Review of glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus in patients with chronic kidney disease and their renal effects

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Highlights
- Diabetic kidney disease is a common comorbidity of type 2 diabetes mellitus.
- In studies investigating the effect of renal function on the efficacy of treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs), these agents improved glycemic control in patients with mild to moderately impaired kidney function, without significant differences compared with patients with normal renal function.
- GLP-1RAs were associated with a lower incidence of diabetic nephropathy, mostly driven by a reduction in albuminuria, compared with placebo in several large cardiovascular outcome trials.

Abstract
Type 2 diabetes mellitus (T2DM) is the most common cause of chronic kidney disease (CKD), and when it causes CKD it is collectively referred to as diabetic kidney disease. One of the newer therapies for managing hyperglycemia is the glucagon-like peptide-1 receptor agonist (GLP-1RA) drug class. This review summarizes the effects of GLP-1RAs in patients with T2DM with CKD and evidence for renoprotection with GLP-1RAs using data from observational studies, prospective clinical trials, post hoc analyses, and meta-analyses. Evidence from some preclinical studies was also reviewed. Taken together, subgroup analyses of patients with varying degrees of renal function demonstrated that glycemic control with GLP-1RAs was not markedly less effective in patients with mild or moderate renal impairment vs that in patients with normal function. GLP-1RAs were associated with improvements in some cardiorenal risk factors, including systolic blood pressure and body weight. Furthermore, several large cardiovascular outcome studies showed reduced risks of composite renal outcomes, mostly driven by a reduction in macroalbuminuria, suggesting potential renoprotective effects of GLP-1RAs. In conclusion, GLP-1RAs effectively reduced hyperglycemia in patients with mild or moderately impaired kidney function in the limited number of studies to date. GLP-1RAs may be considered in combination with other glucose-lowering medications because of their ability to lower glucose in a glucose-dependent manner, lowering their risk for...
hypoglycemia, while improving some cardiorenal risk factors. Potential renoprotective effects of GLP-1RAs, and their renal mechanisms of action, warrant further investigation.

**KEYWORDS**
chronic kidney disease, diabetic kidney disease, glucagon-like peptide-1 receptor agonist, type 2 diabetes mellitus, visceral insulin resistance adiposity syndrome

### 1 | INTRODUCTION

Kidney disease is a common comorbidity in patients with type 2 diabetes mellitus (T2DM). According to National Health and Nutrition Examination Survey data from 2007-2012, the age-adjusted prevalence of chronic kidney disease (CKD) in patients with T2DM was 38.3%, with 18.5% having normal renal function or mild renal impairment (estimated glomerular filtration rate [eGFR] ≥90 or 60 to 89 mL/min/1.73 m², respectively, with urinary albumin-to-creatinine ratio [UACR] ≥30 mg/g), 16.7% having moderate renal impairment (eGFR 30-59 mL/min/1.73 m²), and 3.1% having severe renal impairment or end-stage renal disease (ESRD; eGFR 15 to 29 or <15 mL/min/1.73 m², respectively).¹

Diabetic kidney disease (DKD), a pathognomonic microvascular complication of diabetes, is characterized by albuminuria, impaired GFR, or both, and is associated with molecular, physiologic, and structural changes to the kidney induced by hyperglycemia.²³ People with T2DM typically have high blood pressure (BP) and are usually overweight or obese; hyperglycemia, hypertension, and obesity are all risk factors for the development and progression of CKD.⁴⁻⁶ This triad of clinical findings is driven by an excess of visceral fat and is frequently referred to as “the metabolic syndrome,” although the term “visceral insulin resistance adiposity syndrome (VIRAS)” is more descriptive.⁷

Landmark studies have shown that poor glycemic control increases the risk of developing microvascular and macrovascular complications, while good glycemic control reduces the risk of these complications.⁸⁹ Thus, one of the treatment goals for T2DM is reduction of hyperglycemia to delay onset of and slow progression of microvascular complications, including nephropathy.³⁰⁻¹¹ Recent research efforts have increasingly focused on the renal effects of glucose-lowering therapies, with the greatest benefits for renal outcomes reported for sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs).¹²

