of evaluating HbA1c levels in CKD, specific glycaemic targets for diabetic patients with CKD have not been established. HbA1c levels of ~ 7%, consistent with NKF-KDOQI guidelines,[19] are recommended if they can be achieved without compromising safety, and most importantly, without increasing the number and severity of episodes of hypoglycaemia. Target HbA1c levels are also uncertain for patients with diabetes on chronic dialysis or with a kidney transplant, and will depend on age, comorbidities and the risk of hypoglycaemia.[19,20] Therefore, the approach to glycaemic management in patients with T2D and advanced CKD should be individualized, taking account of the needs and preferences of each patient, including the presence of comorbidities and concomitant therapies.[19]

1.3 | What are the challenges associated with treating T2D in patients with advanced CKD?

Kidney disease increases the complexity and risks associated with management of T2D.[19] In particular, advanced CKD is an important risk factor for hypoglycaemia, as gluconeogenesis by the kidney is impaired.[21] In addition, hepatic glycogenolysis and gluconeogenesis are reduced in advanced CKD.[22,23] The risk of hypoglycaemia in patients with CKD is further increased because the drugs commonly used to treat diabetes in these patients, insulin and sulfonylureas (SUs), are themselves associated with a risk of hypoglycaemia.[17] Many glucose-lowering drugs, including insulin, undergo clearance by the kidney, and therefore require dose adjustments or are contraindicated in patients with advanced CKD.[19] Thus, choices of glucose-lowering therapies have been limited for patients with T2D with advanced CKD.[24]

TABLE 1 Clinical trials including patients with type 2 diabetes and advanced chronic kidney disease (CKD)

Study	Intervention and study size	Advanced CKD by baseline eGFR[2] (mL/min/1.73m^2)[a]	Patients with advanced CKD[b], n (%)	Duration of follow-up	Mean HbA1c change versus baseline (%)	Kidney outcomes	Occurrence of 3P-MACE[c,d]
Rosenstock et al[51]	Linagliptin or placebo N = 6991	<30	1062 15	2.2 years	−0.51 (−0.55, −0.46)	Composite kidney outcome:[c,e] 1.04 (0.89, 1.22); *P* = 0.62 Progression of albuminuria:[c,f] 0.86 (0.78, 0.95); *P* = 0.003	1.02 (0.89, 1.17) *P* < 0.001 for non-inferiority
McGill et al[52]	Linagliptin or placebo N = 133	15–30 <15	100 (75) 14 (11)	1 year	−0.72 (−1.03, −0.41) *P* = 0.0001	Median difference in eGFR[a] from baseline to last value on treatment: linagliptin, 20.8 mL/min/1.73m^2 versus placebo, 22.2 mL/min/1.73m^2	–
Leiter et al[72]	Weekly albiglutide or daily sitagliptin N = 771	≥15 to ≤29	36 (7.3)	1 year	−0.32 (−0.49, −0.15) *P* = 0.0003	–	–
Arjona Ferreira et al[30]	Sitagliptin or glipizide N = 426	<30	73 (25.4–27.4)[g]	1 year	−0.11 (−0.29, 0.06)[h]	Number of patients with moderate CKD at baseline who transitioned to severe CKD status: sitagliptin group, 28 (18.8%); glipizide group, 17 (11.0%)	–
Arjona Ferreira et al[29]	Sitagliptin or glipizide N = 129	ESKD on dialysis	129 (100)	54 weeks	−0.15 (−0.18, −0.49)	–	–
Lukashevich et al[54]	Vildagliptin or placebo N = 515	<30	221 (42.9)	24 weeks	Moderate CKD:−0.5 ± 0.1; *P* < 0.0001 Severe CKD: −0.6 ± 0.1%; *P* < 0.0001		–
Kothny et al[55]	Vildagliptin or placebo N = 369	<30	158 (42.8)	1 year	Moderate CKD: −0.4 ± 0.1%; *P* = 0.005 Severe CKD: −0.7 ± 0.2%; *P* < 0.0001	Moderate CKD: mean change from baseline eGFR[a], −1.62 and − 1.80 for vildagliptin and placebo, respectively Severe CKD: mean change from baseline eGFR, −1.98 and − 2.44, respectively	–
Satirapoj et al[41]	Standard- versus low-dose pioglitazone N = 75	≥15 to ≤29	19 (25.3)	24 weeks	Standard dose: decreased from 9.2 ± 1.8 to 7.9 ± 1.4; *P* < 0.05 Low-dose: decreased from 8.9 ± 1.4 to 7.6 ± 0.9; *P* < 0.05	–	–

