REVIEW

Glucagon-Like Peptide-1 Receptor Agonist Use in People Living with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Narrative Review of the Key Evidence with Practical Considerations

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin-mimetic agents that are effective adjuncts in the treatment of diabetes. This class of medications is also associated with promoting weight loss and a low risk of hypoglycemia, and some have been shown to be associated with a significant reduction of major cardiovascular events. Mounting evidence suggests that GLP-1 RAs have benefits beyond reducing blood glucose that include improving kidney function in people living with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD), a common microvascular complication of T2DM. Several large clinical studies, the majority of which are cardiovascular outcome trials, indicate that GLP-1 RA therapy is safe and tolerable for people living with T2DM and compromised renal function, and also suggest that GLP-1 RAs may have renoprotective properties. Although evidence from clinical trials has shown GLP-1 RAs to be safe and efficacious in people living with T2DM and renal impairment, their use is uncommon in this patient population. With continuing developments in the field of GLP-1 RA therapy, it is important for physicians to understand the benefits and practical use of GLP-1 RAs, as well as the clinical evidence, in order to achieve positive patient outcomes. Here, we review evidence on GLP-1 RA use in people living with T2DM and CKD and summarize renal outcomes from clinical studies. We provide practical considerations for GLP-1 RA use to provide an added benefit to guide treatment in this high-risk patient population.

GRAPHICAL ABSTRACT

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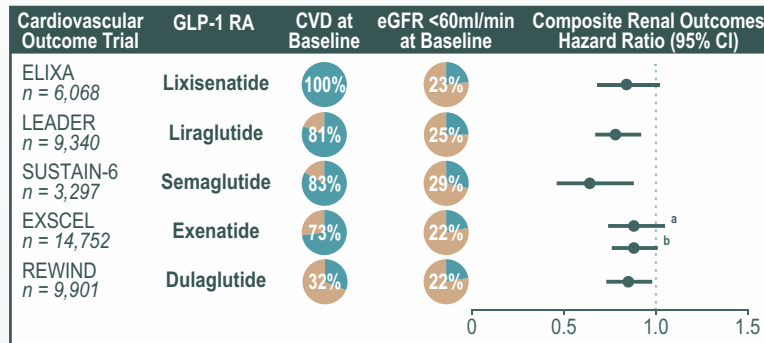
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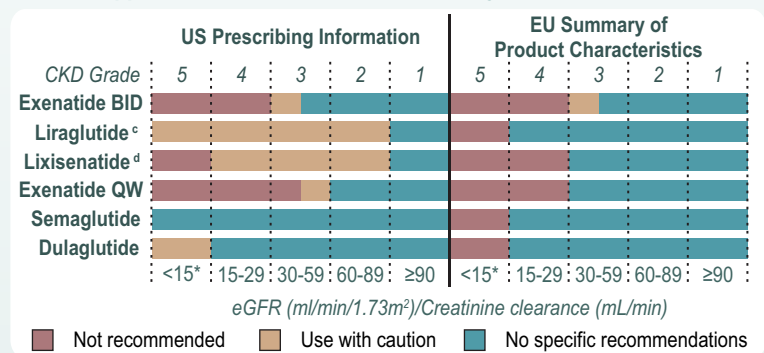
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Renal outcomes from GLP-1 RA CVOTs

Cardiovascular Outcome Trial	GLP-1 RA	CVD at Baseline	eGFR <60ml/min at Baseline	Composite Renal Outcomes Hazard Ratio (95% CI)
ELIXA n = 6,068	Lixisenatide	100%	23%	
LEADER n = 9,340	Liraglutide	81%	25%	
SUSTAIN-6 n = 3,297	Semaglutide	83%	29%	
EXSCEL n = 14,752	Exenatide	73%	22%	a / b
REWIND n = 9,901	Dulaglutide	32%	22%	

(Hazard ratio axis: 0 — 0.5 — 1.0 — 1.5)

Use of approved GLP-1 RA in the US and EU by CKD Grade

	US Prescribing Information					EU Summary of Product Characteristics				
CKD Grade	5	4	3	2	1	5	4	3	2	1
Exenatide BID										
Liraglutide c										
Lixisenatide d										
Exenatide QW										
Semaglutide										
Dulaglutide										
	<15*	15-29	30-59	60-89	≥90	<15*	15-29	30-59	60-89	≥90

eGFR (ml/min/1.73m²)/Creatinine clearance (mL/min)

■ Not recommended   ■ Use with caution   ■ No specific recommendations

Frequency and recommended dosages of currently available GLP-1 RAs

Generic name (Commercial)	Frequency	Initial Dosage	Recommended Dosage
Exenatide BID (Byetta©)	Twice-daily	5 mcg for 1 month	5 or 10 mcg f
Liraglutide (Victoza©)	Once-daily	0.6 mg for 1 week	1.2 or 1.8 mg
Lixisenatide (Lyxumia©/Adlyxin©)	Once-daily	10 mcg for 14 days	20 mcg
Oral semaglutide (Rybelsus©)	Once-daily	3 mg for 1 month	7 or 14 mg
Exenatide QW (Bydureon©)	Once-weekly	2 mg	2 mg
Semaglutide (Ozempic©)	Once-weekly	0.25 mg for 4 weeks	0.5 or 1 mg
Dulaglutide e (Trulicity©)	Once-weekly	0.75 or 1.5 mg	0.75, 1.5, 3.0, or 4.5 mg

No dose adjustment is needed for patients with renal impairment, with the following exception: Caution should be applied when initiating or escalating doses of Byetta from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30-50 mL/min).

Notes: * For the purposes of graphically summarizing the information on GLP-1 RA use in people with renal impairment provided in the US Prescribing Information (USPI) and EU Summary of Product Characteristics (SmPC), end stage renal disease (ESRD) is defined as an eGFR less than 15 mL/min/1.73m². ª Renal composite consisting of 40% eGFR decline, renal replacement, or renal death. ᵇ Renal composite consisting of eGFR decline, renal replacement, or renal death plus macroalbuminuria. ᶜ Limited experience exists for liraglutide use in people with ESRD. ᵈ Limited experience exists for lixisenatide use in people with eGFR from 15 to 30 mL/min/1.73m². ᵉ Based on EMA SPC, the recommended dose is 0.75 mg once-weekly if used as monotherapy and 1.5 mg once-weekly if used as an add-on therapy. The initial dose for dulaglutide is 0.75 mg, as indicated in the FDA-approved label for Trulicity. ᶠ The EMA Summary of Product Characteristics (SPC) recommends a dose of 5 or 10 mcg for exenatide twice-daily, while the FDA-approved label recommends 10 mcg twice daily after one month based on clinical response. **Abbreviations:** BID, twice per day; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; QW, once per week; UACR, urinary-to-albumin ratio.

PLAIN LANGUAGE SUMMARY

Type 2 diabetes mellitus (T2DM) is a common disorder characterized by insulin resistance and dysfunction of insulin-producing beta cells of the pancreas. People living with T2DM have an increased risk of developing complications, including chronic kidney disease (CKD), which itself is associated with increased mortality. Both the American Diabetes Association and Kidney Disease Improving Global Outcomes organization provide updated pharmacological recommendations for treating T2DM in people with CKD that include the use of sodium-glucose co-transporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1 RAs). GLP-1 RAs are effective and safe treatments for controlling blood sugar levels and reducing body weight, and evidence from large clinical trials also suggests that GLP-1 RAs may be renoprotective. Despite the benefits of GLP-1 RAs, they are not commonly prescribed in people living with T2DM and CKD. Healthcare practitioners need to be aware of the most recent information so that they can make informed decisions when selecting treatment options. The objective of this review is to summarize the main renal outcomes from clinical studies while providing practical guidance on the use of GLP-1 RAs.

Keywords: Chronic kidney disease; Diabetic kidney disease; Glucagon-like peptide-1 receptor agonists; Renal impairment; Type 2 diabetes mellitus

Key Summary Points

Chronic kidney disease (CKD), characterized by a reduced estimated glomerular filtration rate (eGFR) or the presence of albuminuria and/or other markers of kidney damage for over 3 months, is a common complication of type 2 diabetes mellitus (T2DM) associated with high morbidity and mortality.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a safe and effective treatment for T2DM that augment insulin secretion and suppress glucagon release via the stimulation of GLP-1 receptors.

Evidence from several large clinical studies indicate that GLP-1 RA therapy is safe for people living with T2DM and compromised renal function and may have renoprotective properties mediated via direct and indirect mechanisms; however, despite evidence of safety and efficacy, and the low risk of hypoglycemia, GLP-1 RA use is uncommon in people living with T2DM and renal impairment.

We review the evidence of GLP-1 RA use in people living with T2DM and CKD and summarize the renal outcomes from key clinical studies. We also provide practical considerations for GLP-1 RA use to provide an added benefit to guide treatment in this high-risk patient population.

The current evidence indicates that GLP-1 RA could add to the arsenal available that addressing persistent gaps in the care of people living with T2DM with or at the risk of developing CKD while reducing the residual renal risk present in those who have already developed CKD.

				Persistent Albuminuria Categories Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR Categories (ml/min/1.73m²) Description and Range	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60-89		Monitor	Refer*
	G3a	Mild to moderately decreased	45-59	Monitor	Monitor	Refer
	G3b	Mild to severely decreased	30-44	Monitor	Monitor	Refer
	G4	Severely decreased	15-29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Fig. 1 Classification of CKD based on GFR and albuminuria categories. The risk of CKD progression, morbidity, and mortality are depicted by color (green, low risk; yellow, moderately increased risk; orange, high risk; red, very high risk) and include general decision-making recommendations that are based on expert opinion based on GFR and albuminuria. "Monitor" indicates that eGFR and albuminuria be monitored more frequently. "Refer" indicates referral to a nephrologist; "Refer*" indicates that clinicians may wish to discuss treatment or referral with their nephrology service. *CKD* Chronic kidney disease, *GFR* glomerular filtration rate. Figure is reproduced with permission (Kidney Disease: Improving Global Outcomes CKD Work Group [133])

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.17315696

INTRODUCTION

Type 2 Diabetes Mellitus and Chronic Kidney Disease

Chronic kidney disease (CKD) in people living with type 2 diabetes mellitus (T2DM) involves the gradual loss of kidney function, characterized by a reduced estimated glomerular filtration rate (eGFR) or the presence of albuminuria for > 3 months [1]. The Kidney Disease: Improving Global Outcomes (KDIGO) organization provide a classification system for determining CKD risk based on *cause*, *GFR*, and *albuminuria* (Fig. 1) [2]. Of the complications that arise from T2DM, CKD is among the most common, affecting approximately 20–40% of people [3]. Within 10 years of T2DM diagnosis, 24.9% of people develop microalbuminuria, 5.3% develop macroalbuminuria, and 0.8% develop advanced CKD that includes persistently elevated plasma creatinine or the need for renal replacement therapy [4]. The progression of CKD can lead to end-stage renal disease

(ESRD), increasing the risk of kidney failure with a need for renal replacement therapy involving dialysis or renal transplant. The predominance of CKD accounts for the increased mortality observed in people living with T2DM [5]. Despite advances in the understanding of disease pathogenesis, and the increased availability of treatment options, the prevalence of ESRD continues to rise in people living with T2DM [6]. With diabetes and CKD projected to be the seventh and fifth leading cause of premature mortality worldwide by 2040, respectively [7], novel and effective treatment options are critical.

