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CKJ Review

CKJ REVIEW

GLP-1 receptor agonists in patients with chronic kidney disease and either overweight or obesity

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as game-changers across the cardiovascular–kidney–metabolic (CKM) spectrum: overweight/obesity, type 2 diabetes mellitus (T2DM) and associated chronic kidney disease (CKD) and cardiovascular disease (CVD). Liraglutide, semaglutide and tirzepatide are European Medicines Agency approved to improve metabolic control in T2DM and to decrease weight in persons with obesity [body mass index (BMI) ≥30 kg/m^2] or with overweight (BMI ≥27 kg/m^2) associated with weight-related comorbidities such as hypertension, dyslipidaemia, CVD and others. Additionally, liraglutide and semaglutide are approved to reduce CVD risk in patients with CVD and T2DM. Semaglutide is also approved to reduce CVD risk in patients with CVD and either obesity or overweight and in phase 3 clinical trials showed kidney and cardiovascular protection in patients with T2DM and albuminuric CKD (FLOW trial) as well as in persons without diabetes that had CVD and overweight/obesity (SELECT trial). Thus, nephrologists should consider prescribing GLP-1 RAs to improve metabolic control, reduce CVD risk or improve kidney outcomes in three scenarios: patients with overweight and a related comorbid condition such as hypertension, dyslipidaemia or CVD, patients with obesity and patients with T2DM. This review addresses the promising landscape of GLP-1 RAs to treat persons with overweight or obesity, with or without T2DM, within the context of CKD, assessing their safety and impact on weight, metabolic control, blood pressure and kidney and cardiovascular outcomes, as part of a holistic patient-centred approach to preserve CKM health.

Keywords: chronic kidney disease, glucagon-like peptide-1 (GLP-1) receptor agonists, hypertension, obesity, overweight

INTRODUCTION

Chronic kidney disease (CKD) is among the fastest growing causes of death worldwide, driven by population aging and the increasing prevalence of overweight/obesity, type 2 diabetes mellitus (T2DM) and hypertension [1]. Overweight and obesity are defined by the World Health Organization as having a body mass index (BMI) ≥25–<30 and ≥30 kg/m^2, respectively [2]. More than half of the world's population is projected to have overweight/obesity by 2035 [3]. Overweight and obesity are independently associated with an increased risk of cardiovascular disease (CVD), which causes death in more than two-thirds of patients [4]. Furthermore, obesity increases the risk of T2DM, hypertension and CKD [5, 6]. The three conditions frequently coexist, as recently emphasized by the cardiovascular–kidney–metabolic (CKM) syndrome scientific statement from the

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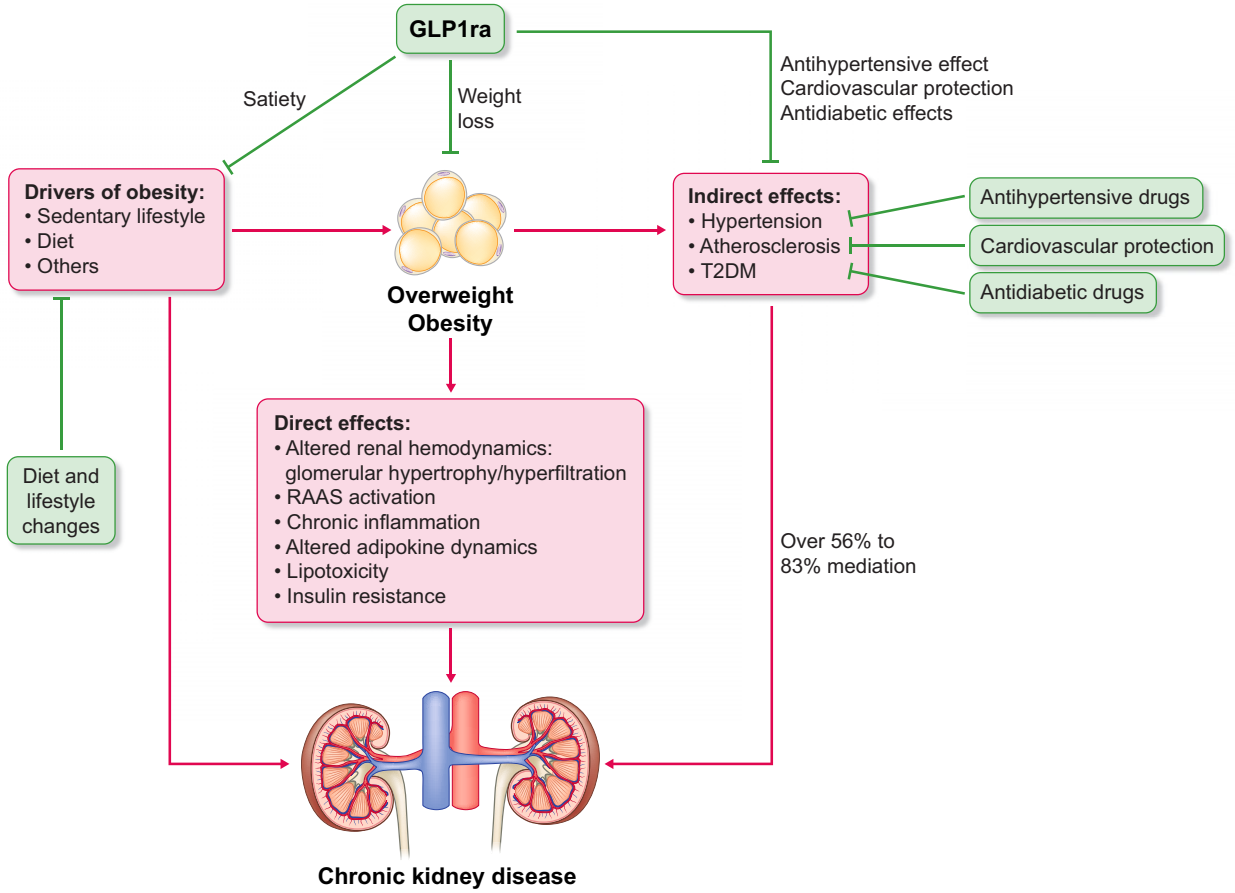