Abbreviations: 3P-MACE, three-point major adverse cardiovascular events; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

[a]eGFR measured in mL/min/1.73m^2.

[b]Advanced CKD as defined in each study and shown in preceding column; termed 'moderate' or 'severe' in some studies.

[c]Results expressed as hazard ratios (95% confidence intervals) for whole study population, active treatment versus placebo or comparator.

[d]3P-MACE, composite of CVD death, non-fatal myocardial infarction, and non-fatal stroke.

[e]Composite kidney outcome, adjudicated death because of kidney failure, ESKD, or sustained 40% or higher decrease in eGFR from baseline.

[f]Progression of albuminuria = change from normoalbuminuria to microalbuminuria/macroalbuminuria or change from microalbuminuria to macroalbuminuria.

[g]For this analysis, n = 277 (patients who completed the study with available data).

[h]Met criterion for non-inferiority.

1.4 | What are the treatment options for patients with T2D and advanced CKD?

Only a few studies have evaluated the efficacy and safety of glucose-lowering drugs in patients with advanced CKD. The number of patients studied with eGFR <30 mL/min/1.73m^2 is low because these patients are often excluded from clinical trials of glucose-lowering agents (Table 1).[24] Because cardiovascular outcomes trials (CVOTs) follow the approved indications for these agents, this patient population has been under-represented in the CVOTs (Table 2).[25] There remains a need for effective glucose-lowering therapies that have shown safety, especially for hypoglycaemia, in patients with T2D and advanced CKD.

2 | NON-INCRETIN THERAPIES

2.1 | Insulin

Many oral glucose-lowering agents must be discontinued or administered at a reduced dose because of the risk of adverse effects in diabetic patients with advanced CKD, including those with ESKD treated by dialysis. Thus, insulin is frequently used to control hyperglycaemia. However, a low GFR also results in a prolonged pharmacokinetic profile of insulin, so the dose and the schedule must be modified.[26] Glycaemic control with insulin can be difficult to achieve in patients with advanced CKD because of impaired insulin clearance by the kidney as well as reduced insulin sensitivity.[12,27] Some studies of newer insulin analogues suggest less impact on pharmacokinetics than with the older insulins. Therefore, these agents may be more suitable for insulin-requiring patients with advanced CKD.[12,28]

2.2 | SUs

As kidney function declines, clearance of most SUs and their active metabolites falls progressively, necessitating a decrease in drug dose to avoid hypoglycaemia.[19] First-generation SUs (eg, chlorpropamide, tolazamide and tolbutamide) should not be used in CKD because these agents rely on elimination by the kidney of both the parent drug and active metabolites, resulting in a higher risk of hypoglycaemia.[19] Of the second-generation SUs (eg, glipizide, glyburide and glimepiride), glipizide is preferred as it is cleared by the liver without active metabolites and does not require dose adjustment in advanced CKD.[19] However, glipizide therapy is associated with higher rates of hypoglycaemia and weight gain compared with incretin therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors.[29,30]