GLP-1RAs are a class of glucose-lowering agents that have been shown to reduce hyperglycemia in a glucose-dependent manner and are associated with weight loss and improvement in some other cardiorenal risk factors, including BP and lipid levels, in patients with T2DM.¹³⁻¹⁶ GLP-1RAs are generally well tolerated, with a low risk of hypoglycemia when not taken with concomitant insulin or sulfonylurea,¹⁷⁻²³ but are associated with an increased frequency of gastrointestinal adverse events (AEs) such as nausea, vomiting, and diarrhea.²⁴ Gastrointestinal symptoms associated with GLP-1RAs occur early in the course of therapy and generally lessen over time.²⁵⁻²⁷ Hydration is important for all patients with diabetes, particularly those with DKD, given that severe vomiting without commensurate fluid replacement can lead to hypovolemia and acutely worsening renal function.²⁶⁻²⁷ Postmarketing cases of acute kidney failure associated with GLP-1RA use have been reported,²⁸ resulting in warnings and precautions in the prescribing information for their use in patients with impaired renal function.

Because renal impairment and T2DM are often comorbid conditions, a need exists for effective glucose-lowering therapies in patients with renal impairment. GLP-1RAs vary in their primary mechanism of metabolism and elimination, and while some agents undergo renal clearance, GLP-1RAs are not nephrotoxic. However, impaired renal function would be expected to affect the pharmacokinetics of renally eliminated GLP-1RAs, potentially increasing drug exposure and the risk of AEs. GLP-1RAs currently available in the United States include exenatide twice daily (bid), exenatide once weekly (qw), lixisenatide once daily (qd), liraglutide qd, dulaglutide qw, and semaglutide qw; albiglutide qw has been withdrawn from the market. Exenatide undergoes renal elimination and generalized proteolysis; exenatide qw is not recommended for patients with an eGFR below 45 mL/min/1.73 m².¹⁸⁻¹⁹ Lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation; patients treated with lixisenatide who have mild, moderate, or severe renal impairment should be monitored for changes in renal function and for gastrointestinal AEs.²¹ The “glutides”: liraglutide, dulaglutide, and semaglutide are human GLP-1 analogs eliminated by general proteolysis pathways by mechanisms other than renal elimination but should be used with caution in patients with renal impairment, particularly during treatment initiation or dose escalation, as adverse gastrointestinal reactions associated with GLP-1RAs can increase the risk of developing volume depletion and worsen renal function.²⁰⁻²²⁻²³
Given the relationship between diabetes and kidney disease, the objective of this review is to summarize the efficacy of GLP-1RAs and their effects on renal outcomes in patients with T2DM and renal impairment. To identify studies reporting effects of GLP-1RAs in patients with renal impairment, the US National Library of Medicine PubMed database was searched for combinations of relevant terms including “exenatide,” “lixisenatide,” “liirlaglutide,” “dulaglutide,” “semaglutide,” “glucagon-like peptide-1 receptor agonists,” “kidney,” “renal,” “nephropathy,” and “diabetic kidney disease.” The search was limited to English-language publications. Articles were manually searched to identify studies reporting the efficacy of GLP-1RAs in patients with varying degrees of renal function and effects of GLP-1RAs on renal outcomes, with additional studies identified within the reference lists of resultant articles.

2 | RENAL EFFECTS OF GLP-1RAS

Experiments evaluating exenatide and liraglutide in animal model systems have demonstrated improvements in glomerular hyperfiltration, albuminuria, oxidative stress, and histologic features indicative of DKD, suggesting a role for exenatide and liraglutide in protecting renal function (Table 1).29-34 These effects may extend across the GLP-1RA class; although to date no preclinical studies directly examining renoprotective effects with other GLP-1RAs are known. Importantly, preclinical studies have generated hypotheses regarding potential renoprotective effects of GLP-1RAs. While clinical studies on renoprotection are limited, several suggest that GLP-1RAs may promote improved kidney function in humans (Table 2). In addition, clinical studies including subgroup analyses stratified by renal function have examined the effect of impaired renal function on the efficacy of GLP-1RAs in patients with T2DM.