Figure 1: Obesity is an independent risk factor for CKD with a complex pathophysiology involving shared risk factors, direct effects of obesity and indirect effects through promotion of vascular disease, hypertension and T2DM. Indirect effects through BP and hyperglycaemia are estimated to mediate up to 83% of the negative impact of obesity on CKD [14]. Mediation analyses of liraglutide and semaglutide in the T2DM CVOTs estimated up 48% mediation of kidney effects indirectly, through BP and hyperglycaemia [15]. Similar analyses are awaited for overweight/obesity trials in which participants did not have T2DM.

American Heart Association [7]. Treatment for T2DM, obesity, CVD and CKD has converged on two families of drugs that have convincing evidence of improved metabolic control of T2DM, decreased body weight, improved control of blood pressure (BP) and decreased risk of cardiovascular and kidney events: sodium–glucose co-transporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs; incretin analogues) [8–12]. While both families of drugs are approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to treat T2DM, other indications diverge. From the nephrologist's point of view, clinical guidelines recommend SGLT2is for kidney protection in persons with CKD with or without T2DM and also GLP-1 RAs to optimize metabolic control in persons with T2DM and CKD [11, 12]. Guidelines will likely be updated soon, given the kidney protection offered by semaglutide in the FLOW trial (NCT03819153) in T2DM with albuminuric CKD [13], expanding from the current indication and guideline-recommended use to improve metabolic control. Thus the new frontier is using GLP-1 RAs to treat obesity/overweight in people at risk of CKD or already having CKD, even if T2DM is not present, with a holistic CKM aim of improving CVD, metabolic and kidney outcomes. This review addresses the promising landscape of GLP-1 RAs to treat persons with overweight/obesity, with or without T2DM, within the context of CKD or CKD prevention, assessing their impact on weight, metabolic control, BP and kidney and cardiovascular protection and their safety within a comprehensive patient-centred approach.

UNRAVELLING THE COMPLEX RELATIONSHIP BETWEEN OVERWEIGHT/OBESITY AND CKD

Overweight and obesity are independent risk factors for the development and progression of CKD [6]. The association between overweight/obesity and CKD is thought to be causal and mediated mainly by T2DM and hypertension: 56–83% mediation, depending on the methodology [14, 15] (Fig. 1). Overall, assuming causality, an estimated 39% (range 36–42%) of advanced CKD in women and 26% (range 22–30%) in men 40–79 years of age may result from overweight/obesity in England [5]. Other potential links between obesity and CKD include the adverse impact on kidney health of the lifestyle and dietary patterns that caused overweight/obesity as well as direct effects of overweight/obesity on kidney disease (Fig. 1) [14, 16]. The term obesity-related glomerulopathy refers to glomerular hypertrophy and adaptive focal segmental glomerulosclerosis (FSGS) resulting from obesity-induced glomerular hyperfiltration [17]. The clinical manifestations are indistinguishable from

Table 1: Risk of kidney disease in persons with overweight/obesity [5, 23].

BMI (kg/m^2)	CKD G4–G5, HR (95% CI)	BMI (kg/m^2)	Kidney failure, HR (95% CI)
25–<30	1.34 (1.30–1.38)	25–<30	1.87 (1.64–2.14)
30–<35	1.94, 1.87–2.01	30–<35	3.57 (3.05–4.18)
≥35	3.10, 2.95–3.25	35–<40	6.12 (4.97–7.54
	≥40	7.07 (5.37–9.31	

other forms of secondary FSGS and characterized by single-nephron hyperfiltration, with or without global hyperfiltration, and subnephrotic proteinuria that responds to antiproteinuric drugs that decrease hyperfiltration, such as renin–angiotensin system (RAS) blockers, mineralocorticoid receptor antagonists (MRAs) and, more recently, SGLT2is [17–20]. As recently as 2016, weight loss by hypocaloric diet or bariatric surgery was considered to obtain the best antiproteinuric results. However, implicitly recognizing the difficulty to lose weight, the 2016 report emphasized novel research targeting molecular mechanisms of lipotoxicity [17]. Ectopic lipids (sometimes referred to as fatty kidneys) and renal sinus fat have been proposed to contribute to CKD in obesity [21, 22].

While most literature refers to obesity, we should emphasize that overweight, which is more common than obesity, is also associated with an increased risk of CKD, and GLP-1 RAs are approved for the treatment of overweight when BMI ≥27 kg/m^2 is associated with CVD risk factors, including hypertension. Each 5-kg/m^2 increase in BMI above 25 kg/m^2 was associated with higher renal mortality {hazard ratio [HR] 1.59 [95% confidence interval (CI) 1.27–1.99]} [6]. Higher BMI was also independently associated with an increased risk of CKD stage G4–G5 and kidney failure, already starting in the overweight range [HR 1.34 (95% CI 1.30–1.38) and 1.87 (95% CI 1.64–2.14), respectively] for BMI 25–<30 kg/m^2 [5, 23] (Table 1). High BMI has been causally linked to >253 million global disability-adjusted life years, 6.5 million deaths and almost 62 million years lived with disability from CKD, resulting in a higher global BMI-related burden for CKD than for other conditions traditionally linked to obesity, such as colorectal cancer [4].