Treatments for CKD in People Living with T2DM

Findings from systematic reviews and meta-analyses indicate that improved renal outcomes can be achieved through obesity management [8], intensive glycemic control using glucose-lowering medications [9], and anti-hypertension drugs [10]. A caveat of using these medications is that many have reduced renal clearance due to declining kidney function or are contraindicated and often require careful dose adjustments [11–13]. Furthermore, several of these therapies have only a modest glucose-lowering effect in people with reduced glomerular filtration [14]. For these reasons, limited treatment options exist for this patient population.

Both the American Diabetes Association (ADA), in conjunction with the European Association for the Study of Diabetes (EASD), and KDIGO provide clinical practice guidelines for diabetes management in CKD [2, 3]. These guidelines recommend a comprehensive strategy be followed to reduce risks of CKD in people living with T2DM and are summarized in Fig. 2. In the Standards of Medical Care in Diabetes—2021, the ADA recommend that for people with indications of high risk or established CKD either a sodium-glucose co-transporter-2 inhibitor (SGLT2i) or a glucagon-like peptide-1 receptor agonist (GLP-1 RA) be considered as a treatment option, independently of metformin use [15]. Guidelines provided by KDIGO

similarly recommend SGLT2i for people with an eGFR of $\geq$ 30 ml/min/1.73 m^2 due to the vascular and renal benefit, despite its modest effect on glucose control [2]. The current KDIGO guidelines do not recommend SGLT2i for people in more advanced stages of CKD (eGFR < 30 ml/min/1.73 m^2), as the efficacy for lowering glycated hemoglobin (HbA1c) is blunted. This is indicated in the label information for empagliflozin [16, 17] and canagliflozin [18, 19], with both of these SGLT2i not recommended for individuals with an eGFR < 30 ml/min/1.73 m^2. For dapagliflozin, recently updated prescribing information indicates that initiation of treatment with this SGLT2i is not recommended in individuals with an eGFR < 25 ml/min/1.73 m^2 [20, 21]. In people with T2DM and CKD, who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or are unable to use those medications due to contraindications, long-acting GLP-1 RAs are recommended [2]. The use of GLP-1 RAs in this population is not only due to the limited use of SLGT2i in more severe stages but also because the glycemic lowering efficacy of SLGT2i is reduced in individuals with moderate renal impairment and likely absent in those with severe renal impairment. These anti-hyperglycemic therapies have shown promise in directly improving renal outcomes and reducing CKD progression independently of glycemic control [2, 15]. The use of GLP-1 RAs is also associated with a low risk for hypoglycemia, which is a limiting factor for many other diabetes medications in people with renal impairment.

Treatment with GLP-1 RA in People Living with T2DM and CKD

The GLP-1 RA class of medications are incretin-mimetics that have been available from 2005, of which exenatide was the first to receive approval from the U.S. Food and Drug Administration (FDA). Since then, additional GLP-1 RAs have gained regulatory approval in both the USA and Europe. These medications have been demonstrated to be safe and effective in controlling glycemia through HbA1c reduction
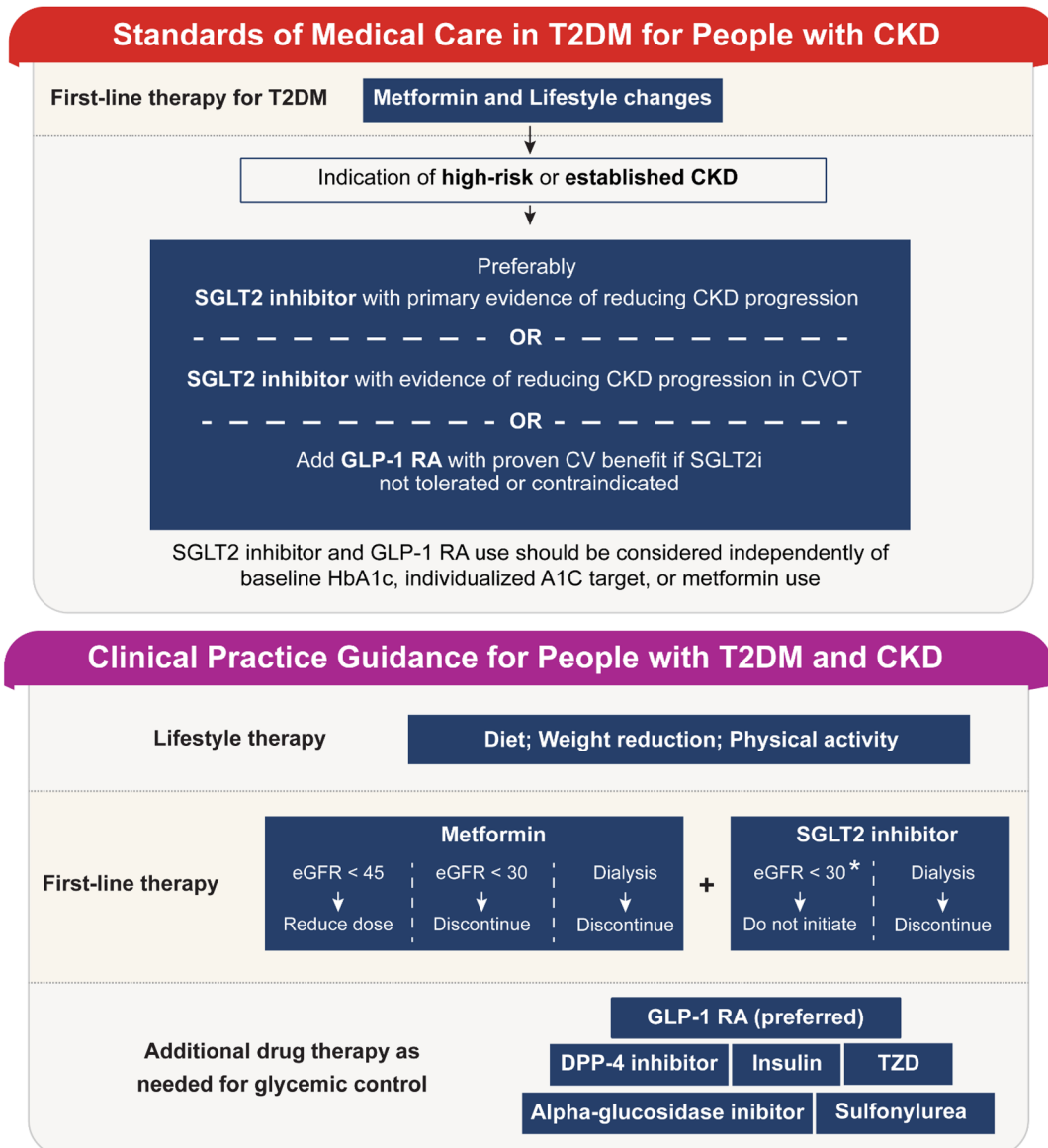
Fig. 2 Summary of ADA and KDIGO guidelines of use for glucose-lowering medication in people living with T2DM and CKD. Upper panel: ADA guidelines were abbreviated for specific treatment for people living with T2DM and CKD. Proven CVD benefit means it has label indication of reducing CVD events. For more context regarding glucose lowering medication in this population, refer to the *Standards of Medical Care in Diabetes—2021* [15]. Lower panel: KDIGO recommend guidelines of glycemic management for people living with T2DM and CKD begin with lifestyle therapy followed by first-line pharmacological therapy with metformin and SGLT2i. For people contraindicated for SGLT2i, GLP-1 RAs are recommended. Additional drug therapy is guided by patient preferences, comorbidities, eGFR, and cost, and includes people with eGFR < 30 ml/min per 1.73 m^2 or those treated with dialysis [2]. *: Dapagliflozin; it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 ml/min/1.73 m^2 [20, 21]. *ADA* American Diabetes Association, *CV* cardiovascular, *CVOT* cardiovascular outcome trial, *DPP-4* dipeptidyl peptidase-4, *eGFR* estimated GFR, *GLP-1 RA* glucagon-like peptide-1 receptor antagonist, *HbAc1* glycated hemoglobin, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *T2DM* type 2 diabetes mellitus, *TZD* thiazolidinediones. The figure was created by Lilly using the data from the American Diabetes Association [15] and Kidney Disease: Improving Global Outcomes Diabetes Work Group [2]. Permission is not required as only data were used

[22]. The glucose-lowering effect is due to GLP-1 RA binding to the glucagon-like peptide-1 (GLP-1) receptor in the pancreas where insulin secretion is promoted while glucagon secretion is suppressed. Additional benefits include improved metabolic control and weight loss by acting on the gut, where they slow gastric emptying, and the central nervous system, where they suppress appetite [23, 24]. Target tissues for GLP-1 are highlighted in Fig. 3 and include the heart and kidney [25]. The GLP-1 RAs have been shown to improve cardiovascular outcomes, with liraglutide, semaglutide, albiglutide, and dulaglutide demonstrating a reduction of major cardiovascular events in people with established cardiovascular disease [26–29]. Dulaglutide has also demonstrated reduced cardiovascular outcomes in people without established cardiovascular disease. These agents act on the kidneys, with clinical evidence suggesting they promote renal protection [30–33]. Direct renal benefits include decreased glomerular atherosclerosis, inhibition of the renin–angiotensin system, stimulation of proximal tubule natriuresis, and reduced fibrosis, inflammation, and oxidative stress, while they indirectly reduce renal risk factors by reducing hypertension, decreasing weight, and improving glycemic control. The potential direct and indirect benefits mediated by GLP-1 RA are summarized in Fig. 4. For a more detailed overview on the potential mechanisms by which GLP-1 RA may exert these effects on the kidney, we refer readers to recent review articles [34, 35]. Importantly unlike many other glucose-lowering medications, including metformin, sulfonylureas, and alpha-glucosidase inhibitors [36], GLP-1 RAs do not have a relative contraindication in people with renal impairment.

Despite demonstrating benefits beyond blood glucose control, GLP-1 RAs are not yet commonly prescribed in people living with T2DM and CKD [37]. The purpose of this review is to summarize the clinical evidence regarding the effect of GLP-1 RAs on renal outcomes in people living with T2DM and CKD and to provide an overview of the practical aspects of use of these compounds that include specific considerations for this high-risk patient population.