2.1 | Exenatide

Several studies have examined the effect of renal function on the efficacy of exenatide treatment. A post hoc analysis of a randomized controlled trial (RCT) compared the effects of exenatide qw formulated for autoinjection with exenatide bid by renal function status.51 As renal function decreased, the glycemic effect of exenatide bid increased (glycated hemoglobin [HbA1c] reductions of −0.7%, −1.3%, and −1.4% [−7.5, −14.6, and −15.2 mmol/mol] for the eGFR subgroups ≥90, 60-89, and 30-59 mL/min/1.73 m², respectively), while there was no effect on body weight. In contrast, renal impairment had no effect on HbA1c reductions associated with exenatide qw for autoinjection (−1.5%, −1.4%, and −1.4% [−16.7, −15.0, and −15.2 mmol/mol] for eGFR subgroups ≥90, 60-89, and 30-59 mL/min/1.73 m², respectively), but greater weight loss was observed as renal function decreased. These findings suggest impaired renal function may increase exposure, and thereby glycemic response, to exenatide bid. Renal function status showed no clear effect on the safety profile of either formulation. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) examined the effects of exenatide qw compared

| First author | Study design | Main renal outcomes of treatment |
|--------------|--------------|----------------------------------|
| Kodera et al29 | Exendin-4 10 μg/kg for 8 weeks in a streptozotocin-induced rat model of diabetes | Reduced albuminuria, glomerular hyperfiltration, glomerular hypertrophy, mesangial matrix expansion, and ICAM-1 and type IV collagen |
| Ojima et al30 | Exendin-4 1.5 μg/kg for 2 weeks in a streptozotocin-induced rat model of diabetes | Inhibited expression of the AGE receptor, which mediates oxidative stress pathways; reduced albuminuria; and improved histopathologic changes in the kidney |
| Park et al31 | Exendin-4 0.5-1.0 nmol/kg for 8 weeks in a db/db mouse model of diabetes | Reduced albuminuria, glomerular hypertrophy, mesangial matrix expansion, TGF-β expression, type IV collagen accumulation, infiltrating macrophages, and apoptosis |
| Rieg et al32 | Exendin-4 10 μg/kg (acute) in a db/db mouse model of diabetes | Induced diuresis and natriuresis due to increased GFR in wild-type mice; effects on natriuresis were preserved in db/db mice |
| Hendarto et al33 | Liraglutide 0.3 mg/kg/12 h for 4 weeks in a streptozotocin-induced rat model of diabetes | Reduced oxidative stress markers, TGF-β1, fibronectin in renal tissues, and albuminuria |
| Zhao et al34 | Liraglutide applied to HK-2 cells and liraglutide 0.3 mg/kg/12 h for 5 weeks in a streptozotocin-induced rat model of diabetes | Attenuated high glucose-induced toxicity in HK-2 cells; inhibited glomerular hypertrophy and attenuated high glucose-induced autophagy in diabetic rats |

Abbreviations: AGE, advanced glycation end products; GFR, glomerular filtration rate; HK-2, human renal tubular epithelial cell line; ICAM-1, intercellular adhesion molecule 1; TGF-β1, transforming growth factor β1.


| First author (study name; ClinicalTrials.gov identifier) | Study design | Main renal outcomes of treatment |
|----------------------------------------------------------|--------------|---------------------------------|
| **Short-term clinical studies**                           |              |                                 |
| Zhang et al35                                            | 16-week, randomized, comparator-controlled study of exenatide 10 μg bid vs glimepiride 1-4 mg qd in patients with T2DM and microalbuminuria | Exenatide bid resulted in reductions from baseline in 24-h urinary albumin (−38.0%), urinary TGF-β1 (−37.3%), and type IV collagen (−25.3%; P < .01 for all); there were no significant reductions with glimepiride |
| von Scholten et al (NCT02545738)36                      | 12-week, randomized, placebo-controlled, crossover trial of liraglutide 1.8 mg qd in patients with T2DM and persistent albuminuria who were receiving RAS blockers | Liraglutide reduced UAER vs placebo (−32%; P = .017) |
| Tuttle et al (pooled analysis of NCT01149421; NCT01064687; NCT00734474; NCT01075282; NCT01191268; and NCT01126580)37 | Pooled analysis of 26-week results from six phase 2/3 studies of dulaglutide 0.75-1.5 mg qw vs placebo, active comparators, or insulin glargine in patients with T2DM | Dulaglutide decreased median percent changes in UACR vs placebo (−16.7% vs −10.0%; P = .043), active comparators (−20.0% vs −12.5%; P = .054), and insulin glargine (−20.0% vs −9.4%; P = .100) |
| **Long-term clinical studies**                            |              |                                 |
| Zavattaro et al38                                         | 12-month observational study of liraglutide 0.6-1.8 mg qd in patients with T2DM | eGFR reached the normal range for 7 of 41 patients with baseline eGFR <90 mL/min/1.73 m² |
| Imamura et al39                                           | 12-month observational study of liraglutide 0.3-0.9 mg qd in patients with T2DM and diabetic kidney disease | Liraglutide reduced proteinuria from 2.53 to 1.47 g/g creatinine and reduced the rate of eGFR decline from 6.6 to 0.3 mL/min/1.73 m² per year |
| Desai et al40                                              | 3-year observational study of exenatide and liraglutide compared with other glucose-lowering drugs in patients with T2DM | GLP-1RA treatment decreased albuminuria (−39.6 mg/g; P < .0001) vs other glucose-lowering drugs, which were associated with an increase in albuminuria (+5.6 mg/g) |
| Tuttle et al (AWARD-7; NCT01621178)41                    | 52-week, randomized, open-label trial of dulaglutide 1.5 mg and dulaglutide 0.75 mg compared with insulin glargine, each added to insulin lispro, in patients with T2DM and stage 3-4 CKD | eGFR was higher with dulaglutide 1.5 mg (34.0 mL/min/1.73 m²; P = .005) and dulaglutide 0.75 mg (33.8 mL/min/1.73 m²; P = .009) vs insulin glargine (31.3 mL/min/1.73 m²); reductions in UACR were −22.5% for dulaglutide 1.5 mg, −20.1% for dulaglutide 0.75 mg, and −13.0% for insulin glargine |