2.3 | Metformin

Metformin is eliminated by the kidneys and has historically been considered unsuitable for use in patients with advanced CKD because of concerns about development of lactic acidosis attributed to metformin accumulation.[31,32] These concerns were largely based on case reports, and observational studies have not shown the predicted increase in the risk of metformin-associated lactic acidosis.[33] Consequently, changes to recommendations for metformin use occurred in 2016 when the US Food and Drug Administration (FDA) relaxed its restrictions for metformin use in CKD following a review of the safety of this agent in patients with impairment of kidney function.[34] For patients with CKD, the guidance states that starting metformin in patients with an estimated glomerular filtration rate (eGFR) of 30–45 mL/min/1.73m^2 is not recommended. For patients taking metformin whose eGFR falls below 45 mL/min/1.73m^2, the benefits and risks of continuing treatment should be evaluated, and metformin should be discontinued in patients whose eGFR falls below 30 mL/min/1.73m^2.[34]

Recent evidence suggests that low-dose metformin (500 mg once-daily) may be used in patients with an eGFR of 15–30 mL/min/1.73m^2, provided the dosage is adjusted on an individual patient basis and that the drug is stopped during acute illness.[35,36] However, the FDA has not approved metformin use in patients with an eGFR below 30 mL/min/1.73m^2.[37]

2.4 | Thiazolidinediones

Pioglitazone undergoes hepatic metabolism and is effective in patients with T2D and CKD without increasing the risk of hypoglycaemia.[38] The pharmacokinetics of pioglitazone are not altered in patients with impaired kidney function, and dose adjustment is not required for patients with T2D and CKD.[39] The main concern with thiazolidinedione (TZD) therapy is that it is associated with fluid retention and oedema, which are frequent causes of therapy discontinuation. These agents should be used with caution in patients at risk of heart failure and are not recommended for patients with symptomatic heart failure.[40] However, a recent meta-analysis of the use of TZDs in patients with T2D and kidney impairment, which included 19 randomized controlled trials and three cohort studies (a total of 21 803 patients), found that although TZDs significantly increased the risk of weight gain and oedema, the risk of heart failure, angina, myocardial infarction, CVD mortality and all-cause mortality were not increased.[38]

The risk of fluid retention in patients with CKD can be reduced by the use of low-dose pioglitazone. A 24-week study of standard- versus low-dose pioglitazone (15 or 7.5 mg once-daily) in 75 patients with T2D and CKD (25.3% of whom had category 4 CKD) showed that the lower dose produced a similar degree of glycaemic control as the standard dose without adverse effects on weight gain and fluid retention (Table 1).[41] In an earlier study, the effect of adding pioglitazone (30 mg) versus placebo to existing insulin therapy was evaluated in a randomized phase 2 study of 36 patients with T2D who were undergoing haemodialysis.[42] The addition of pioglitazone to insulin in this patient population with ESKD was well tolerated and led to improved glycaemic control with a reduced requirement for

TABLE 2 Cardiovascular outcomes trials (CVOTs) and a glycaemic control clinical trial including patients with type 2 diabetes and advanced chronic kidney disease (CKD)

Study	Intervention and study size	Baseline eGFR[a] (mL/min/1.73m^2)	Patients with advanced CKD[b], n (%)	Duration of follow-up (years)	Glycaemic outcomes	Kidney outcomes[c]	Effect on progression of kidney disease[c]	CV outcomes[c]
Udell et al[53]	Saxagliptin versus placebo N = 16 492	<30	336 (2.04)	2.0	Advanced CKD group: HbA1c 7.1% saxagliptin versus 7.7% placebo at 1 year	Kidney composite outcome[d] in patients with eGFR[a] ≤50: 1.06 (0.78–1.44; *P* (interaction) = 0.90	Advanced CKD group: no overall change in risk of progressive microalbuminuria with saxagliptin (53.4%) versus placebo (46.6%); *P* = 0.61[d]	Advanced CKD group: 3P-MACE[e] adjusted HR 0.83 (0.49–1.39); *P* = 0.48 HHF: 0.94 (0.52–1.71); *P* = 0.84
LEADER[61]	Liraglutide or placebo N = 9340	<30	224 (2.4)	3.8	–	Kidney composite outcome[f] in patients with eGFR[a] <60 and microalbuminuria or macroalbuminuria (n = 1130): 0.81 (0.64–1.03) *P* = 0.09	New onset persistent macroalbuminuria: 161, liraglutide group versus 215 in placebo group, HR, 0.74 (0.60 to 0.91; *P* = 0.004)	–
AWARD-7[64]	Once-weekly dulaglutide or daily insulin glargine, all + insulin lispro N = 577	≥15–30 <15	171 (29.6) 2 (0.003)	1.0	HbA1c change LSM −1.1% (SE 0.1), dulaglutide 1.5 mg; −1.1% (0.1), dulaglutide 0.75 mg; −1.0% (0.1), insulin glargine	eGFR[a]: dulaglutide 1.5 mg LSM 34.0 (SD 0.7); *P* = 0.005 versus insulin glargine; dulaglutide 0.75 mg, 33.8 (0.7); *P* = 0.009 versus insulin glargine, 31.3 (0.7). UACR: dulaglutide 1·5 mg, −22·5% (−35·1 to −7·5); dulaglutide 0·75 mg, −20·1% (−33·1 to −4·6); insulin glargine, −13·0% (−27·1 to 3·9)	–	–
REWIND[65]	Dulaglutide or placebo N = 9901	<30	105 (1)	5.4	–	Kidney composite outcome[g]: dulaglutide versus placebo: 0.85 (0.77–0.93); *P* = 0.0004	–	–