EVIDENCE FROM CLINICAL TRIALS

General Overview of Cardiovascular Outcome Trials

Currently, clinical trials that report kidney outcomes as the primary endpoint of GLP-1 RA therapy are lacking. The most reliable evidence for positive renal outcomes from GLP-1 RA use comes from cardiovascular outcomes trials (CVOTs); however, these studies were not designed or powered for this specific purpose. These trials were conducted in response to guidelines mandated by the U.S. FDA in 2008 which suggested that sponsors evaluate new T2D therapies for cardiovascular risk [38]. Since 2015, seven CVOTs have been completed that assess the cardiovascular safety and efficacy of GLP-1 RAs, including ELIXA (lixisenatide) [39], LEADER (liraglutide) [26], SUSTAIN-6 (semaglutide) [27], EXSCEL (exenatide) [40], HARMONY (albiglutide) [28], REWIND (dulaglutide) [29], and PIONEER-6 (oral semaglutide) [41]. Although only the CVOTs investigating liraglutide, semaglutide, albiglutide, and dulaglutide independently demonstrated a reduction in the three-component major adverse cardiovascular events (MACE-3) score (consisting of cardiovascular death, myocardial infarction, and stroke), a meta-analysis combining results demonstrated that GLP-1 RA treatment decreased MACE-3 by 12% (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.82–0.94), indicating improved cardiovascular outcomes in people living with T2DM and established cardiovascular disease [42].

Evidence Regarding Renal Outcomes With GLP-1 RA Use

Although no clinical trials have been published reporting kidney outcomes as the primary endpoint of GLP-1 RA therapy, several CVOTs indicate that GLP-1 RAs may promote renal benefits and delay CKD progression through secondary or exploratory endpoints that include decreased onset of macroalbuminuria and reduced eGFR decline [43–45]. Secondary endpoints of the CVOTs LEADER [46],
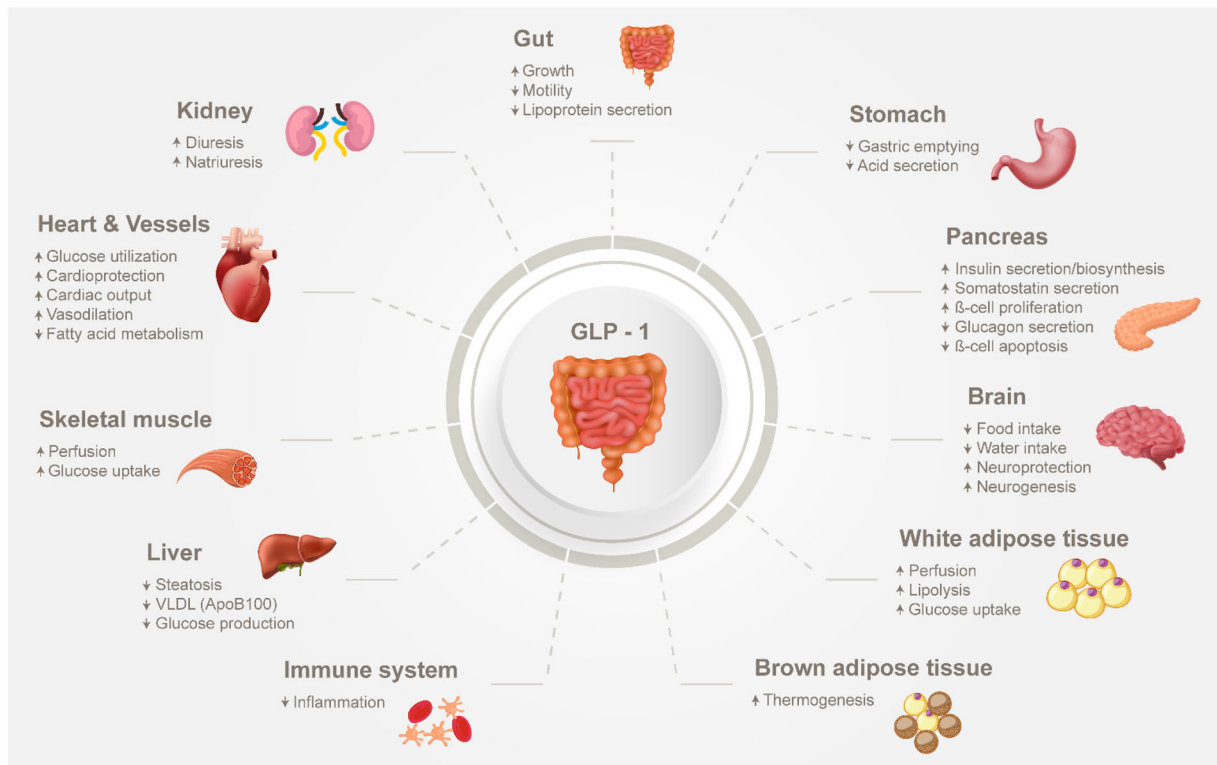
Fig. 3 Physiological targets of GLP-1. GLP-1 exhibits pleotropic attributes that affect various tissues and organs, including the pancreas, stomach, brain, liver, adipose, heart, and kidney. *GLP-1* Glucagon-like peptide-1, *VLDL* very-low-density lipoprotein. The figure was created by Lilly using the data from Muskiet et al. [25]; permission is not required as only data were used

SUSTAIN-6 [27], and REWIND [32] showed reduced progression of nephropathy with no increase in acute kidney injury. Although the reported outcomes differ from trial to trial, there are strong indications that give confidence to the net benefit of GLP-1 RAs. Indeed, in a meta-analysis of CVOTs examining renal outcomes of GLP-1 RAs, the authors found that GLP-1 RAs clearly reduced the risk of worsening of kidney function when assessed using a broad composite renal outcome [42]. A summary of these large clinical studies is presented below and summarized in Table 1.

The ELIXA Trial (Once-Daily Lixisenatide)
The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) CVOT trial assessed the effects of lixisenatide on cardiovascular outcomes in people living with T2DM with a previous acute coronary event [47]. In a

following exploratory analysis, renal outcomes were investigated that consisted of percentage change in urine albumin-to-creatinine ratio (UACR) and eGFR according to prespecified albuminuria status at baseline using a mixed-effect model with repeated measures. Lixisenatide was associated with a reduced risk of new-onset macroalbuminuria (> 300 mg/g) and reduced progression of UACR in people with macroalbuminuria when compared with placebo; however, no significant differences in eGFR decline were identified in any of the treatment groups [44].

The LIRA-RENAL Trial (Once-Daily Liraglutide)
The Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL) trial
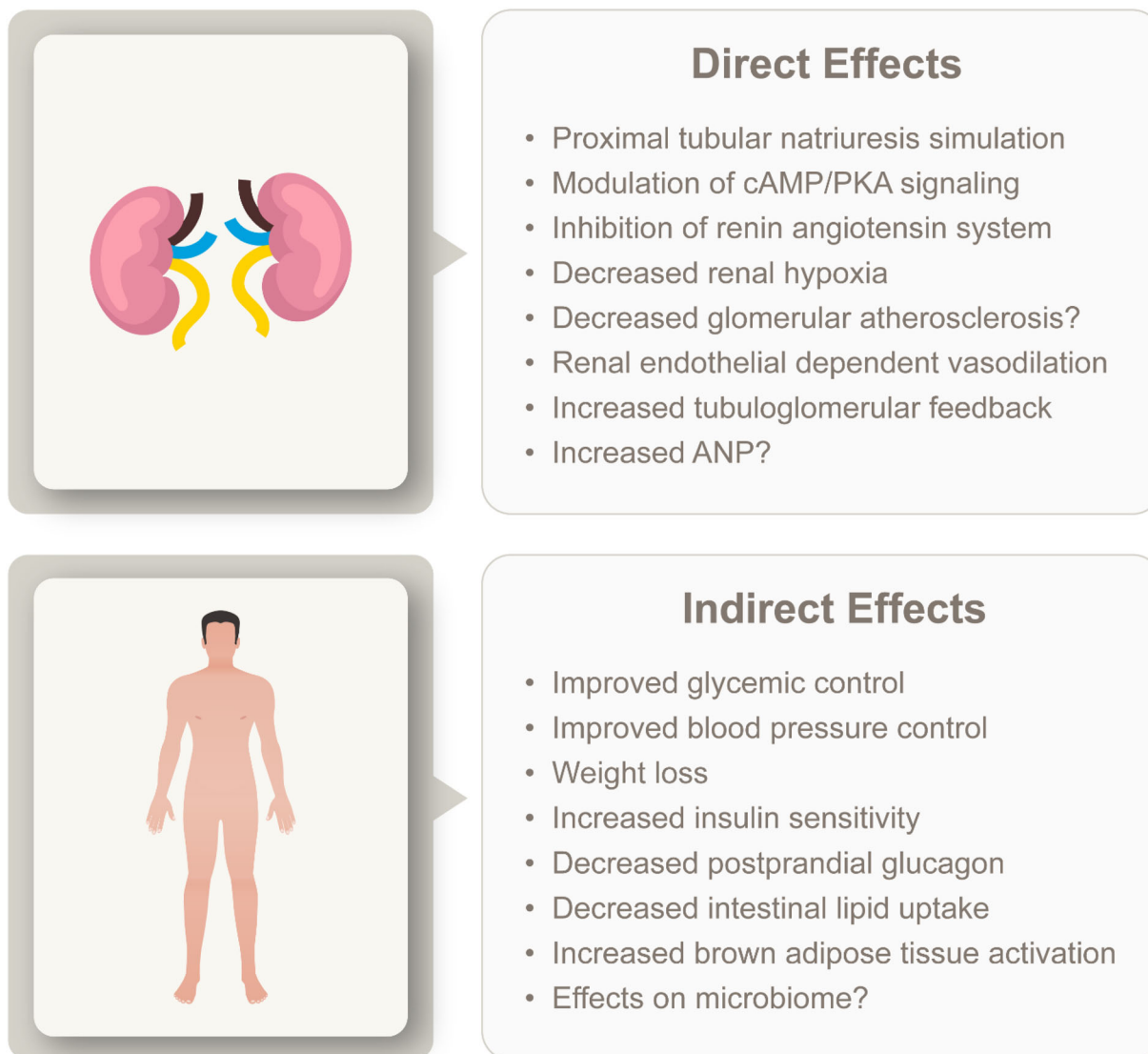
Fig. 4 Potential direct and indirect renoprotective effects of GLP-1 RAs. *cAMP/PKA* Cyclic adenosine monophosphate/protein kinase A, *ANP* atrial natriuretic peptide. The figure was created by Lilly using the data from Greco et al. (see Table 1) [35]. Permission is not required as only data were used

investigated the efficacy and safety of liraglutide as an add-on to existing glucose-lowering medications in people with inadequately controlled T2DM and moderate renal impairment (stage 3 CKD, eGFR 30–59 ml/min/1.73 m^2) [48]. After 26 weeks, along with a greater change in HbA1c from baseline, no changes in renal function were observed with liraglutide when compared to placebo.