OVERWEIGHT, OBESITY, LIFESTYLE INTERVENTIONS AND CKD

There is some evidence that lifestyle interventions to reduce weight in T2DM may be beneficial for CKD, although it is derived from a secondary analysis of a clinical trial terminated for futility. The Look AHEAD: Action for Health in Diabetes (NCT00017953) clinical trial randomized 5145 overweight or obese persons 45–76 years of age with T2DM to intensive lifestyle intervention to achieve and maintain weight loss through reduced caloric intake and increased physical activity (intervention) or diabetes support and education (control) [24]. Although planned for >13 years, the trial was stopped for futility on the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or hospitalization for angina after a median follow-up of 9.6 years. In the intervention arm, weight loss was greater in the first year than at the end of follow-up (8.6% versus 0.7% in controls at 1 year; 6.0% versus 3.5% at study end). Haemoglobin A1c (HbA1c; −0.64% versus −0.14% in the first year) and systolic blood pressure (SBP) (−6.8 versus −2.8 mmHg) also decreased, but differences between arms got narrower over time (e.g. average over time difference in SBP was 1.9 mmHg). The primary event cumulative incident curves started to diverge at 2–3 years, but then converged again as other differences narrowed over time. However, a secondary analysis showed a 31% reduction [HR 0.69 (95% CI 0.55–0.87)] in the risk of Kidney Disease: Improving Global Outcomes (KDIGO) very-high-risk CKD, an effect only partly attributable to reductions in body weight, HbA1c and SBP [25]. Unlike for cardiovascular events, renal event cumulative incident curves diverged over time, especially in women and in those with BMI <35 kg/m^2. In any case, lifestyle interventions should always be recommended given their potential for benefit in multiple chronic conditions. However, the fundamental challenge of treating obesity solely with 'lifestyle interventions' is the difficulty of maintaining these changes over time.

INCRETINS, TWINCRETINS AND TRIAGONISTS

The incretin phenomenon refers to an insulin secretory response to oral glucose intake mediated by the gut-derived hormones (incretins) GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [26]. GLP-1 and GIP are released by gut epithelium in response to meals and stimulate their respective receptors to promote insulin secretion and block glucagon release (Fig. 2). Incretins increase satiety and slow gastric emptying, decreasing food intake and contributing to weight loss. They are degraded by dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors are used as antidiabetic drugs but have not convincingly shown the cardiovascular- and kidney-protective properties of GLP-1 RAs, likely because they also degrade multiple other peptides [27]. GLP-1 RAs are analogues of GLP-1 or similar peptides from other species (e.g. exenatide is derived from Gila monster exendin-4) whose amino acid sequence has been modified to resist degradation by DPP-4, increasing their half-life, with an initial aim of treating T2DM.

More recently, the tirzepatide amino acid sequence was designed to activate both GLP-1 and GIP receptors, which accounts for the label of twincretin [28] (Fig. 3). Activation of two or three receptors may potentiate the effect on weight loss and glycaemic control [29]. Interestingly, a dual GLP-1/GIP receptor antagonist also induced pronounced weight loss, raising questions as to our understanding of incretin physiology, as GIP receptor agonists may downregulate the receptor and actually decrease signalling [30, 31]. The latest approach is represented by triagonists, such as retatrutide, which activate the GLP-1, GIP and glucagon receptors [32] (Figs. 3 and 4). Glucagon receptor agonism is aimed at reducing energy uptake, increasing energy consumption or both. Peptides can be combined, as in cagrisema (semaglutide plus cagrilintide, an amylin receptor agonist) [33, 34]. Natural amyline is a pancreatic hormone inducing satiety.

Unless otherwise specified, and given that twincretins also have GLP-1 RA activity, the term GLP-1 RA will be used for both types of drugs in the present review.