Abbreviations: 3P-MACE, three-point major adverse cardiovascular events; AWARD-7, Assessment of Weekly Administration of Dulaglutide in Diabetes clinical trial program-7; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LSM, least squares mean; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes; SE, standard error; UACR, urine albumin-to-creatinine ratio.

[a]eGFR, measured in mL/min/1.73m^2.

[b]Advanced CKD as defined in each study and shown in preceding column.

[c]Results expressed as hazard ratios (95% confidence intervals) for whole study population, active treatment versus placebo.

[d]Progressive diabetic kidney disease defined by albumin-to-creatinine ratio.

[e]3P-MACE, composite of CVD death, non-fatal myocardial infarction, and non-fatal stroke.

[f]Composite outcome of new onset of persistent macroalbuminuria, doubling of serum creatinine and eGFR <45 mL/min/1.73m^2, need for continuous kidney replacement therapy (end-stage kidney disease) or death because of kidney disease.

[g]Composite of first occurrence of new macroalbuminuria (UACR >33.9 mg/mmol), sustained decline in eGFR of 30% or more from baseline, or chronic kidney replacement therapy.

Note: Composite of a doubling of serum creatinine level, initiation of long-term dialysis, kidney transplantation, or serum creatinine level of 0.6 mg/dL.

insulin. TZDs have been associated with an increased risk of fracture,[43] which is concerning in patients who may have higher fracture risk because of bone and mineral metabolism disorders that occur in advanced CKD.

2.5 | Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors exert their glucose-lowering effects by increasing glucose excretion through the kidneys. Because the glucose-lowering efficacy of these agents attenuates in patients with low eGFR, SGLT-2 inhibitors are not recommended for glycaemic control in patients with T2D and an eGFR below 45 mL/min/1.73m^2.[44] However, canagliflozin has recently received FDA approval for patients with T2D and diabetic kidney disease with macroalbuminuria (>300 mg/day) and eGFR of 30-90 mL/min/1.73m^2 to reduce the risk of doubling of serum creatinine, ESKD, CVD death and hospitalization for heart failure,[45] based upon the landmark Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.[46]