The LEADER Trial (Once-Daily Liraglutide)
The LEADER trial primarily assessed the cardiovascular safety of once-daily liraglutide compared to placebo [26]. The trial included 9340 participants ($\geq$ 50 years; HbA1c $\geq$ 7.0%), the majority with established cardiovascular disease (81%). Renal outcomes were explored in a prespecified secondary analysis [30]. The secondary renal outcome was a composite of the following components: new-onset persistent

Table 1 Large glucagon-like peptide-1 receptor antagonist clinical trials with renal outcomes or measures reported

Study, GLP-1RA, ClinicalTrials.gov Identifier	Population; subgroups	Follow-up or study duration	Change in HbA1c	Renal outcomes or measures	Summary of renal outcomes
ELIXA [39, 44] Lixisenatide (10 or 20 μg, once-daily inj.) vs. placebo NCT01147250	$N = 5978$ People with T2DM and a recent coronary artery event Normoalbuminuria = UACR < 30 mg/ g, $n = 4441$; microalbuminuria = UACR $\geq$ 30 to < 300 mg/g, $n = 1148$; and macroalbuminuria UACR = $\geq$ 300 mg//g, $n = 389$ Percentage CVD: :100%	Median follow-up: 108 weeks	Average difference of − 0.27 percentage points (95% CI − 0.31 to − 0.22; $p < 0.001$) between lixisenatide and placebo across all visits	Renal measures: eGFR and UACR	Composite renal outcome: HR 0.84 (95% CI 0.68–1.02; $p = 0.083$) Lixisenatide reduces progression of UACR in patients with macroalbuminuria Placebo-adjusted LSM percentage change in UACR from baseline with lixisenatide: − 39.18% (95% CI − 68.53 to − 9.84; $p = 0.0070$) Lixisenatide was associated with a reduced risk of new-onset macroalbuminuria compared with placebo when adjusted for: Baseline HbA1c: HR 0.808; 95% CI 0.660–0.991; $p = 0.0404$ Baseline and on-trial HbA1c: HR 0.815; 95% CI 0.665–0.999; $p = 0.0491$ No significant differences in eGFR decline were identified between treatment groups LSM percentage change in eGFR stratified by baseline albuminuria status: Normoalbuminuria LSM − 0.42 (SE 0.7; 95% CI − 1.80 to 0.96; $p = 0.5549$) Microalbuminuria LSM − 2.64 (SE 1.85; 95% CI − 6.26 to 0.98; $p = 0.1530$) Macroalbuminuria LSM − 0.03 (SE 3.64; 95% CI − 7.19 to 7.14; $p = 0.9944$)

Table 1 continued

Study, GLP-1RA, ClinicalTrials.gov Identifier	Population; subgroups	Follow-up or study duration	Change in HbA1c	Renal outcomes or measures	Summary of renal outcomes
LIRA-RENAL [48] Liraglutide (1.8 mg once-daily inj.) vs. placebo NCT01620489	N = 279 People with T2DM and moderate renal impairment (eGFR 30–59 ml/min/1.73 m²) Percentage CVD: Not defined	26 weeks	Reduction of 1.05% [− 11.4 mmol/mol] in liraglutide at 26 weeks Reduction of − 0.38% [− 4.18 mmol/mol] in placebo at 26 weeks ETD of − 0.66% [− 7.25 mmol/mol] (95% CI − 0.90 to − 0.43 [− 9.82 to − 4.69]; p < 0.0001)	Renal measures: Changes in eGFR and UACR when compared to placebo at 26 weeks	At 26 weeks, no changes in renal function were observed when compared to placebo eGFR ETR = 0.98 (95% CI 0.94–1.02; p = 0.36) UACR ETR = 0.83 (95% CI 0.62–1.10; p = 0.19)
LEADER [26, 30] Liraglutide (1.8 mg once-daily inj.) vs. placebo NCT01179048	N = 9340 People with T2DM Percentage CVD: 81%	Median follow-up: 3.84 years	Mean difference of − 0.40 percentage points (95% CI − 0.45 to − 0.34) between liraglutide and placebo at 36 months	Composite outcome: New onset macroalbuminuria, sustained serum creatinine duplication, initiation of renal replacement therapy, or renal death Individual outcome: New onset macroalbuminuria	The renal composite outcome, and persistent macroalbuminuria occurred less in the liraglutide group than in the placebo group Composite renal outcome: HR 0.78 (95% CI 0.67–0.92; p = 0.003) Individual component: Persistent macroalbuminuria: HR 0.74 (95% CI 0.60–0.91; p = 0.004)

Table 1 continued

Study, GLP-1RA, ClinicalTrials.gov Identifier	Population; subgroups	Follow-up or study duration	Change in HbA1c	Renal outcomes or measures	Summary of renal outcomes
SUSTAIN-6 [27] Semaglutide (0.5 or 1.0 mg once-weekly inj.) vs. placebo NCT01720446	$N = 3297$ People with T2DM Percentage CVD:= 83%	Median follow-up: 104 weeks	Decrease from 8.7% [71.6 mmol/mol] at baseline to 7.6% [59.7 mmol/mol] at 104 weeks in 0.5 mg semaglutide group Mean difference (ETD) of − 0.7 percentage points [− 7.2 mmol/mol] (95% CI − 0.8 to − 0.5 [− 8.7 to − 5.7], $p < 0.0001$) between 0.5 mg semaglutide and placebo at 104 weeks Decrease from 8.7% [71.6 mmol/mol] at baseline to 7.3% [56.2 mmol/mol] at 104 weeks in 1.0 mg semaglutide group Mean difference (ETD) of − 1.1 percentage points [− 11.5 mmol/mol] (95% CI − 1.2 to − 0.9 [− 13.0 to − 10.0], $p < 0.0001$) between 1.0 mg semaglutide and placebo at 104 weeks	Composite outcome: New onset macroalbuminuria, doubling serum creatinine reaching eGFR < 45 ml/min/1.73 m², initiation of renal replacement therapy, or renal death Individual outcome: Persistent albuminuria	The renal composite outcome and persistent macroalbuminuria occurred less in the semaglutide group than in the placebo group Composite renal outcome: HR 0.64 (95% CI 0.46–0.88; $p = 0.005$) Individual component: Persistent macroalbuminuria: HR 0.54 (95% CI 0.37–0.77; $p = 0.001$)
EXSCEL [40, 49] Exenatide (2 mg, once-weekly inj.) vs. placebo NCT01144338	$N = 14,752$ People with T2DM Percentage CVD: 73%	Median follow-up: 3.2 years	Difference of − 0.7 percentage points (95% CI − 0.7 to − 0.6) between exenatide and placebo at 6 months Overall LSM difference of − 0.53% (95% CI, − 0.57 to − 0.50, $p < 0.001$) in exenatide compared to placebo during the course of the trial	New macroalbuminuria Composite outcome 1: 40% eGFR decline, renal replacement, renal death Composite outcome 2: 40% eGFR decline, renal death, new renal replacement, new albuminuria	Exenatide did not reduce the rate of new onset macroalbuminuria: HR 0.87 (95% CI 0.70–1.07; $p = 0.19$); adjusted HR 0.84 (95% CI 0.67 to 1.04; $p = 0.11$) Neither renal composite was reduced with exenatide in unadjusted analyses Composite outcome 1: HR 0.88 (95% CI 0.74–1.05; $p = 0.16$); adjusted HR 0.87 (95% CI 0.73 to 1.04; $p = 0.13$) Composite outcome 2: HR 0.88 (95% CI 0.76–1.01; $p = 0.07$); adjusted HR 0.85 (95% CI 0.74–0.98; $p = 0.03$)

Table 1 continued

Study, GLP-1RA, ClinicalTrials.gov Identifier	Population; subgroups	Follow-up or study duration	Change in HbA1c	Renal outcomes or measures	Summary of renal outcomes
AWARD-7 [33] Dulaglutide (0.75 or 1.5 mg, once-weekly inj.) vs. insulin glargine NCT01621178	$N = 577$ People with T2DM and moderate-to-severe CKD (stages III–IV) Percentage CVD: Not defined	26 and 52 weeks	LSM change from baseline to 26 weeks: 1.5 mg dulaglutide: − 1.2% (SE 0.1) [− 13.0 mmol/mol (SE 1.4)] 0.75 mg dulaglutide: − 1.1% (SE 0.1) [− 12.2 mmol/mol (SE 1.3)] Insulin glargine: − 1.1% (SE 0.1) [− 12.4 mmol/mol (SE 1.3)] LSM change from baseline to 52 weeks: 1.5 mg dulaglutide: − 1.1% (SE 0.1) [− 12.0 mmol/mol (SE 1.4)] 0.75 mg dulaglutide: − 1.1% (SE 0.1) [− 12.0 mmol/mol (SE 1.3)] Insulin glargine: − 1.0% (SE 0.1) [− 10.9 mmol/mol (SE 1.3)] All $p < 0.0001$	Secondary outcomes: Difference in eGFR and UACR compared to insulin glargine at 52 weeks	eGFR was higher with dulaglutide than insulin glargine at 52 weeks 1.5 mg dulaglutide: 34.0 ml/min/1.73 m² (SEM 0.7, $p = 0.005$) 0.75 mg dulaglutide: 33.8 ml/min/1.73 m² (SEM 0.7, $p = 0.009$) insulin glargine: 31.3 ml/min/1.73 m² (SEM 0.7) eGFR decline in UACR > 300 mg/g group 0.5 ml/min/1.73 m² 1.5 mg dulaglutide (vs. insulin glargine, $p = 0.0223$) 0.7 ml/min/1.73 m² 0.75 mg dulaglutide (vs. insulin glargine, $p = 0.0272$) 5.5 ml/min/1.7 3m² insulin glargine (vs. baseline, $p = 0.0004$) No significant difference in UACR compared to insulin glargine 1.5 mg dulaglutide: LSM -22.5% (95% CI − 35.1 to − 7.5) 0.75 mg dulaglutide: LSM -20.1% (95% CI − 33.1 to − 4.6) Insulin glargine: LSM − 13.0% (95% CI − 27.1 to 3.9)

Table 1 continued

Study, GLP-1RA, ClinicalTrials.gov Identifier	Population; subgroups	Follow-up or study duration	Change in HbA1c	Renal outcomes or measures	Summary of renal outcomes
HARMONY Outcomes [22] Albiglutide (30 or 50 mg once-weekly inj.) vs. placebo NCT02465515	$N = 9463$ People with T2DM with CVD Percentage CVD: 100%	Median follow-up: 1.5 years	Difference of albiglutide compared to placebo at 8 months: −0.63% (95% CI −0.69 to −0.58) Difference of albiglutide compared to placebo at 16 months: −0.52% (95% CI −0.58 to −0.45)	Mean difference in eGFR between participants receiving albiglutide and those receiving placebo at 8 and 16 months	Albiglutide demonstrated a decrease in eGFR decline at 6 and 18 months when compared to placebo −1.11 ml/min/1.73 m² (95% CI −1.84 to −0.39) at 8 months −0.43 ml/min/1.73 m² (95% CI −1.26 to 0.41) at 16 months
REWIND [29, 32] Dulaglutide (1.5 mg once-weekly inj.) vs placebo NCT01394952	$N = 9901$ People with T2DM with CVD risk or event Macroalbuminuria: $n = 791$ (7.9%) Mean eGFR: 76.9 ml/min/1.73 m² (SD 22.7) Baseline prevalence of albuminuria: $n = 3467$ (35.0%) Percentage CVD: 31%	Median follow-up: 5.4 years	LSM between-group difference of 0.61% (95% CI 0.58–0.65, $p < 0.0001$) between dulaglutide and placebo during the entire follow up period	Composite outcome: New onset macroalbuminuria, sustained decline of eGFR < 30%, or initiation of renal replacement therapy Individual outcome: New onset macroalbuminuria, sustained decline in eGFR (≥ 40% / ≥ 50%)	Dulaglutide associated with reduced composite renal outcomes when compared to placebo Composite renal outcome: HR 0.85 (95% CI 0.77–0.93; $p = 0.0004$) Individual components: New macroalbuminuria: HR 0.77 (95% CI 0.68–0.87; $p < 0.0001$) Sustained decline in eGFR < 30%: HR 0.89 (95% CI 0.78–1.01; $p = 0.066$) Chronic renal replacement therapy: HR 0.75 (95% CI 0.39–1.44; $p = 0.39$)