| **Cardiovascular outcome trials**                          |              |                                 |
| Pfeffer et al (ELIXA; NCT01147250)42                      | Randomized, placebo-controlled, event-driven study (median 25 months) of lixisenatide 10-20 μg qd in patients with T2DM and a recent acute coronary syndrome | Lixisenatide resulted in a smaller increase in UACR vs placebo (+24% vs +34%; P = .004) |
| Muskiet et al43                                           |              |                                 |
| Holman et al (EXSCEL; NCT01144338)44                      | Randomized, placebo-controlled, event-driven study (median 3.2 years) of exenatide qw 2 mg in patients with T2DM and with or without previous CV disease | The renal composite outcome was lower with exenatide qw vs placebo (5.8% vs 6.5%; HR, 0.85 [95% CI, 0.73-0.98]; P = .027) |
| Bethel et al45                                            |              |                                 |
| Marso et al (LEADER; NCT01179048)46                       | Randomized, placebo-controlled, event-driven study (median 3.8 years) of | Nephropathy was lower with liraglutide vs placebo |

(Continues)
with placebo on cardiovascular outcomes in patients with T2DM who had a wide range of cardiovascular risk (N = 14 752); in addition, ~22% of patients had moderate renal impairment (eGFR 30-59 mL/min/1.73 m²), and 0.1% had severe renal impairment (eGFR <30 mL/min/1.73 m²). A subanalysis of the primary outcome of major adverse cardiovascular events (MACE; first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in prespecified renal function subgroups demonstrated no significant treatment interaction, suggesting no effect modification by renal function status. In the total population, exenatide qw showed improvement in terms of overall difference from placebo for some cardiorenal risk factors, including reductions in systolic BP (SBP: −1.57 mmHg; P < .001) and body weight (−1.27 kg; P < .001). Furthermore, a composite renal outcome consisting of 40% eGFR decline, renal replacement, renal death, or new macroalbuminuria (UACR >300 mg/g) was significantly reduced with exenatide qw vs that with placebo in an analysis adjusted for age, sex, ethnicity, race, region, duration of diabetes, history of cardiovascular event, insulin use, baseline HbA1c, eGFR, and body mass index (5.8% vs 6.5%; adjusted hazard ratio [HR], 0.85 [95% confidence interval (CI), 0.73-0.98]; P = .027) (Figure 1).

The effect of exenatide on renal fibrosing factors has also been examined in patients with T2DM and renal impairment. Transforming growth factor β1 (TGF-β1) and type IV collagen both contribute to extracellular matrix accumulation in DKD. In a small study (N = 31) of patients with T2DM and microalbuminuria (defined as urinary albumin 30-300 mg/24 hours), after 16 weeks, exenatide bid significantly reduced 24-hour urinary albumin (−38.0%), urinary TGF-β1 (−37.3%), and type IV collagen (−25.3%; P < .01 for all), whereas the glimepiride-treated group had no significant reductions in these measurements. Exenatide also resulted in a small, nonsignificant reduction in SBP vs glimepiride. However, neutral effects of exenatide bid on renal function have also been observed. A post hoc analysis of 54 patients without overt nephropathy treated with exenatide bid or insulin glargine for 52 weeks found no significant change from baseline in creatinine clearance or albuminuria (urinary albumin excretion and UACR) among exenatide-treated patients.