3 | INCRETIN THERAPIES

3.1 | DPP-4 inhibitors

The DPP-4 inhibitors slow the breakdown of incretin hormones, glucagon-like peptide-1 (GLP-1) in particular, and improve both fasting and postprandial glucose levels. Alogliptin, sitagliptin and saxagliptin are primarily eliminated via the kidneys and, consequently, they require dose adjustment in patients with any category of CKD. By contrast, linagliptin is excreted via the bile and gut and does not require dose adjustment in patients with CKD.[19,47-50] Linagliptin has been evaluated in a large population of patients with T2D and CKD in the Cardiovascular and Renal Microvascular Outcome study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) trial (62% of the trial population with an eGFR <60 mL/min/1.73m^2, and 15% with an eGFR <30 mL/min/1.73m^2) (Table 1).[51] The CARMELINA trial was a randomized, placebo-controlled, multicentre, non-inferiority trial that evaluated lingaliptin versus placebo on top of standard-of-care for prespecified CVD and CKD endpoints in patients with T2D and elevated CVD and CKD risks. After a median of 2.2 years of follow-up for 6979 participants, those allocated to linagliptin showed no increase in the risk of three-point major adverse CVD events (3P-MACE) versus placebo: hazard ratio (HR) 1.02 (95% confidence interval [CI] 0.89–1.17); P < 0.001 for non-inferiority. There was also no increase in the risk of hospitalization for heart failure for linagliptin versus placebo (HR 0.90 [0.74–1.08]). There was no significant difference in the rates of the secondary composite CKD endpoint (≥40% sustained reduction in eGFR, ESKD or death from kidney failure with linagliptin; Table 1). For exploratory CKD endpoints, there was no increased risk of progression to ESKD or death because of kidney disease (HR 0.87 [0.69–1.10]), but progression of albuminuria was less frequent in patients who received linagliptin versus placebo (HR 0.86 [0.78–0.95]). The results of CARMELINA extend the findings of an earlier study in 133 patients with severely impaired kidney function, in which linagliptin was shown to provide clinically relevant improvements in glycaemic control with a low risk of hypoglycaemia, stable body weight, and no occurrence of drug-related kidney failure.[52]

Sitagliptin has also been evaluated in patients with CKD. In a study of 426 patients with T2D and moderate-to-severe CKD, sitagliptin showed similar glucose-lowering efficacy to glipizide (Table 1).[30] At week 54, similar reductions from baseline HbA1c (mean: 7.8% in both groups) were observed in both treatment groups. Sitagliptin was generally well tolerated, with a lower risk of hypoglycaemia and weight loss versus weight gain, relative to glipizide. Sitagliptin has also been evaluated in comparison with glipizide in 129 patients with T2D and ESKD who were on chronic dialysis with HbA1c levels of 7.0%–9.0%.[29] After 54 weeks, reductions in HbA1c were similar between groups and symptomatic hypoglycaemia was reported less frequently in the sitagliptin group versus the glipizide group (Table 1). More recently, a prespecified secondary analysis of saxagliptin in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial evaluated the efficacy and safety of saxagliptin compared with placebo according to baseline kidney function in patients with T2D (Table 2).[53] Saxagliptin was shown to have a neutral impact on the risk of ischaemic CVD events while increasing the risk of hospitalization for heart failure. Although only a minority of patients had severe CKD, saxagliptin reduced progressive albuminuria, irrespective of baseline kidney function.

The safety and efficacy of adding vildagliptin or placebo to standard therapy was evaluated in 515 patients with T2D and moderate-to-severe CKD (Table 1).[54] After 24 weeks, vildagliptin was shown to produce clinically and statistically significant reductions in HbA1c with a safety profile similar to placebo. A 1-year study of vildagliptin versus placebo in 369 patients with T2D and moderate-to-severe CKD found similar results, which were maintained in the long term.[55] In a subsequent clinical trial, the safety and efficacy of vildagliptin therapy was evaluated over 2 years in 32 patients with T2D and ESKD treated by chronic dialysis.[56] Vildagliptin improved glycaemic control in patients with T2D and ESKD, and was well tolerated, notably without an increased risk of hypoglycaemia or weight gain.