Studies listed in order of publication date. The PIONEER-6 cardiovascular outcome trial is not listed as defined renal measures or outcomes were not reported

CI Confidence interval, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *ETD* estimated treatment difference, *ETR* end of treatment response, *GLP-1RA* glucagon-like peptide-1 receptor antagonist, *HbA1c* glycated hemoglobin, *HR* hazard ratio, *inj.* injection, *LSM* least squares mean, *SD* standard deviation, *SEM* standard error of the mean, *T2DM* type 2 diabetes mellitus, *UACR* urinary-to-albumin ratio

macroalbuminuria, persistent doubling of the serum creatinine level, ESRD, or death due to renal disease. The composite renal outcome was observed less frequently in participants using liraglutide than placebo (HR 0.78, 95% CI 0.67–0.92; $p = 0.003$). Of the individual components, only new-onset persistent macroalbuminuria was observed less frequently in people treated with liraglutide (HR 0.74, 95% CI 0.60–0.91; $p = 0.004$) [30].

The SUSTAIN-6 Trial (Once-Weekly Semaglutide)
The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) consisted of 3297 people living with T2DM, 83% with established cardiovascular disease, receiving once-weekly semaglutide (0.5 and 1.0 mg) or placebo. New or worsening nephropathy, defined as persistent macroalbuminuria, persistent doubling of the serum creatinine level, and a creatinine clearance of < 45 ml/min/1.73 m^2, or the need for continuous renal-replacement therapy, was observed less in participants treated with semaglutide (3.8%) than placebo (6.1%) [27].

A recent post-hoc analysis of the SUSTAIN trials (SUSTAIN 1–5 and SUSTAIN 7) assessed the effects of semaglutide (0.5 and 1.0 mg) versus comparators (active treatments or placebo) on kidney function (eGFR), albuminuria status (UACR), and adverse kidney events in 8416 people living with T2DM [31]. Semaglutide was associated with initial reductions in eGFR that plateaued and marked reductions in UACR when compared to active comparators.

The EXSCEL Trial (Once-Weekly Exenatide)
The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) was a multinational, placebo-controlled, randomized CVOT designed to assess the impact of once-weekly exenatide compared to placebo when added to usual care in people living with T2DM and risk of cardiovascular disease. In a recent post-hoc analysis, renal outcomes were measured, including new macroalbuminuria and two composite outcomes consisting of 40% decline in eGFR, renal

replacement, and renal death, with or without new macroalbuminuria. Neither renal composite was reduced with exenatide in unadjusted analyses; however, the second renal composite containing macroalbuminuria was reduced after adjustment when compared to placebo (HR 0.85, 95% CI 0.74–0.98) [49].

The AWARD-7 Trial (Once-Weekly Dulaglutide)
The Assessment of Weekly Administration of LY2189265 in Diabetes-7 (AWARD-7) study assessed the glycemic efficacy and overall safety of once-weekly 1.5 and 0.75 mg dulaglutide compared to insulin glargine in 577 people living with T2DM and moderate-to-severe CKD (eGFR < 60 ml/min/1.73 m^2) [33]. At 52 weeks, in addition to producing glycemic control similar to that achieved with insulin glargine but with lower rates of symptomatic hypoglycemia, dulaglutide was associated with a reduced decline in eGFR. However, the reduction of UACR with dulaglutide was not significantly different from that of insulin glargine. This study was the first to demonstrate that in people with moderate-to-severe CKD, GLP-1 RA treatment may slow eGFR decline.

The Harmony Outcomes Trial (Once-Weekly Albiglutide)
The Harmony Outcomes study evaluated the cardiovascular safety of once-weekly treatment with 30 or 50 mg albiglutide in 9463 people living with T2DM and cardiovascular disease compared with placebo. Renal outcomes were not reported, however, eGFR was measured [28]. The mean difference in eGFR between participants receiving albiglutide and those receiving placebo was -1.11 and -0.43 ml/min/1.73 m^2 at 8 and 16 months, respectively. In August 2017, GlaxoSmithKline announced that it would discontinue albiglutide due to limited prescribing of the drug and not because of safety concerns.

The REWIND Trial (Once-Weekly Dulaglutide)
The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial consisted of 9901 participants, of whom 31.5% had

previous cardiovascular disease, with a median follow-up of 5.4 years [29]. Predefined secondary outcomes showed that 1.5 mg once-weekly dulaglutide was associated with reduced composite renal outcomes, defined as the first occurrence of new macroalbuminuria, sustained decline in eGFR of ≥ 30%, or chronic renal replacement therapy [32]. A post-hoc analysis evaluated the effect of dulaglutide and placebo on renal outcomes related to kidney function, defined as the composite endpoint of sustained eGFR decline ≥ 40%, ESRD, or all-cause death [50]. The incidence rate of the composite endpoint was determined to be significantly lower in participants treated with dulaglutide compared with placebo (HR 0.83, 95% CI 0.75–0.92, $p < 0.001$).

The PIONEER-6 Trial (once-daily semaglutide)

The Peptide Innovation for Early Diabetes Treatment-6 (PIONEER-6) trial assessed CV safety of oral semaglutide in 3,183 participants of whom 856 had an eGFR < 60 ml/min/1.73 m^2 and 1051 had microalbuminuria or proteinuria [41]. Renal or microvascular composite endpoints were not assessed; however, a CVOT of oral semaglutide is planned with renal outcomes as secondary endpoints (A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes [SOUL]) [51].

Future studies are needed dedicated to understanding the primary kidney outcomes of GLP-1 RA use and to confirm the renoprotective benefits of this drug class.

The FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial will be the first study designed to specifically examine the effects of a GLP-1 RA on primary kidney outcomes.[52]. The trial is ongoing with results to be expected between 2024 and 2025. Challenges for conducting such trials include their expense, due to being both large and long-term, a high regulatory bar, and difficulty in enrolling enough participants in this particular population [53, 54].

Other Clinical Evidence for GLP-1 RAs

In addition to the larger randomized controlled trials described above, evidence for GLP-1 RA use in people living with CKD comes from non-randomized clinical studies and clinical trials with small sample sizes. In a prospective study published in 2017, the Hiramatsu group reported that in Japanese people living with T2DM and mild renal impairment (eGFR 30–60 ml/min/1.73 m^2) liraglutide was associated with decreased albuminuria (baseline β2-microglobulin 2.52 ± 0.7 mg/dL, 24-month β2-microglobulin 2.13 ± 0.9 mg/dL; $p < 0.05$) and an increased eGFR after 24 months (baseline eGFR 51.2 ± 8.1 mL/min/1.73 m^2, 24-month eGFR 60.5 ± 13.8 mL/min/1.73 m^2; $p < 0.05$) [55]. Two other studies with low participant number also reported that liraglutide positively impacted renal function while demonstrating reductions in HbA1c and body weight [56, 57]. Inamura et al. reported that 12-month administration of liraglutide decreased both the rate of eGFR decline (6.6 ± 1.5 to 0.3 ± 1.9 ml/min/1.73 m^2/year; $p = 0.003$) and proteinuria (2.53 ± 0.48 to 1.47 ± 0.28 g/g creatinine; $p = 0.002$) [57] while von Scholten et al. showed, in a randomized, placebo-controlled, crossover trial, that liraglutide reduced the urinary albumin excretion rate (32% reduction, 95% CI 7–50; $p = 0.017$) and eGFR (− 5 mL/min/1.73 m^2, 95% CI − 11 to 2; $p = 0.15$) over a 12-week period, a reduction that may be attributed to decreased 24-h systolic blood pressure [56]. As hyperglycemia can affect filtration rates [58], a limitation of these studies is that the renal findings reported were not determined to be independent of glucose lowering.

Evidence from Real-world Studies

Other supporting evidence for the use of GLP-1 RAs in this patient population comes from real-world evidence studies. A retrospective study examining the effects of initiating GLP-1 RA therapy on eGFR in people living with T2DM with renal impairment showed that after 1 year from initiating GLP-1 RA therapy, people living

with stage 4 CKD (eGFR of < 30 and ≥ 15 ml/min/1.73 m^2) or stage 5 CKD (eGFR of < 15 ml/min/1.73 m^2) had a significantly smaller decline in eGFR compared to those using other glucose-lowering agents [37]. In a retrospective study evaluating the effectiveness of dulaglutide in routine clinical practice that included patient subgroups underrepresented in clinical trials, including elderly people, non-obese individuals, and those with CKD, a significant and consistent improvement in HbA1c with declining body weight was observed [59]. Specifically, of the participants in the study who had CKD, dulaglutide achieved significant reductions in HbA1c ($- 0.9\%$) and body weight ($- 4.6$ kg), consistent with results of the AWARD-7 trial [33].

Evidence from Kidney Transplant and People Living with Dialysis

Currently, no prospective clinical trials have yet assessed the effectiveness, safety, and tolerability of GLP-1 RAs in people living with T2DM and stage 5 CKD in dialysis programs or in those who have undergone kidney transplant [60]. Several retrospective studies indicate no significant changes in renal function and suggest that GLP-1 RAs have no effect on transplant outcomes [61, 62]. In a retrospective review of kidney transplant recipients with pre- or post-transplant diabetes who initiated a GLP-1 RA therapy for at least 12 months, recipients showed a significant reduction in the total daily insulin dose, a reduction in the risk of hypoglycemia, and the maintenance of kidney function with no acute rejection, indicating that GLP-1 RA may be a relatively safe and effective treatment for kidney transplant recipients with T2DM [62]. Another retrospective study involving people living with T2DM treated with GLP-1 RAs who had received kidney transplants showed decreased HbA1c and weight but no change in renal function after a mean follow-up period of 12 months [61]. In a separate smaller study ($n = 7$), improvements in renal function were observed along with HbA1c and weight reductions after a mean follow-up period of 19.4 ± 7.6 months [63]. Furthermore,

a retrospective chart review of people living with T2DM and a solid organ transplant, of which the majority had a kidney transplant (81%), dulaglutide treatment resulted in a sustained reduction in weight, body mass index (BMI), and insulin use over a 24-month period with no increase in graft failure, cardiovascular morbidity, or all-cause mortality [64]. The lack of major concerns indicates that GLP-1 RAs may be a viable treatment for people living with T2DM post-kidney transplant, although more studies are needed to determine whether these medicines improve patient survival.