An observational study examined renal outcomes with glucose-lowering treatments among 466 patients studied sequentially over 3 years, 275 of whom were treated with a GLP-1RA (exenatide or liraglutide). GLP-1RA-treated patients had no significant changes in urinary albumin excretion and proteinuria compared to patients treated with sulfonylureas or metformin.

**Table 2 (Continued)**

| First author (study name; ClinicalTrials.gov identifier) | Study design | Main renal outcomes of treatment |
|----------------------------------------------------------|--------------|----------------------------------|
| Marso et al (SUSTAIN-6; NCT01720446) | 104-week, randomized, placebo-controlled study of semaglutide 0.5-1.0 mg qw in patients with T2DM and established CV disease or CV risk factors | New or worsening nephropathy was lower with semaglutide vs placebo (3.8% vs 6.1%; HR, 0.64 [95% CI, 0.46-0.88]; P = .005) Results driven by 46% decrease in new-onset macroalbuminuria |
| Gerstein et al (REWIND; NCT01394952) | Randomized, placebo-controlled, event-driven study (median 5.4 years) of dulaglutide 1.5 mg qw in patients with T2DM and established CV disease or CV risk factors | The renal composite outcome was lower with dulaglutide vs placebo (17.1% vs 19.6%; HR, 0.85 [95% CI, 0.77-0.93]; P = .0004) Results driven by 23% decrease in new-onset macroalbuminuria |

Abbreviations: AGE, advanced glycation end products; bid, twice daily; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; qd, once daily; qw, once weekly; RAS, renin-angiotensin system; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; T2DM, type 2 diabetes mellitus; TGF-β1, transforming growth factor β1; UACR, urinary albumin-to-creatinine ratio; UAER, urinary albumin excretion rate.

aAdjusted for baseline HbA1c.
b40% eGFR decline, renal replacement, renal death, or new macroalbuminuria.
cAdjusted for age, sex, ethnicity, race, region, duration of diabetes, history of CV event, insulin use, baseline HbA1c, eGFR, and body mass index.
dNew-onset macroalbuminuria, persistent doubling of serum creatinine level and creatinine clearance <45 mL/min/1.73 m², continuous renal replacement therapy, or death due to renal disease.

eNew macroalbuminuria, sustained ≥30% decline in eGFR, or chronic renal replacement therapy.

with placebo on cardiovascular outcomes in patients with T2DM who had a wide range of cardiovascular risk (N = 14 752); in addition, ~22% of patients had moderate renal impairment (eGFR 30-59 mL/min/1.73 m²), and 0.1% had severe renal impairment (eGFR <30 mL/min/1.73 m²). A subanalysis of the primary outcome of major adverse cardiovascular events (MACE; first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in prespecified renal function subgroups demonstrated no significant treatment interaction, suggesting no effect modification by renal function status. In the total population, exenatide qw showed improvement in terms of overall difference from placebo for some cardiorenal risk factors, including reductions in systolic BP (SBP: −1.57 mmHg; P < .001) and body weight (−1.27 kg; P < .001). Furthermore, a composite renal outcome consisting of 40% eGFR decline, renal replacement, renal death, or new macroalbuminuria (UACR >300 mg/g) was significantly reduced with exenatide qw vs that with placebo in an analysis adjusted for age, sex, ethnicity, race, region, duration of diabetes, history of cardiovascular event, insulin use, baseline HbA1c, eGFR, and body mass index (5.8% vs 6.5%; adjusted hazard ratio [HR], 0.85 [95% confidence interval (CI), 0.73-0.98]; P = .027) (Figure 1).
patients had a mean decrease in albuminuria (−39.6 mg/g; P < .0001) compared with a mean increase in albuminuria (+5.6 mg/g) in patients treated with unspecified glucose-lowering drugs. Among those with macroalbuminuria at baseline, greater proportions of GLP-1RA-treated patients developed microalbuminuria (UACR 30-300 mg/g; 23%) or normoalbuminuria (UACR <30 mg/g; 2.8%) compared with those receiving unspecified glucose-lowering therapies (microalbuminuria, 12.3%; normoalbuminuria, 0%; P = .0005). SBP was also lower among patients receiving GLP-1RAs (by 3 mmHg).