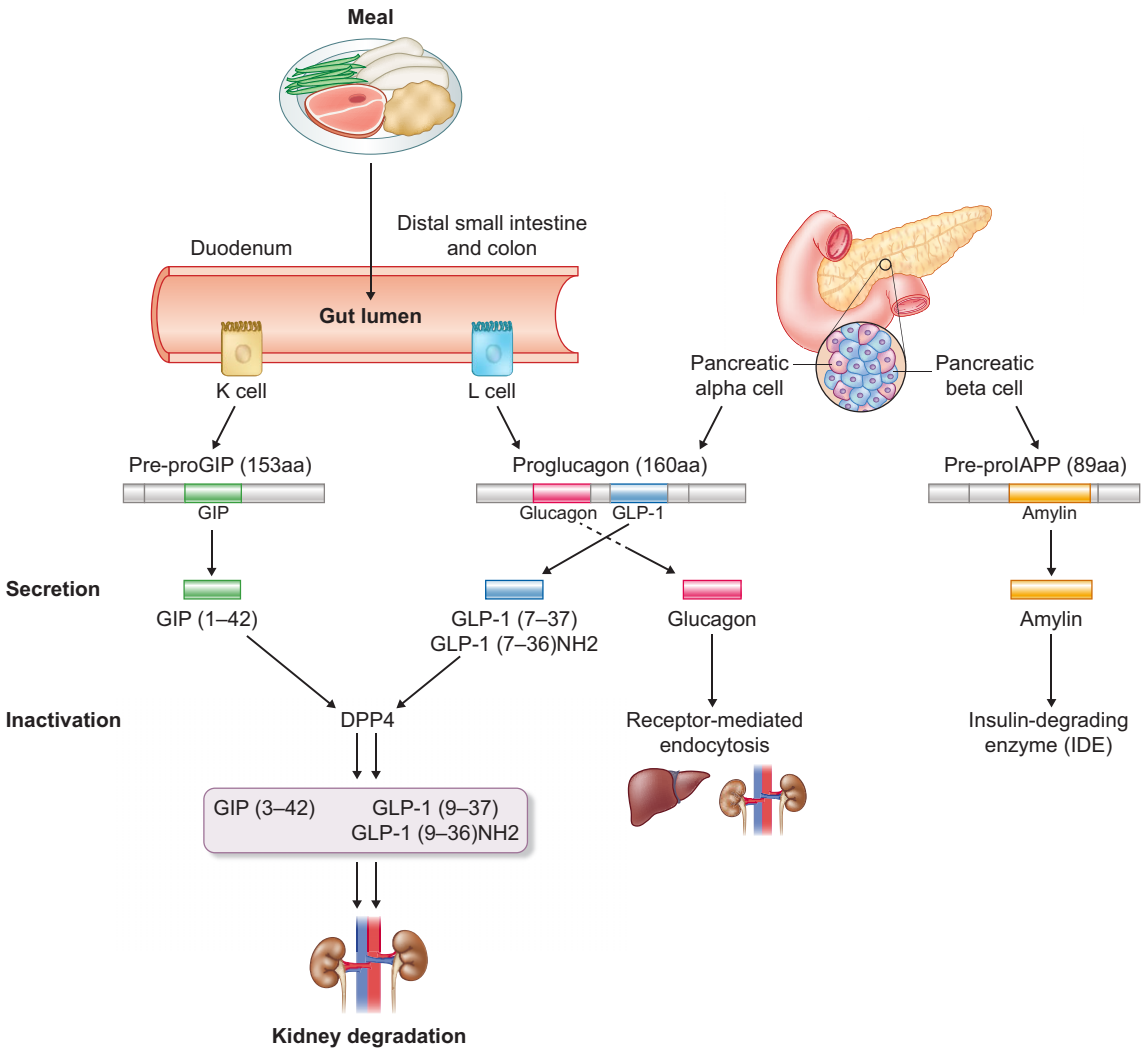


Figure 2: Physiology of GIP and GLP-1. Food ingestion triggers the release of incretins from gut neuroepithelial cells. GIP is encoded by the *GIP* gene and is generated by proteolysis of a precursor peptide (preproGIP) by K cells in the duodenum. GLP-1 is encoded by the *GCG* gene that also encodes glucagon and GLP-2. GLP-1 is generated by proteolysis of a precursor peptide (proglucagon) by L cells from the distal small intestine. Glucagon is also released from proglucagon, but in a different cell type (pancreatic alpha cells). Amylin is a product of pancreatic beta cells. Both GIP and GLP-1 have incretin effects (i.e. promote insulin release from pancreatic beta cells) and have additional shared and unique actions as reflected in Fig. 4. Both have a short half-life (≈5 and 2 min for GIP and GLP-1, respectively) and are metabolized by DPP-4 into inactive peptides that are filtered by glomeruli and reabsorbed and further degraded by kidney proximal tubular cells. DPP-4 inhibitors are also antidiabetic drugs, but they degrade other peptides beyond the incretins and the clinical impact of DPP-4 inhibitors may thus differ from that of GLP-1R agonists or dual GLP-1R/GIPR agonists. Initially adapted from Baggio and Drucker [89] and expanded from reference Bosch *et al.* [28].

CLINICAL USE OF GLP-1 RAS AND TWINCRETINS

Six GLP-1 RAs (exenatide, lixisenatide, dulaglutide, albiglutide, liraglutide, subcutaneous and oral semaglutide) and a dual GIP–GLP-1 RA (tirzepatide) have been approved by the EMA since 2005 to improve metabolic control in T2DM [35]. However, we will focus on liraglutide, semaglutide and tirzepatide, which are also approved to promote weight loss in overweight/obesity (Table 2, Fig. 5) [36–40]. Beyond glycaemic control, GLP-1 RAs promote weight loss and improve lipid and BP control and cardiovascular and kidney outcomes, leading to trials addressing weight loss and cardiovascular outcomes in overweight/obesity as well as kidney outcomes in persons living with T2DM and CKD [38, 41]. Additionally, liraglutide and semaglutide are approved to reduce CVD risk in patients with CVD who also have T2DM and semaglutide is approved to reduce CVD risk in adults with CVD and overweight/obesity. The kidney protection observed in the FLOW trial [13] is expected to result in a novel indication to slow CKD progression in persons with T2DM and CKD.

OVERWEIGHT, OBESITY AND CKD IN THE 2024 KDIGO GUIDELINES ON CKD

The 2024 KDIGO guidelines on CKD state that physicians should consider advising/encouraging people with obesity and CKD to lose weight [12]. Although no specific guidance is provided on