A retrospective analysis of 200 patients with ESKD who were receiving DPP-4 inhibitor therapy (sitagliptin, vildagliptin, linagliptin) also showed that these agents are effective, with no significant difference among the individual agents in terms of glucose-lowering efficacy after 12 weeks of treatment, in addition to beneficial effects on serum lipid profiles.[57] Subsequently, a meta-analysis of randomized controlled trials of DPP-4 inhibitors in patients with CKD (eGFR <60 mL/min/1.73m^2) identified 12 studies of 24–84 weeks' duration that included 4403 patients with CKD and 239 patients on chronic dialysis. This systematic review showed that DPP-4 inhibitors reduced HbA1c by ~ 0.5%, without a higher rate of adverse events compared with placebo.[58]

3.2 | GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have an incretin-like action and control blood glucose levels through several pathways, including pancreatic stimulation of insulin secretion and inhibition of glucagon release along with delay in gastric emptying.[59] Although clinical trials with primary outcomes of kidney disease endpoints have not yet been performed in patients with CKD, post hoc and secondary analyses of CVOTs have shown that treatment with GLP-1 RAs is associated with reductions in albuminuria and stabilization of eGFR (liraglutide and semaglutide).[60-62] A recent meta-analysis of seven CVOTs that compared GLP-1 RAs with placebo in 56 004 patients showed that these agents reduce the risk of macroalbuminuria.[63] The broad composite kidney outcome was reduced by 17%, mainly driven by a reduction in macroalbuminuria. Furthermore, some GLP-1 RAs (liraglutide, semaglutide, abiglutide, dulaglutide) have been associated with a reduction in the occurrence of MACE, particularly among patients with pre-existing CVD, in addition to a reduced risk of all-cause mortality.[63]

Several recent CVOTs that evaluated GLP-1 RAs included patients with CKD (Table 2). A prespecified secondary analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial evaluated kidney outcomes in 9340 patients with T2D and high CVD risk, including subgroups with CKD.[61] The results showed that the addition of liraglutide to usual care resulted in a reduction in development and progression of CKD in patients with T2D and high CVD risk, compared with placebo. Subsequently, the AWARD-7 trial (part of the Assessment of Weekly Administration of Dulaglutide in Diabetes clinical trial programme) evaluated glycaemic control and kidney disease outcomes in patients with T2D and moderate-to-severe CKD (categories 3 and 4). The results showed a favourable efficacy profile of dulaglutide compared with insulin glargine for glycaemic control in addition to other benefits, including lower rates of hypoglycaemia, weight loss, reduced decline in eGFR, and greater reduction in albuminuria.[64] To date, AWARD-7 is the only study that has been conducted in patients with T2D selected for moderate-to-severe CKD (mean baseline eGFR: 38 mL/min/1.73m^2). Over 1 year of treatment, dulaglutide produced no significant eGFR decline (mean – 0.7 mL/min/1.73m^2) compared with insulin glargine (mean – 3.3 mL/min/1.73m^2 overall and mean – 5.5 mL/min/1.73m^2 in the macroalbuminuric subgroup). An exploratory analysis of the AWARD-7 data also showed the risk of a ≥ 40% eGFR decline and ESKD to be reduced by more than half with dulaglutide.[64] In addition, a secondary analysis of the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial evaluated kidney outcomes in a population of patients with T2D and high CVD risk who received dulaglutide versus placebo, added to usual care.[65] This secondary analysis showed a reduction in the progression of kidney disease associated with dulaglutide therapy, in particular a reduction in albuminuria and a greater than 50% reduced risk of an eGFR decline ≥40%. The role of these agents to reduce kidney disease outcomes in patients with T2D and CKD is being further evaluated in an ongoing clinical trial (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease [FLOW]; NCT03819153), with an estimated enrolment of 3160 patients (including participants with eGFR as low as 25 mL/min/1.73m^2). The results of FLOW are expected in 2024.

Dulaglutide, liraglutide, semaglutide and lixisenatide can be used in patients with T2D and concomitant CKD without dose adjustment.[66-69] However, lixisenatide should not be used if eGFR <15 mL/min/1.73m^2, and there are limited data for the use of liraglutide in patients with advanced CKD. Kidney function should be monitored if patients have severe adverse gastrointestinal reactions to treatment. For exenatide, caution is advised when treatment is initiated or the dose is escalated in those patients with moderate impairment of kidney function (creatinine clearance 30–50 mL/min).[70,71] Of note, twice-daily and once-weekly exenatide, as well as lixisenatide, should not be used in patients with ESKD or severe impairment of kidney function. In summary, GLP-1 RAs can be used safely and effectively for glycaemic control in patients with T2D and advanced CKD. Lower doses may be considered to mitigate gastrointestinal side effects.