### 2.2 Lixisenatide

A post hoc meta-analysis of nine RCTs that examined lixisenatide in patients with normal renal function or with mild or moderate renal impairment found no difference in efficacy on the basis of renal status (end-of-study placebo-adjusted differences in HbA1c of −0.52%, −0.50%, and −0.85% [−5.7, −5.5, and −9.3 mmol/mol] for creatinine clearance subgroups ≥90, 60-89, or 30-59 mL/min, respectively). However, a higher incidence of gastrointestinal AEs occurred with mild renal impairment vs the incidence with normal renal function.

In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study (N = 6068), which examined cardiovascular outcomes with lixisenatide treatment in patients with T2DM who had a recent acute coronary syndrome, 23% of patients had eGFR 30 to 60 mL/min/1.73 m² and 0.1% had eGFR <30 mL/min/1.73 m². A subgroup analysis of the primary outcome (time to event for composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) demonstrated no significant interactions in prespecified renal function subgroups. In the total population, lixisenatide showed improvement in terms of average difference from placebo across all visits for some cardiorenal risk factors, including modest reductions in SBP (−0.8 mmHg; P = .001) and body weight (−0.7 kg; P < .001). In addition, lixisenatide resulted in a smaller increase in the UACR vs placebo (+24% vs +34%; P = .004) after 108 weeks of treatment. Subgroup analyses demonstrated significant reductions in UACR with lixisenatide vs those with placebo among patients with macroalbuminuria (UACR >300 mg/g) at baseline (treatment difference for percent change from baseline: −39.18%; P = .0070). Further, lixisenatide showed a reduced risk of progression to macroalbuminuria compared...
with placebo when adjusted for baseline HbA1c (6.5% vs 7.7%; adjusted HR, 0.81 [95% CI, 0.66-0.99]; \( P = .0404 \)).

### 2.3 | Liraglutide

Multiple studies have examined the glycemic effects of liraglutide in patients with T2DM and renal impairment. A 26-week RCT investigating liraglutide 1.8 mg (n = 140) vs placebo (n = 139) in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m²) demonstrated significant HbA1c reductions with liraglutide (−1.05% vs −0.38% with placebo [−11.5 vs −4.2 mmol/mol]; \( P < .0001 \)), with no effect on renal function as measured by UACR or eGFR.\(^{54}\) In a separate RCT of 24 patients with dialysis-dependent ESRD, liraglutide reduced HbA1c at 12 weeks (−0.5% [−5.5 mmol/mol]) from baseline (6.7% [50 mmol/mol]), but not significantly vs placebo.\(^{55}\) Nausea and vomiting occurred more frequently with liraglutide than placebo in this subpopulation. In a meta-analysis of six 26-week RCTs of liraglutide, patients with normal, mild, or moderate/severe renal impairment had similar mean HbA1c reductions (liraglutide 1.2 mg: −1.29%, −1.40%, and −1.34% [−14.1, −15.3, and −14.6 mmol/mol], respectively; liraglutide 1.8 mg: −1.40%, −1.34%, and −1.39% [−15.3, −14.6, and −15.2 mmol/mol], respectively), although the number of patients in the moderate/severe group was too small to draw firm conclusions in this subpopulation.\(^{56}\) There was a trend toward increased nausea in patients with moderate or severe renal impairment.

The effects of liraglutide on renal measurements have also been examined in patients with T2DM and impaired renal function. In a 12-month longitudinal study of liraglutide (N = 84), eGFR reached the normal range (>90 mL/min using the Chronic Kidney Disease-Epidemiology Collaboration equation) in 7 of 41 patients with baseline eGFR <90 mL/min.\(^{38}\) Furthermore, three of five patients with baseline microalbuminuria returned to normal albuminuria. Among 23 patients with DKD who had received renin-angiotensin system blockers, 12-month treatment with liraglutide significantly decreased proteinuria from 2.53 to 1.47 g/g creatinine and reduced the rate of eGFR decline from 6.6 to 0.3 mL/min/1.73 m² per year.\(^{39}\) In a small randomized controlled crossover trial (N = 32), treatment with liraglutide for 12 weeks significantly reduced the urinary albumin excretion rate vs placebo (−32%; \( P = .017 \)) in patients with persistent albuminuria (UACR ≥30 mg/g) and eGFR ≥30 mL/min/1.73 m² who were receiving stable renin-angiotensin system-blocking treatment, further suggesting a renoprotective role for liraglutide.\(^{36}\)