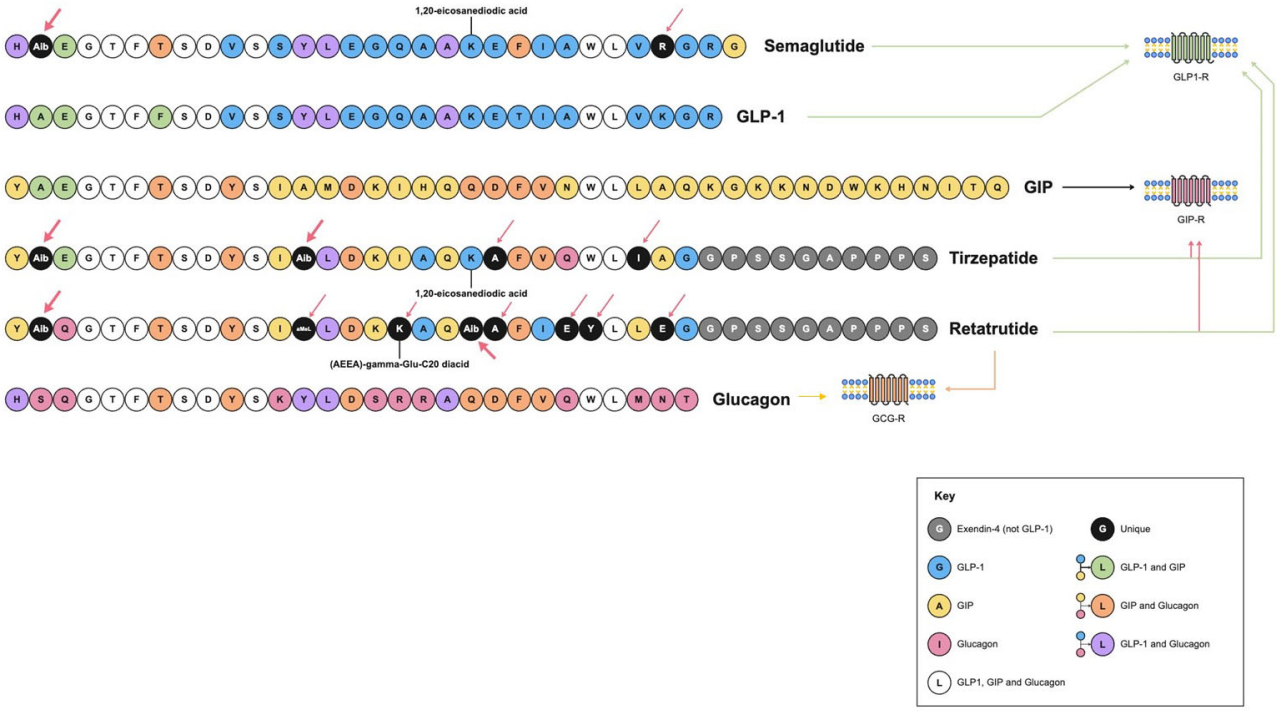


Figure 3: Structure of GLP-1, the GLP-1 RA semaglutide, GIP, the dual GLP-1 and GIP RA tirzepatide, glucagon and the triple agonist retatrutide. Amino acids are colour-coded reflecting shared or unique amino acids. Arrows identify amino acids that are unique for synthetic agonists. The thick arrow indicates aminoisobutyric acid (Aib) residues in positions 2 and 13, which are shared by semaglutide and tirzepatide, as well as in position 2 for retatrutide. Tirzepatide has a C-terminal amide and a lysine residue at position 20 attached to 1,20-eicosanedioic acid via a linker. The GLP-1, GIP and glucagon receptors are also shown. Initially adapted from Novikoff *et al.* [90] and then expanded from Bosch *et al.* [28].

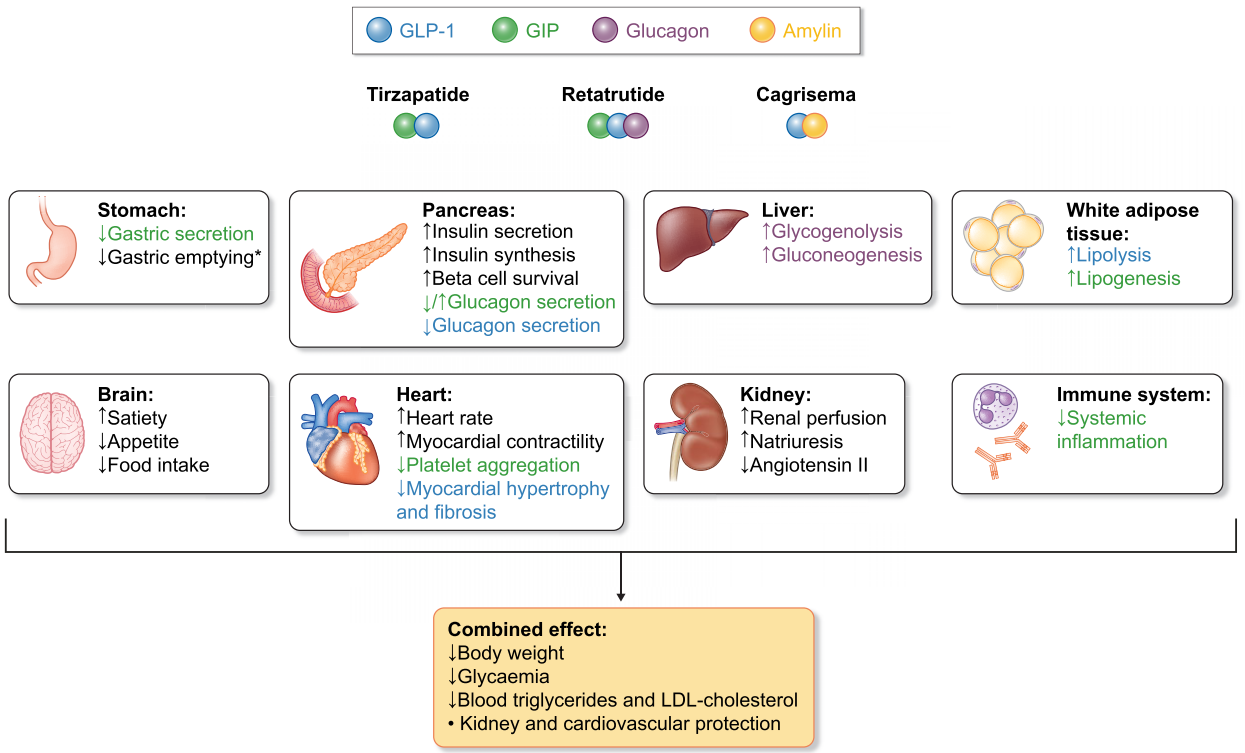


Figure 4: Shared and unique metabolic actions by GLP-1, GIP, glucagon and amylin in key target organs that may be reproduced by tirzepatide, retatrutide and cagrisema. Putative direct cardiovascular and kidney effects are less well characterized in humans than metabolic effects. Expanded from Bosch *et al.* [28].