Limited studies have been performed examining GLP-1 RA use in individuals with ESRD (eGFR < 15 ml/min/1.73 m^2), and the recommendations of their use in this population differ depending on GLP-1 RA as well as the prescribing information set by the regulator (summarized in Fig. 5). Clinical pharmacology studies have demonstrated that renal impairment, including ESRD requiring dialysis, does not impact the pharmacokinetics of semaglutide or dulaglutide as indicated in their label information [65, 66]. The pharmacokinetic characteristics of GLP-1 RAs together with the potential benefit of these drugs in reducing HbA1c without risk of hypoglycemia, warrant further research on the possible use of GLP-1 RA in people with advanced CKD and those on dialysis.

PRACTICAL USE OF GLP-1 RAS IN PEOPLE LIVING WITH CKD

In this section we provide general recommendations for GLP-1 RA use in people with CKD. The information for GLP-1 RA use for patients without CKD will also be included to enhance the context.

Current Treatment Guidelines for People Living with CKD

By nature, T2DM is a heterogenous and progressive disease for which a wide variety of treatment options exist and where treatment paradigms continue to evolve. Several
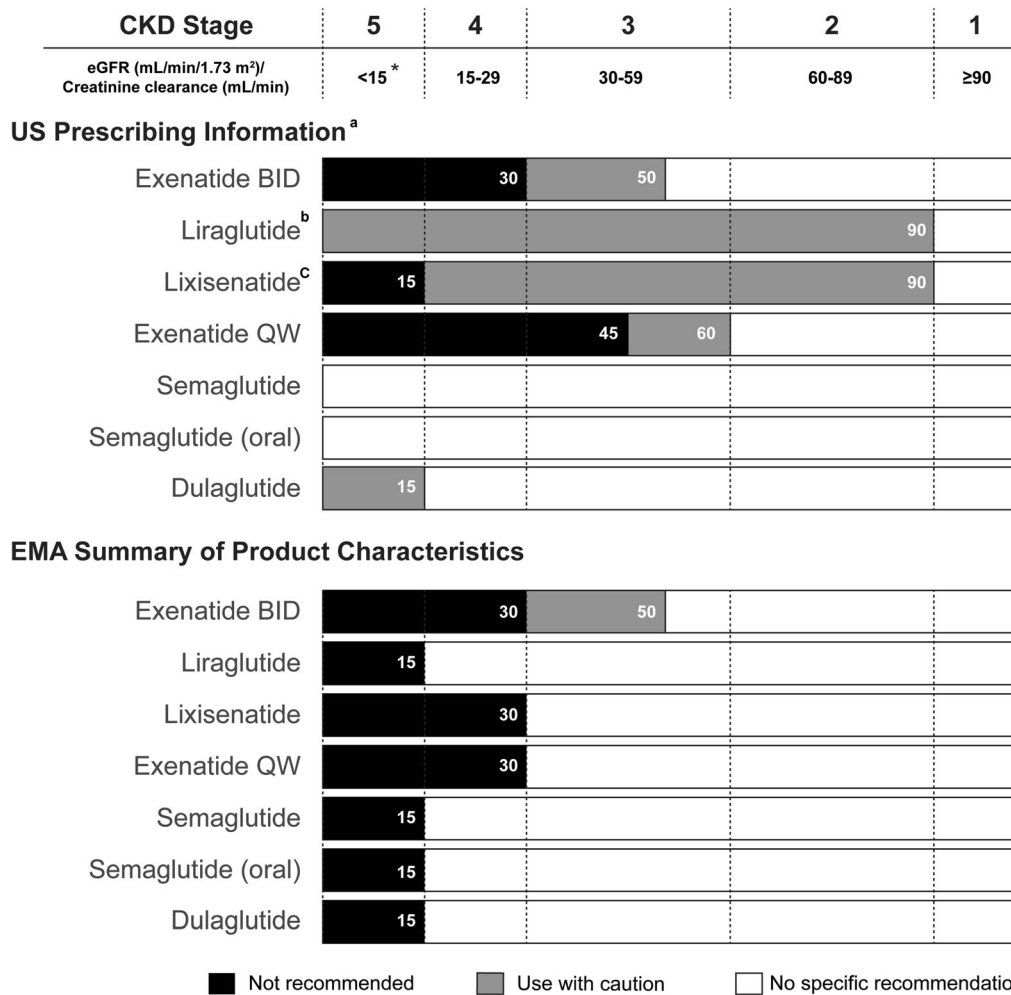
CKD Stage	5	4	3	2	1
eGFR (mL/min/1.73 m²)/ Creatinine clearance (mL/min)	<15 *	15-29	30-59	60-89	≥90

US Prescribing Information [a]

Drug	5	4	3	2	1
Exenatide BID	Not recommended (30)	Use with caution (50)			
Liraglutide [b]	Use with caution (90)				
Lixisenatide [c]	Not recommended (15)	Use with caution (90)			
Exenatide QW	Not recommended (45)	Use with caution (60)			
Semaglutide	No specific recommendations				
Semaglutide (oral)	No specific recommendations				
Dulaglutide	Use with caution (15)				

EMA Summary of Product Characteristics

Drug	5	4	3	2	1
Exenatide BID	Not recommended (30)	Use with caution (50)			
Liraglutide	Not recommended (15)				
Lixisenatide	Not recommended (30)				
Exenatide QW	Not recommended (30)				
Semaglutide	Not recommended (15)				
Semaglutide (oral)	Not recommended (15)				
Dulaglutide	Not recommended (15)				

■ Not recommended   ▨ Use with caution   ☐ No specific recommendations

Fig. 5 Information on the use of GLP-1 RA in people with T2DM and CKD based on USPI and the European Union SmPC. The FDA-approved prescribing information and EMA-approved SmPC summarizing GLP-1RA use in populations with renal impairment. Recommendations are depicted by color (white, no specific recommendation; gray, use with caution; black, not recommended). *: For the purposes of graphically summarizing the information on GLP-1 RA use in people with renal impairment, end-stage renal disease, as described in the SmPC and USPI, is defined as eGFR < 15/mL/min/1.73² when specific eGFR values are not provided in the label information. [a]Information is based on FDA-approved label unless superseded by the most recent USPI as of 20 May 2021. [b]Limited experience exists for liraglutide use in people with end-stage renal disease. [c]Limited experience exists for lixisenatide in people with an eGFR from 15 to 30 ml/min/1.73 m². *BID* twice daily, *EMA* European Medicines Agency, *FDA* U.S. Food and Drug Administration, *QW* once weekly, *SmPC* Summary of Product Characteristics, *USPI* U.S. Prescribing Information

international organizations have provided clinical practice guidelines to aid physicians in optimizing therapy for people living with CKD.

The general guidelines for management of T2DM that are provided by the ADA can aid physicians in navigating the overall treatment landscape. Pharmacologic intervention is usually initiated with a single oral agent, usually metformin, combined with lifestyle modifications [15]. If HbA1c remains elevated, metformin treatment is followed by sequential addition of oral agents before intensification to injectables in a stepwise approach. Although the primary goal of diabetes management is to

reduce glycemia and diabetes-related complications, special consideration needs to be taken in people living with compromised renal function. For example, metformin is regarded as contraindicated if eGFR < 30 ml/min/1.73 m^2 due to the increased risk of hypoglycemia [2, 67].

In 2020, the ADA provided a revision to the Standards of Medical Care in Diabetes with updated guidelines recommending the use of SGLT2i and GLP-1 RAs to treat people living with T2DM and CKD independently of baseline A1C, individualized A1C target, or metformin use [68] (summarized in Fig. 2). These revised changes take into consideration the latest trial findings on SGLT2i and GLP-1 RA and suggest that these medications are the preferred option for people when CKD predominates, independent of HbA1c. If CKD is the predominant condition, the recommendation is to start with an SGLT2i with evidence of reducing CKD progression, assuming eGFR is adequate. If SGLT2i is not tolerated or contraindicated, or if eGFR is less than adequate (< 30 ml/min/1.73 m^2), then a GLP-1 RA is recommended.

The KDIGO 2020 Clinical Practice Guideline for Diabetes Management Chronic Kidney Disease recommend that people living with T2DM and CKD with eGFR > 30 ml/min/1.73 m^2 should receive metformin and SGLT2i (Fig. 2). For those who do not achieve glycemic targets with lifestyle therapy, metformin, and SGLT2i, or who cannot tolerate these agents, whether due to adverse events or because other restrictions apply, other medications are recommended. Of these, GLP-1 RAs are generally preferred because of their demonstrated cardiovascular benefits and potential for improved renal outcomes [2]. In addition, GLP-1 RAs are particularly effective in reducing HbA1c, which is especially relevant as HbA1c levels ≥ 6.5% have been shown to be associated with increased incidence of microvascular complications [69] while it is challenging to achieve HbA1c levels < 6.5% with other treatments without increasing the risk of hypoglycemia.

The *Lancet* Commission on Diabetes recently performed a comprehensive analysis of available data on diabetes care to provide a summary of the best evidence for effectively managing diabetes [70]. Of the key messages provided in their summary, the commission states that SGLT2i and GLP-1 RA therapies can reduce cardiovascular–renal diseases and all-cause death by up to 40% in people living with T2DM, independently of their effect on lowering blood glucose concentration.

Should a physician decide that a GLP-1 RA would benefit their patient, the next challenge is deciding upon which to prescribe as there are a variety of GLP-1 RAs with regulatory approval in U.S. and European markets, each with different profiles in relation to duration of action (short-acting vs. long-acting), indications (monotherapy and/or combined therapy), timing and ease of dosing, efficacy, and tolerability [71–73]. The variation in profiles means that GLP-1 RAs can be used for treating most stages of CKD, although as described above, there is an exception for people with ESRD (< 15 ml/min/1.73 m^2 or on dialysis) that is dependent on the prescribing information set by regulators. According to the U.S. and European prescribing information, the majority of GLP-1 RAs can be used without dose adjustments in people with mild (eGFR 60–89 ml/min/1.73 m^2) or moderate (eGFR 30–59 ml/min/1.73 m^2) renal impairment. The use of exenatide and its analog, lixisenatide, both GLP-1RAs that cannot be metabolized in circulation and must be cleared renally, is more restricted depending on the CKD grade and prescribing information set by regulators. Currently, dulaglutide, semaglutide, and liraglutide are the only GLP-1 RAs recommended by the European Medicines Agency (EMA) without any dose adjustment in people living with mild, moderate, or severe renal impairment (eGFR ≥ 15 ml/min/1.73 m^2) [65, 66, 74]. Figure 5 summarizes the use of GLP-1 RAs in people with renal impairment that is based on either the FDA-approved U.S. prescribing information or the EMA-approved summary of product characteristics.