4 | HOW TO MANAGE PATIENTS WITH T2D AND ADVANCED CKD

The following case studies provide a clinical context and practical guidance for the use of incretin therapies as glucose-lowering agents in patients with T2D and advanced CKD.

4.0.1 | Case 1: Advanced CKD

A 66-year-old man with T2D was referred for assessment of glucose-lowering therapy following worsening glycaemic control, symptomatic hypoglycaemia 2–3 times per week, and progression to severe CKD. The patient reported an increasingly sedentary lifestyle because of reduced physical activity following retirement, and worsening back and joint pain. He had a 15-year history of T2D, in addition to hypertension, osteoarthritis and chronic obstructive pulmonary disease. His current medication regimen was glipizide extended-release 10 mg once-daily; ramipril 5 mg twice-daily; and over-the-counter ibuprofen 200 mg taken three times daily. Key clinical data: blood pressure (BP) 139/77 mmHg, body mass index (BMI) 31.1 kg/m^2, HbA1c 7.8%, fasting plasma glucose 151 mg/dL, eGFR 29 mL/min/1.73m^2, UACR 220 mg/g, blood urea nitrogen 50 mg/mL, serum creatinine 2.3 mg/dL. The patient's glucose-lowering therapy was changed to dulaglutide 1.5 mg weekly instead of glipizide, with the instruction to discontinue ibuprofen because of potential nephrotoxicity; the ramipril dose was unchanged. The patient was also advised to increase physical activity. After 6 months, HbA1c had fallen to 7.2%, eGFR was stable at 30 mL/min/1.73m^2, UACR decreased to 50 mg/g, BP had fallen to 134/74 mmHg, and BMI was reduced to 29.3 kg/m^2. He reported no symptoms of hypoglycaemia.

4.0.2 | Take home message

In patients with T2D and advanced CKD, hyperglycaemia can be safely and effectively managed by a GLP-1 RA with stabilization of kidney function and reduction of albuminuria, along with improvements in CVD risk factors such as hypertension and obesity.

4.0.3 | Case 2: ESKD

A 58-year-old woman with T2D and ESKD was referred from her dialysis centre after a hypoglycaemic event that caused her to fall and suffer a head injury with subdural haematoma. She was treated for T2D with Humulin 70/30 (human insulin isophane suspension and human insulin injection), 30 units in the morning and 20 units in the evening. HbA1c upon admission was 9.1%. For this patient, the treatment goals were to improve glycaemic control and avoid hypoglycaemia. Her medication regimen was changed to linagliptin 5 mg daily with insulin glargine 22 units on non-dialysis days and 16 units administered after dialysis on those days. After 6 months, HbA1c was 7.2% and mild hypoglycaemia occurred rarely.

4.0.4 | Take home message

For patients with T2D on haemodialysis, a DPP-4 inhibitor combined with lower doses of a longer-acting insulin preparation can improve glycaemic control and reduce hypoglycaemic risk.

5 | CONCLUSIONS

For patients with T2D and advanced CKD, there is a need to better understand how to appropriately manage hyperglycaemia. The goal of treatment should be glycaemic control to targets based upon individual risk profiling as well as patient preferences and values. Treatment approaches should take into account the need to avoid hypoglycaemia, and to protect kidney function while reducing CVD risk. To date, there is a relative lack of data from clinical trials to inform choices of glucose-lowering agents for this population. Although data are available for the use of incretin therapies, DPP-4 inhibitors and GLP-1 RAs, in patients with T2D and advanced CKD, additional studies are needed to establish optimal strategies for glycaemic control. Until such data are available, treatment regimens with currently available glucose-lowering agents can be individually tailored to meet the needs of these patients.

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AUTHOR CONTRIBUTIONS

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, and were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version that reflects the authors' interpretations and conclusions.

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