Table 2: GLP-1 RA use in overweight/obesity: drugs approved to treat both T2DM and overweight/obesity.

Drug	Approved indications		Use in CKD
	FDA	EMA	
Liraglutide (Saxenda)	Adults: BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. hypertension, T2DM or dyslipidaemia) (2014) Adolescents ≥12 years of age with a body weight >60 kg and BMI corresponding to 30 kg/m^2 for adults	Adults: BMI ≥30 kg/m^2 or ≥27–<30 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. prediabetes or T2DM, hypertension, dyslipidaemia or obstructive sleep apnoea) (2015) Adolescents ≥12 years of age with a body weight >60 kg and BMI corresponding to 30 kg/m^2 for adults	No dose adjustment required[a]
Semaglutide (Wegovy)	Adults: BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. hypertension, T2DM or dyslipidaemia) (2021) Adults: Indicated for reducing risks of MACE if overweight/obesity and established CVD (2024) Adolescents ≥12 years of age: obesity (BMI ≥95th percentile for sex and age)	Adults: BMI ≥30 kg/m^2 or ≥27–<30 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. prediabetes or T2DM, hypertension, dyslipidaemia, obstructive sleep apnoea or CVD) (2022) Adolescents ≥12 years of age: obesity (BMI ≥95th percentile for sex and age) and body weight >60 kg	No dose adjustment required[a]
Tirzepatide (Zepbound, Mounjaro)	Zepbound. Adults: BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. hypertension, dyslipidaemia, T2DM obstructive sleep apnoea or CVD) (2023)	Mounjaro. Adults: BMI ≥30 kg/m^2 or ≥27–<30 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. hypertension, dyslipidaemia, obstructive sleep apnoea, CVD, prediabetes or T2DM) (2023)	No dose adjustment required

The year of approval for adults is shown in parentheses.
MACE: cardiovascular death or non-fatal myocardial infarction or stroke.
[a]According to the FDA and KDIGO-ADA 2022. The EMA still indicates that it is not recommended if creatinine clearance is <30 ml/min, including kidney failure.

how to achieve weight loss, subsequent practice points state that physicians should encourage people with CKD to undertake physical activity and to adopt healthy and diverse diets with a higher consumption of plant-based than animal-based foods and a lower consumption of ultraprocessed foods, since this may help slow CKD progression via a reduction of CKM risk factors such as hypertension, CVD, T2DM and obesity.

The KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD statement on obesity is also quite mild: physicians should consider advising/encouraging patients with obesity, diabetes and CKD to lose weight, particularly patients with an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2, although they also state that GLP-1 RA may be preferentially used in patients with obesity, T2DM and CKD to promote intentional weight loss, without warning about GFR thresholds. The caveat for those with lower eGFRs relates to concern about spontaneous reductions in dietary intake, malnutrition and muscle wasting, which apparently is not considered an issue when using GLP-1 RAs.

Neither guideline covers overweight, despite the existence of GLP-1 RAs approved to decrease weight in persons with overweight and conditions common in CKD such as hypertension and CVD (Table 2) [5, 6]. We believe this is a major shortcoming of current CKD guidelines. However, the 2024 KDIGO guidelines on CKD recommend research to evaluate the effects of GLP-1 RAs on the risk of adverse cardiovascular outcomes and kidney disease progression by designing trials that include persons with overweight/obesity without T2DM [12], trials that are discussed below.

OVERWEIGHT, OBESITY, GLP-1 RAS AND CKD: UPDATED EVIDENCE

In T2DM cardiovascular outcomes trials (CVOTs), GLP-1 RAs protected against CVD (primary endpoint) and from CKD progression (secondary endpoint) [41, 42]. The impact on kidney protection was mainly driven by albuminuria [43]. Additionally, in SUSTAIN-9 (NCT03086330), GLP-1 RAs further decreased glycaemia and body weight in persons with T2DM who were on SGLT2i [44]. As a result, the 2022 and 2024 KDIGO guidelines for the treatment of CKD in T2DM indicate GLP-1 RAs as third-line antidiabetic drugs to improve glycaemic control when not achieved by metformin and/or SGLT2i or if SGLT2i contraindicated [11, 12]. In contrast, the American Diabetes Association 2024 standards of care for T2DM list GLP-1 RAs as CKM drugs recommended to reduce cardiorenal risk and to attain metabolic goals (glycaemic and weight control), emphasizing that semaglutide and tirzepatide are the only antidiabetic drugs that combine very high efficacy to achieve both metabolic goals [45]. Thus the role of GLP-1 RAs in patients with CKD and T2DM is well established to improve metabolic control and was recently expanded to include improved cardiorenal outcomes based on the FLOW trial of semaglutide [13], fulfilling a holistic CKM role when CKD is already present in patients with T2DM. Most participants in the T2DM CVOTs for liraglutide, semaglutide and tirzepatide had overweight or obesity (92–100%) [15, 39, 46, 47] (Table 3). Thus we may frame the evidence for the CKM benefit of GLP-1 RA as mainly obtained in people with overweight/obesity either with T2DM (initial CVOT) or without T2DM (more recent trials), including persons with CKD [13, 20].