Recommendations when Combining a GLP-1 RA with Other Glucose-Lowering Medication

In general, GLP-1 RAs are indicated for use in combination with metformin and with oral

glucose-lowering agents, including SGLT2i, when glycemic control is not achieved [75, 76]. When metformin is considered unsuitable as therapy due to intolerance or contraindications, or if there is inadequate glycemic control, several GLP-1 RAs are indicated as monotherapy, including liraglutide, dulaglutide, and semaglutide.

General Recommendations on the Use of a GLP-1 RA Add-on to Insulin

Basal insulin is effective in reducing fasting blood glucose but is associated with a high risk of hypoglycemia and weight gain [77]. In the revised ADA guidelines, GLP-1 RAs are prioritized as the first injectable glucose-lowering medications ahead of insulin if HbA1c is above the individual target [15]. When compared to insulin, GLP-1 RAs have shown the same or even more efficacy in lowering HbA1c in head-to-head trials, with lower risk of hypoglycemia [78–80]. Additional benefits of GLP-1 RA use over insulin include weight reduction, rather than weight gain, which is associated with insulin use, and for GLP-1 RAs administrated weekly, less frequent injections [81].

If HbA1c remains elevated after treatment with GLP-1 RA, basal insulin can be added as adjuvant to the treatment regimen [15] Several meta-analyses of randomized controlled trials found that adding GLP-1 RA to basal insulin led to decreased HbA1c, weight loss, and a lower rate of hypoglycemia when compared to basal bolus insulin [79, 80, 82–84]. Caution needs to be exercised when combining a GLP-1 RA and insulin and, in most cases, the insulin dose needs to be adjusted. Based on reported evidence, the dose of basal insulin should be reduced by 10%, and a decrease of prandial insulin by 30–40% is recommended when starting concomitant treatment with the addition of a GLP-1 RA [85]. Recently, injection devices that deliver both GLP-1 RA and basal insulin simultaneously have become available, which may have additional benefits, such as improved adherence [86]. Although there is an increased risk of gastrointestinal side effects along with increased costs when adding a GLP-1

RA to the therapeutic regimen, this combination therapy has been shown as an offset to the weight gain observed with insulin therapy [87].

Treatment Decisions: GLP-1 RA, SGLT2i, or Both?

Both GLP-1 RAs and SGLT2i are recommended after metformin in the treatment of T2DM, as both are associated with renal and cardiovascular disease benefits, a low risk for hypoglycemia, improved glycemia efficacy, and weight loss [15]. Guidelines provided by KDIGO recommend metformin with SGLT2i as first-line therapy in people with eGFR > 30 ml/min/1.73 m^2 [2], with a GLP-1 RA as the preferred agent if additional therapy is needed for glycemic control. The preference for SGLT2i is due to more robust evidence regarding renal outcomes. Based on the results of the CREDENCE study [88], canagliflozin is currently allowed in people with eGFR > 30 ml/min/1.73 m^2 if they have an albuminuria/creatinine ratio > 300 mg/g [89]. Similarly, as a result of the positive findings from the recent DAPA-CKD trial [90], dapagliflozin is now indicated for the treatment of CKD, and can be initiated if eGFR ≥ 25 ml/min/1.73 m^2. The higher cost of GLP-1 RAs may also be a factor in this choice [91]. For people living with T2DM and CKD who (1) do not achieve glycemic targets with lifestyle intervention, metformin, and SGLT2i, (2) cannot take these medications due to intolerances, or (3) have eGFR < 30 ml/min/1.73 m^2, GLP-1 RAs are the preferred agent [2]. As GLP-1 RAs are contraindicated for people with gastrointestinal disease, pancreatitis, or a family history of mutations in multiple endocrine neoplasia type 2/medullary thyroid carcinoma (MEN2/MTC), SGLT2i is the preferred treatment for these patients groups. For people at risk of lower limb ulcerations and neuropathy, GLP-1 RAs are recommended over SGLT2i. Although the findings in the CANVAS trial showed a higher risk of amputation when taking canafliglozin compared to placebo [92], no significant difference in the risk of this complication was observed in the CREDENCE study [88]. However, caution is recommended in the use of SGLT2i in people

with a high risk of amputation or skin ulcers in the lower extremities [89].

Clinical evidence suggests that combined SGLT2i and GLP-1 RA therapy is additive in terms of lowering HbA1c levels, systolic blood pressure, and body weight. In the DURATION-8 study, the SGLT2i dapagliflozin was used in combination therapy with exenatide and showed reductions in HbA1c, systolic blood pressure, and blood glucose, with improved weight loss, when compared to monotherapy [93]. More recently in AWARD-10, the addition of dulaglutide to an SGLT2i also resulted in weight loss, reduced HbA1c, and lower systolic blood pressure [94]. Although combined therapy is still not common practice because of the relatively recent regulatory approval, these studies highlight the potential of dual GLP-1 RA + SGLT2i therapy to synergistically reduce cardiovascular disease and decelerate renal decompensation [75].

Adverse Events, Side Effects, and Safety Considerations

Overall, GLP-1 RAs are very well tolerated considering their high efficacy in controlling glycemia and the net effect they exert on multiple organ systems (Fig. 3). The adverse events associated with GLP-1 RA use are generally mild and include nausea and vomiting. In addition, there are precautions for their use in people with pancreatitis and diabetic retinopathy, the incidence of which is generally increased in T2DM. Based on several studies, it appears that GLP-1 RAs are safe and effective regardless of renal function status. In a post-hoc analysis of AWARD-11, the effect of dulaglutide treatment was associated with consistent safety and efficacy patterns regardless of their renal function status at baseline, with no more gastrointestinal adverse effects nor hypoglycemic events in those subjects with lower renal function [95]. In a post-hoc analysis of LEADER, the use of liraglutide in those with CKD was safe, with no difference in the frequency of serious adverse events between those participants with and without CKD [96]. More detail on adverse events, plus information on side effects and safety considerations, is provided below and summarized in Table 2.

Gastrointestinal Adverse Events

Of the adverse effects reported during GLP-1 RA clinical trials, gastrointestinal symptoms were the most frequent, with nausea and diarrhea very common, and vomiting, constipation, abdominal pain, and dyspepsia considered to be relatively common [97]. These symptoms are primarily due to the mode of action of GLP-1 RAs on the gut, as a GLP-1 may directly or indirectly regulate electrolyte and fluid homeostasis by influencing feeding and drinking behavior as well as electrolyte transport in the kidneys and gastrointestinal tract [25]. Ensuring adequate hydration is therefore an important consideration with GLP-1 RA treatment, as is recommended by the label, particularly for people with renal impairment, as dehydration is known to be associated with renal dysfunction [98]. Individuals should seek medical attention if they have prolonged nausea or vomiting, or an inability to take in fluids. Both nausea and vomiting are usually transient and of mild-to-moderate severity, with the frequency more pronounced at the beginning of treatment and people developing a tolerance over time [99]. Adherence to GLP-1 RA therapy may be improved by slowing dose escalation, as per label instructions, and setting patient expectations for possible gastrointestinal adverse outcomes that should subside over time. Close monitoring by the primary care physician is important for effective management of these effects.

Precaution for Use in People with Pancreatitis

A retrospective analysis of the US FDA's database of reported adverse events from 2004 to 2009 found exenatide increased the odds ratio (OR) for reported pancreatitis by tenfold compared with other therapies [100]. In contrast, recent meta-analyses suggest that GLP-1 RA use does not increase the risk of pancreatitis and/or pancreatic cancer, compared to placebo and/or other treatments [101–103]. From a practical standpoint, people should be informed of the characteristic symptoms of acute pancreatitis,

Table 2 General recommendations

General recommendations
Inform individuals that if gastrointestinal symptoms appear they are generally mild or moderate in severity and disappearance over time is common. Recommend that individuals avoid administering a GLP-1 RA close to a large or high-fat meal because doing so is likely to cause nausea. Consider progressive dose escalation
Individuals treated with GLP-1 RA should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions. and take precautions to avoid fluid depletion
Individuals should be informed of the symptoms of acute pancreatitis. Discontinue if pancreatitis is suspected and do not restart if confirmed
Monitor blood pressure in individuals with high dose of diuretics and normal-to-low blood pressure
In people with concomitant use of sulfonylureas or insulin, consider reducing the dose of sulphonylurea or insulin to reduce the risk of hypoglycemia

and treatment with GLP-1 RA should be discontinued if pancreatitis is suspected and not restarted if confirmed. In the absence of signs and symptoms, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Precaution for Use in People with Diabetic Retinopathy

The prevalence of both CKD and diabetic retinopathy, a microvascular complication of diabetes, is known to increase proportionally to T2DM duration [47]. In LEADER, there was a higher, albeit non-significant, rate of adverse retinal events with liraglutide compared with placebo (HR 1.15, 95% CI 0.87–1.52; $p = 0.33$) [26]. In the SUSTAIN-6 trial, semaglutide was associated with a significant increased risk of diabetic retinopathy complications, including vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent

or photocoagulation (HR 1.76, 95% CI 1.11–2.78) [27]. Conversely, population studies have found no association between increased risk of diabetic retinopathy and GLP-1 RA use [104, 105], with a low odds ratio observed for exenatide (OR 0.16), liraglutide (OR 0.18), albiglutide (OR 0.09), and dulaglutide (OR 0.11) [106]. In addition, recent clinical evidence from the AngioSafe T2DM Study demonstrated no association between GLP-1 RAs and severe diabetic retinopathy [107], suggesting that GLP-1 RA does not have a causal influence on retinopathy independent of glucose lowering. The general consensus is that any increased risk of retinopathy with GLP-1 RA treatment is likely to be related to the abrupt improvement in glycemic control [108], a phenomenon similar to that reported for other neuropathological complications [109].

Natriuresis and Diuresis

Studies in people living with T2DM and obesity have shown that GLP-1 RA administration can induce diuresis and natriuresis [110, 111] that likely contribute to the renoprotective effects of GLP-1 RA. The diuretic and natriuretic effects of GLP-1 are mediated through downregulation of sodium–hydrogen exchanger 3 (NHE3) activity in the renal proximal tubule that consequently affects renal hemodynamics [112]. Although a decrease in systolic blood pressure is observed with GLP-1 RAs (ranging from -1.84 mmHg [95% CI -3.48 to -0.20] to -4.60 mmHg [95% CI -7.18 to 2.03]) [113], the possibility of requiring adjustment of simultaneous diuretic treatment should be considered.

Hypoglycemia

Despite having a pronounced anti-hyperglycemic effect, GLP-1 RAs are not typically associated with hypoglycemia when used as monotherapy. Caution is advised, with dose reduction recommended in some cases, when they are combined with a sulphonylurea or insulin as the risk of hypoglycemia is higher. In clinical trials examining GLP-1 RA in combination with a sulphonylurea (with or without metformin) or insulin, the incidence of hypoglycemia was low overall, but increased when

compared with placebo [114]. When GLP-1 RAs are not used concomitantly with a sulphonylurea or insulin, routine glucose monitoring is unnecessary due to the low risk of developing hypoglycemia.