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (N = 9340), which included ~23% of patients with moderate or severe renal impairment, studied cardiovascular outcomes during treatment with liraglutide vs those with placebo.\(^{46}\) A prespecified subgroup analysis comparing the primary outcome of MACE in patients with moderate or severe renal impairment (eGFR <60 mL/min/1.73 m²) vs patients with eGFR ≥60 mL/min/1.73 m² showed a greater benefit of liraglutide in the moderate or severe renal impairment group (\( P = .01 \)). However, a sensitivity analysis showed no clinically meaningful treatment interaction based on renal function. The LEADER trial also showed a beneficial effect of GLP-1RAs on some renal outcomes. The incidence of nephropathy (defined as new-onset macroalbuminuria or a doubling of serum creatinine level and eGFR ≤45 mL/min/1.73 m², the need for continuous renal replacement therapy, or death from renal disease) was lower with liraglutide vs that with placebo (5.7% vs 7.2%; HR, 0.78 [95% CI, 0.67-0.92]; \( P = .003 \)) (Figure 1).\(^{46}\) This result was driven by a 26% reduction of new-onset persistent macroalbuminuria.\(^{47}\) Placebo-subtracted reductions in cardiorenal risk factors, including SBP (−1.2 mmHg) and body weight (−2.3 kg) at 36 months, were also observed.\(^{46}\)

### 2.4 | Dulaglutide

A pooled analysis of renal effects and safety in nine phase 2 and 3 studies of dulaglutide included 6005 patients, of whom 4.4% had persistent eGFR <60 mL/min/1.73 m², 3.0% had persistent macroalbuminuria, and 7.1% had eGFR <60 mL/min/1.73 m² and/or macroalbuminuria.\(^{37}\) Renal end points were evaluated in six of the trials, while renal safety was evaluated in all nine trials. At 26 weeks, dulaglutide slightly decreased albuminuria, reflected by larger reductions in median percent change in UACR vs placebo (−16.7% vs −10.0%; \( P = .043 \)), active comparators (−20.0% vs −12.5%; \( P = .054 \)), and insulin glargine (−20.0% vs −9.4%; \( P = .100 \)). No significant differences in eGFR were observed with dulaglutide vs those with other treatments. In addition, dulaglutide was not associated with AEs indicative of potential acute renal failure.\(^{37}\)

The AWARD-7 RCT investigated the effects of dulaglutide 1.5 mg, dulaglutide 0.75 mg, or insulin glargine, each added to insulin lispro, in 576 patients with T2DM and moderate-to-severe CKD (stages 3-4).\(^{41}\) After 52 weeks, similar HbA1c reductions from baseline were observed with dulaglutide 1.5 mg (−1.1% [−12.0 mmol/mol]), dulaglutide 0.75 mg (−1.1% [−12.0 mmol/mol]), and insulin glargine (−1.0% [−10.9 mmol/mol]; \( P < .0001 \) for all), while dulaglutide was associated with greater weight loss and a lower rate of hypoglycemia.
Dulaglutide was also associated with a reduced decline in eGFR (a secondary outcome of the trial) compared with insulin glargine. After 52 weeks, eGFR was higher with dulaglutide 1.5 mg (34.0 mL/min/1.73 m²; \( P = .005 \) vs insulin glargine) and dulaglutide 0.75 mg (33.8 mL/min/1.73 m²; \( P = .009 \) vs insulin glargine) compared with insulin glargine (31.3 mL/min/1.73 m²). Reductions in the secondary outcome of UACR were numerically, although not significantly, greater with dulaglutide (dulaglutide 1.5 mg, −22.5%; dulaglutide 0.75 mg, −20.1%; insulin glargine, −13.0%). Thus, while glycemic efficacy was similar with dulaglutide and insulin glargine, dulaglutide demonstrated additional potential renal benefits.