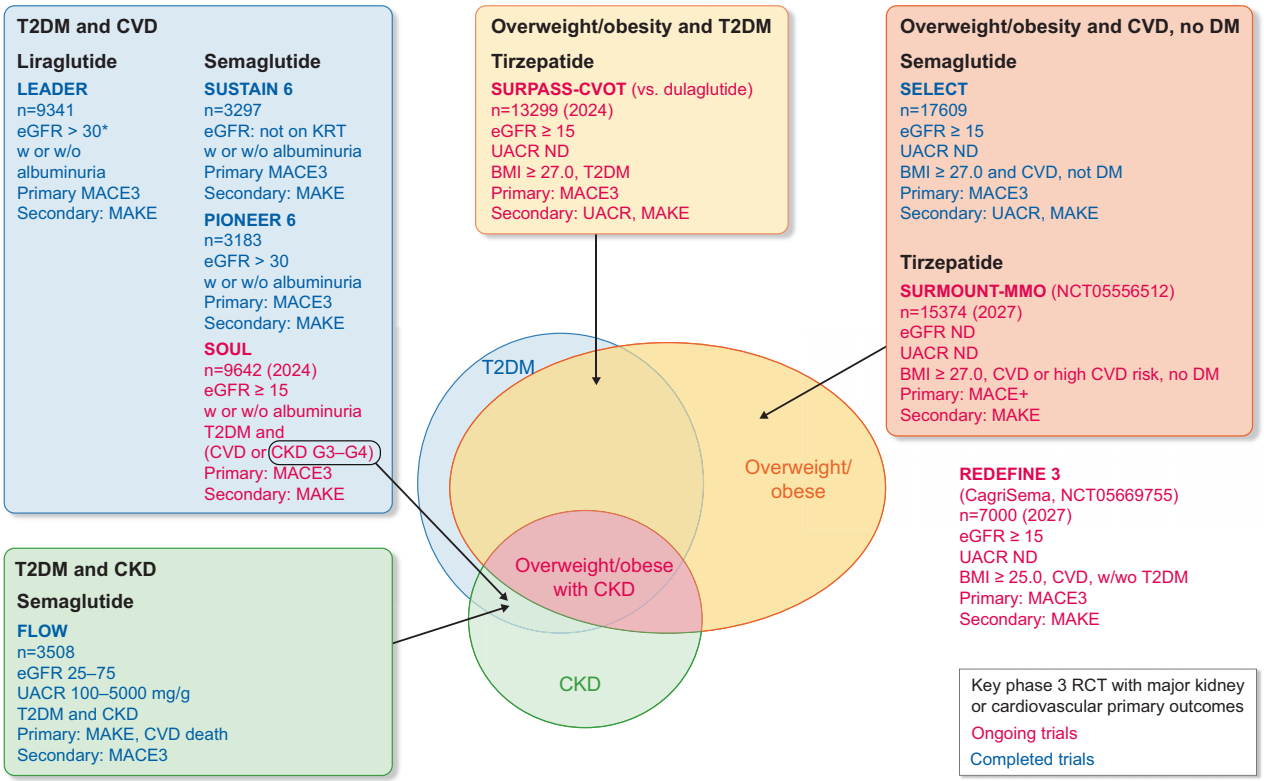


Figure 5: Key phase 3 RCT with kidney or cardiovascular primary outcomes of GLP-1 RAs approved for the treatment of both obesity and T2DM. Kidney failure, end-stage kidney disease or chronic or intermittent haemodialysis or peritoneal dialysis were equated with eGFR <15 ml/min/1.73 m^2. KRT: kidney replacement therapy (haemodialysis, peritoneal dialysis or kidney transplantation); ND: no data in clinicaltrials.gov; MACE3: cardiovascular death or non-lethal stroke or non-lethal myocardial infarction; MACE+: MACE plus additional criterion such as unstable angina; MAKE: major adverse kidney endpoints (refers to endpoint based on decreased eGFR, either kidney failure or a percentage decrease in eGFR from baseline of renal death); UACR: refers to endpoints based on albuminuria; ND: no data. Trials are colour-coded (orange: ongoing; green: completed; as of 24 April 2024). References for trials with either published baseline characteristics or results: [38–40]. For other ongoing trials, the clinicaltrials.gov identifier is provided. Trials are placebo-controlled unless otherwise specified. eGFR expressed as ml/min/1.73 m^2, UACR as mg/g and BMI as kg/m^2. *After randomization of 220 subjects with eGFR <30 ml/min/1.73 m^2, patients on KRT were excluded.

Following the pathophysiological scheme in Fig. 1, liraglutide, semaglutide and tirzepatide modulate shared risk factors for obesity and CKD, as they promote satiety, thus decreasing food intake, with all its components (e.g. salt, phosphate). They also decreased body weight, potentially contributing to mitigate the direct impact of obesity on CKD. Finally, they improved other risk factors for CKD progression (glycaemia, BP) and decreased cardiovascular events.

In addition to being approved to treat T2DM, GLP-1 RAs prevented the development of new-onset T2DM in overweight/obese participants as exemplified by semaglutide in the SELECT CVOT (NCT03574597) [HR for HbA1c ≥ 6.5%: 0.27 (95% CI 0.24–0.31)] [48].

Before GLP-1 RAs, there was low evidence of the impact of weight loss drugs on BP lowering, mostly based on small studies [49]. However, integration of results from recent GLP-1 RA and older weight loss drug trials suggest a good correlation between weight loss and a decrease in BP (R^2 = 0.91 for SBP), a result mainly driven by GLP-1 RAs (Fig. 6). Retatrutide decreased mean SBP by up to 12.1 mmHg in persons with overweight/obesity not having uncontrolled hypertension [50], improving on results reported for tirzepatide [51] and semaglutide [52]. Additionally, 30–41% of participants in the higher-dose groups discontinued at least one antihypertensive medication.