Weight Loss

In addition to improving glycemic control, GLP-1 RAs demonstrate a benefit on body weight. This is an important treatment aspect, as weight reduction most likely plays an important role in the prevention and reduced progression of CKD, an association demonstrated in people with macroalbuminuria having undergone bariatric surgery [115]. Data from an early meta-analysis of 18 trials provided evidence that in people living with T2DM, GLP-1 RAs promote a mean weight loss of 2.8 kg (− 3.4 to − 2.3 kg) [116]. Weight loss varies depending on the dose and type of medication, with differences observed in head-to-head studies [117]. In SUSTAIN-7, a study comparing semaglutide to dulaglutide in patients with inadequately controlled T2DM, a greater reduction in body weight was observed with 0.5 mg semaglutide (4.6 kg, standard error [SE] 0.28) compared with 0.75 mg dulaglutide (2.3 kg, SE 0.27) (estimated treatment difference [ETD] − 2.26 kg, 95% CI − 3.02 to − 1.51; $p < 0.0001$) and with 1.0 mg semaglutide (6.5 kg, SE 0.28) compared with 1.5 mg dulaglutide (3.0 kg, SE 0.27) (ETD − 3.55 kg, 95% CI − 4.32 to − 2.78; $p < 0.0001$) [118] at 40 weeks. Significant reductions in body weight are observed with 3.0 mg and 4.5 mg dulaglutide, doses which have been recently approved for people living with T2DM who are taking metformin but experiencing inadequate glycemic control [66, 119]. In the AWARD-11 trial, the efficacy and safety of 3.0 mg and 4.5 mg dulaglutide was evaluated at 36 and 52 weeks; the results also demonstrated that these doses led to significant reductions in body weight. Specifically, with 4.5 mg dulaglutide, the weight reduction was 5.0 kg at 52 weeks of treatment [120]. Compared with the 1.5 mg dulaglutide group, body weight was significantly decreased in the 3.0 mg (ETD − 0.9, 95% CI − 1.4 to − 0.4 kg; $p < 0.05$ and 4.5 mg (ETD − 1.6, 95% CI − 2.1 to − 1.1 kg; $p < 0.001$) dulaglutide groups at 36 weeks.

General Practical Considerations

Patient-centered Care

Patient-centered care in the treatment of diabetes is considered to be essential in effective disease management. People who are more involved in their treatment decisions and have a better understanding of the treatment strategy are more likely to be satisfied with their healthcare [121], while a lack of shared decision-making between patient and prescriber can affect patient satisfaction and may result in non-adherence [122]. These factors are reflected in the joint ADA–EASD guidelines, which place a focus on putting the patient at the center of the treatment paradigm and consider that shared decision-making between patient and provider is essential to create an effective management plan [68]. An emphasis is placed on assessing the patient's individual factors and engaging the patient prior to creation of a management plan. Once the patient consents to the plan, the next steps involve implementation, routine monitoring and support, and review of the plan. It is essential that people are involved in treatment decisions as this can influence how likely they are to continue taking a medication, which can, in turn, affect treatment success.

Considering the large variety of therapies available, each with different attributes and mechanisms of action, along with the heterogenous nature of T2DM, the treatment landscape is understandably complicated. An important factor in helping healthcare professionals and their patients decide on the best medication for the individual is determining patient preference on the frequency (daily vs. weekly) and route of administration (injectable vs. oral), as well as medication costs. In circumstances where patients cover the cost of treatment, where reimbursement is restricted, or when insurance coverage is limited, the financial expense may influence selection of GLP-1 RA therapy [123]. In a recent review of GLP-1 RA patient preferences, important

attributes driving patient choice included dose frequency, device characteristics (including type of device and needle size), change in HbA1c, and adverse event profile [124].

Dose Frequency

The recommended dosages and administration requirements for each of the GLP-1 RAs are described in greater detail elsewhere [73]. Briefly, the first GLP-1RA started with administration twice-daily (BID; exenatide BID) followed by once-daily (lixisenatide and liraglutide) and then once-weekly (QW; semaglutide, exenatide and dulaglutide). A summary of the dosing characteristics for currently available GLP-1 RAs is summarized in Table 3. As anticipated, patient preference is towards GLP-1 RA profiles associated with less frequent dosing, with once-weekly preferred to once-daily, with the latter preferred over twice-daily [123–125].

Injection Device Characteristics

The GLP-1 RA injection devices consist of either a single-use or multi-dose pen that varies by needle size and thickness, which can be factors in predicting patient preference [125] (Table 4). Injections are subcutaneous and therefore tend to be less painful than intramuscular injections, particularly as the needles are smaller. The pen injectors are pre-filled, which is more convenient than carrying bottles or syringes. The complexity of dose regimens, the patient's perception of administration, and fear of injections may affect the rate of commencing injectable treatment. Understanding the characteristics and features of these devices can therefore aid both physicians and their patients in selecting the most appropriate agent.

Daily formulations of GLP-1 RAs, including exenatide BID, liraglutide, and lixisenatide, require dose selection and attachment of a disposable needle each time the injection device is to be used. Both prolonged-release exenatide QW and dulaglutide are weekly formulations that come in single-use devices and do not require dose selection, while semaglutide comes in a multi-dose pen where the specific dose needs to be set by the user. An older version of the exenatide QW device consists of a pre-filled pen with two chambers containing exenatide powder and solvent that require reconstitution. A newer device is now available that features a pre-attached hidden needle with automatic dose administration that requires 15 s of mixing before administration [126]. The dulaglutide device is ready to use and includes a hidden, pre-attached needle with dose selection or reconstitution not required, which allows for greater ease of use [66].

In an uncontrolled study of 214 people living with T2DM, 99% of participants considered the single-dose pen "easy" or "very easy" to use [127]. In a separate study that evaluated patient perceptions of the injection devices for liraglutide and dulaglutide, the dulaglutide device was associated with a slightly higher score for ease of use and convenience [128]. Patient preferences between liraglutide and twice-daily exenatide BID were also evaluated, with 96% of respondents reporting a preference for the liraglutide device compared to that of exenatide [129]. The PREFER study was an open-label, multicenter, randomized, crossover study assessing patient preference for dulaglutide and semaglutide injection devices [130]. Participants with T2DM preferred the dulaglutide injection device to the semaglutide injection device [130]. An important consideration is that, if people prefer a device, they may be more willing to use the medication, potentially resulting in improved health outcomes.

Route of Administration

The majority of GLP-1 RAs are delivered via injection although an oral formulation has recently become commercially available [131]. While oral administration is less invasive than injection, a recent study indicated no difference in preference between oral semaglutide and dulaglutide [132]. However, it is worth considering that routes of administration cannot be easily compared as dose frequency and specific details of the treatment process administration can impact patient preference. From a patient burden standpoint, people living with advanced CKD take a number of oral medications and may prefer a once-weekly injection to an additional daily oral medication. The once-weekly

Table 3 Frequency and recommended dosages of currently available GLP-1 RAs

Generic name (commercial)	Exenatide BID (Byetta©)	Liraglutide (Victoza©)	Lixisenatide (Lyxumia©/Adlyxin©)	Oral Semaglutide[a] (Rybelsus©)	Exenatide QW (Bydureon©)	Semaglutide (Ozempic©)	Dulaglutide[b] (Trulicity©)
Frequency	Twice-daily	Once-daily	Once-daily	Once-daily	Once-weekly	Once-weekly	Once-weekly
Initial dosage	5 mcg for 1 month	0.6 mg for 1 week	10 mcg for 14 days	3 mg for 30 days or 1 month	2 mg	0.25 mg for 4 weeks	0.75 or 1.5 mg
Recommended dosage	5 or 10 mcg[c]	1.2 or 1.8 mg	20 mcg	7 or 14 mg	2 mg	0.5 or 1 mg	0.75, 1.5, 3.0, or 4.5 mg

[a] Oral semaglutide should be taken on an empty stomach, and patients should wait at least 30 min before eating or drinking or taking other oral medicinal products; tablets should not be split, crushed, or chewed

[b] Based on EMA SPC the recommended dose is 0.75 mg once weekly if used as monotherapy and 1.5 mg once weekly if used as an add-on therapy. For potentially vulnerable populations, 0.75 mg once weekly can be considered as a starting dose. For additional glycemic control, the 1.5 mg dose may be increased after at least 4 weeks to 3 mg once weekly and the 3 mg dose may be increased after at least 4 weeks to 4.5 mg once weekly. The initial dose for dulaglutide is 0.75 mg as indicated in the FDA-approved label for Trulicity [119]

[c] The European Medicines Agency (EMA) Summary of Product Characteristics (SPC) recommends a dose of 5 or 10 mcg for exenatide twice daily, while the U.S. Food and Drug Administration (FDA)-approved label recommends 10 mcg twice daily after 1 month based on clinical response

Table 4 Administration characteristics of currently approved GLP-1 RA prefilled pen devices

Generic name (commercial)	Exenatide twice daily (Byetta©)	Liraglutide (Victoza©)	Lixisenatide (Lyxumia©/ Adlyxin©)	Exenatide QW (Bydureon©)	Dulaglutide (Trulicity©)	Semaglutide (Ozempic©)
Is reconstitution required?	No	No	No	Yes	No	No
Is dose administration automatic?	No	No	No	Yes[a]	Yes	No
Does the device need to be primed?	Yes	Yes	Yes	No	No	Yes
Does a needle need to be attached?	Yes	Yes	Yes	No	No	Yes
Is dose selection required?	Yes	Yes	No	No	No	Yes
Is the device for single use?	No	No	No	Yes	Yes	No

[a]The current device that delivers exenatide once weekly is the Bydureon BCise© pen (AstraZeneca plc, Cambridge, UK) that automatically administers the dose. Previous versions of the pen device do not automatically deliver the dose

injection has received positive patient acceptance [123]; however, shared decision-making between the primary care physician and patient is important for improving patient outcomes.

CONCLUSION

In summary, there is strong evidence from clinical trials for the use of GLP-1 RAs in the management of T2DM in people living with CKD; however, studies that assess renal outcomes as the primary outcome are needed. The recent position statement by the ADA advocating the use of both SGLT2i and GLP-1 RAs is encouraging, indicating that CKD in T2DM is under the spotlight. As different guidelines exist for nephrologists, cardiologists, endocrinologists, primary care practitioners, pharmacists and nurse practitioners, confusion can arise when there is no consensus on the treatment strategy. Guidelines across these specialties

must be written and harmonized for the overall betterment of patient welfare. With the advent of additional GLP-1 RAs, it is critical that the treatment landscape be monitored and reviewed so that healthcare practitioners have the most current information when addressing their patients' needs. The evidence currently available indicates that GLP-1 RA could add to the arsenal available to address persistent gaps in the care of people living with T2DM with, or at the risk of, developing CKD and to reduce the residual renal risk present in those who have already developed CKD.

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