The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial (N = 9901), which included ~22% of patients with eGFR <60 mL/min/1.73 m², studied cardiovascular outcomes with dulaglutide vs placebo among patients with T2DM who had a previous cardiovascular event or cardiovascular risk factors. The incidence of a composite renal outcome, comprising UACR >33.9 mg/mmol in those with a lower baseline concentration, sustained ≥30% decline in eGFR, or chronic renal replacement therapy, was lower with dulaglutide vs placebo (17.1% vs 19.6%; HR, 0.85 [95% CI, 0.77-0.93]; \( P = .0004 \)) (Figure 1). This result was driven by a 23% reduction of new-onset macroalbuminuria. Placebo-subtracted reductions in cardiorenal risk factors, including SBP (−1.70 mmHg; \( P < .0001 \)) and body weight (−1.46 kg; \( P < .0001 \)), were also observed.

### Effect of GLP-1RAs on renal outcomes across cardiovascular outcome trials

A recent meta-analysis of cardiovascular outcomes trials, including EXSCEL, ELIXA, LEADER, and SUSTAIN-6, examined the effect of GLP-1RAs on progression of kidney disease. GLP-1RAs were associated with an 18% reduction in the risk of a broad composite renal outcome consisting of new-onset macroalbuminuria, worsening of eGFR, ESRD, or death due to renal causes compared with placebo (HR, 0.82 [95% CI, 0.75-0.89]; \( P < .001 \)). The reduction in risk was driven primarily by a reduction in macroalbuminuria, as excluding this outcome from the analysis resulted in a non-significant risk reduction. These results suggest that GLP-1RAs reduce renal events mainly by reducing macroalbuminuria.

### 3 MECHANISMS OF ACTION

Renal benefits of GLP-1RAs may be attributable to favorable effects on cardiorenal risk factors, including improved glucose control, BP lowering, and weight loss. In addition, GLP-1RAs may have direct renal effects, as GLP-1 receptors are expressed in the kidney. A gut-renal axis is possible, with regulatory linkages through the gastrointestinal tract, central nervous system, and kidney (Figure 2). The main physiologic effect of GLP-1 on the kidney may possibly be to reduce prandial intraglomerular pressure to reduce macronutrient loss in the glomerular filtrate. This would allow increased time for macronutrient uptake by other tissues without having to expend energy to transport macronutrients back into the body through the proximal tubule or overwhelming the proximal tubule reuptake system for macronutrients, such as glucose, amino acids, and free fatty acids. It may do so by decreasing sympathetic activity at the glomerulus through the central nervous system or by direct effects on the mesangium and renal interstitium.

Several studies have reported GLP-1RA-induced natriuresis in healthy subjects and in patients with T2DM possibly resulting from decreased activity of the sodium-hydrogen exchanger 3 (NHE3). GLP-1 receptor activation has been shown to inhibit activity of NHE3 in the proximal tubule, which would increase distal tubular sodium transport in the kidney to the macula densa, resulting in tubular glomerular feedback with a reduction in intraglomerular pressure, hyperfiltration, and renin-angiotensin system activity. Reducing intraglomerular pressure would be expected to have an antiproteinuric effect in the diabetic kidney and help preserve kidney function.
CONCLUSIONS

DKD is a common comorbidity of T2DM; therefore, glucose-lowering treatments that are efficacious, do not increase hypoglycemia, and may have additional benefits for the kidney are of interest. In the limited number of studies to date investigating the effect of renal function on the efficacy of GLP-1RA treatment, GLP-1RAs improved glycemic control in patients with mild to moderately impaired kidney function, without significant differences compared with patients with normal renal function.

Hyperglycemia, obesity, and hypertension all contribute to the development of kidney and heart disease, and the multiple effects of GLP-1RAs for improving glycemic control, body weight, and BP may be beneficial for delaying the onset or progression of DKD. However, GLP-1RAs may potentially have direct effects on the kidney as well.

In animal models, GLP-1RAs may have a renoprotective effect, as demonstrated by improvement in some renal function measures and histologic features. In addition, these agents were associated with a lower incidence of diabetic nephropathy and/or albuminuria compared with placebo in several large clinical studies. These observations should be the basis for continued research efforts into the long-term effects of GLP-1RAs on kidney function and mechanistic studies examining how GLP-1RAs affect the kidney, potentially through the gut-renal axis.

For now, GLP-1RAs should be considered in combination with other complementary glucose-lowering medications in patients with CKD, due to their safety and ability to lower glucose in a glucose-dependent manner.

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DISCLOSURE

Dr Sloan has served as a consultant, researcher, and speaker for AbbVie, AstraZeneca, Boehringer Ingelheim-Lilly, Janssen, Merck, Novo Nordisk, Pfizer, and Salix.

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