A reduced risk of major adverse cardiovascular events (MACE) was reported in CVOTs for T2DM for dulaglutide [AWARD-7 (NCT01621178)] [53], liraglutide [LEADER (NCT01179048)] [54, 55], semaglutide [SUSTAIN-6 (NCT01720446)] [55], albiglutide [Harmony Outcomes (NCT02465515)] [56] and efpeglenatide [AMPLITUDE-O (NCT03496298)] [57]. CVOTs enrolled participants at high risk of CVD, including those with decreased renal function (GFR >15 ml/min/1.73 m^2). In a combined analysis of subcutaneous (SUSTAIN-6) and oral [PIONEER 6 (NCT02692716)] T2DM CVOTs, semaglutide consistently reduced MACE risk versus placebo across all eGFR and urinary albumin:creatinine ratio (UACR) subgroups [58] Additionally, semaglutide (SELECT) reduced MACE in participants with overweight/obesity and baseline CVD but no T2DM [48]. Cardiovascular protection was also observed for patients with CKD G3+ (eGFR <60 ml/min/1.73 m^2) and T2DM (e.g. liraglutide and semaglutide) or overweight/obesity without T2DM (e.g. semaglutide) [15, 48, 54, 55] (Table 3). In fact, the cardiovascular protection afforded to participants with CKD G3+ was even larger than for participants with GFR >60 ml/min/1.73 m^2, at least numerically, for both T2DM and obesity.

Through any of the mechanisms described above, GLP-1 RAs may improve CKD outcomes in patients with overweight/obesity and CKD. Indeed, kidney secondary outcomes from CVOTs showed a decrease in albuminuria and in events

Table 3: CVOT for GLP-1 RAs approved for the treatment of both T2DM and overweight/obesity.

		T2DM				Ow/Ob, not DM			
	LEADER [54]	SUSTAIN-6 [55]	PIONEER 6 [61, 62]	SUSTAIN-6 + PIONEER 6 [58, 67, 91]	FLOW [13, 68]	SURPASS CVOT [39]	Tirzepatide meta-analysis [92]	SELECT [20, 63]	SURMOUNT-MMO
Key study characteristics									
N	9340	3297	3183	6480	3533	13 299	7215	17 604	15 374
Drug	Liraglutide 1.8 mg/day	Semaglutide sc 1 mg/week	Semaglutide oral 14 mg/day	Semaglutide (sc 0.5–1 mg/week, oral 14 mg/week)	Semaglutide sc 1 mg/week	Tirzepatide 15 mg/week	Tirzepatide 15 mg/week	Semaglutide 2.4 mg/week	Tirzepatide 5, 10 or 15 mg/week
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Dulaglutide 1.5 mg/week	Placebo, insulin or glargine, semaglutide, dulaglutide	Placebo	Placebo
Phase	3	3	3	3	3	3	NA[a]	3	3
Primary endpoint	MACE3	MACE3	MACE3	MACE3	MAKE	MACE3	MACE4	MACE3	MACE4
Baseline data									
Overweight (BMI 25–<30 kg/m^2)	29% [47]	36%	40%		29.9%	All (inclusion criterion)	All (as per inclusion criteria)	28.5%	
Obese (BMI ≥30 kg/m^2)	62% [47])	64%	60%		58.3%			71.5%	
BMI (kg/m^2)	32.5 ± 6.3 [93]	32.8 ± 6.2	32.3 ± 6.5	32.5 ± 6.4	32.0 ± 6.3	32.6 ± 5.5	32.791	33.3 ± 5.0	
eGFR exclusion criterion	KRT	KRT	<30	<30	KRT	<15		KRT	None[b]
Weight (kg)	91.9 ± 21.2	92.1 ± 20.6	91.0 ± 21.4	91.7 ± 21.1	89.6 ± 20.5	92.5 ± 18.8	90.98 ± 20.37	96.5 ± 17.5	
eGFR (ml/min/1.73 m^2)	81.5 ± 28.0 [93]	76 ±27	74 ± 21	75.0 ± 21.8	47.0 ± 15.2	76.5 ± 21.3	89.04 ± 18.76	82.4 ± 17.5 [48]	
UACR (mg/g)	—	–	–	24.7 ± 710.2	567.6	22.0 (9.0–83.0)	12.0	7.4 (4.5–15.7)	
Participants without CKD (eGFR >60 and UACR <30)	52.35% [94]	49.3% [58]	No data	No data	No data	No data	No data	No data for the combination	
CKD G3+	24.7% [54]	28.5%	26.9%	26.1%	79,2%	22.8%	8.3%	10.9%	
CKD A2	26.3% [93]	9.3%	No data	9.6%	28.4%	32.0%	24%	1968 (11.2)	
CKD A3	10.0 % [93]		No data		68.5%	11.5%	5.3%	325 (1.8)	
Study results									
SBP change (mmHg)	1.2 (−1.9 to −0.5)	−2.59 (−4.09 to −1.08)	−3 (−4.25 to −1.75)	–	−2.23 (−3.33 to −1.13)			−3.82 ± 0.16	
Weight loss (kg)	−2.3 (−2.5 to −2)	−4.53 (−5.34 to −3.72) [95]	−4.2	–	−4.10 (−4.56 to −3.65)			−8.51 (−8.75 to −8.27)	
HbA1c decrease (%)	0.40 (0.45–0.34)	1.1 (1.2–0.9)	1 (1.2–0.9)	0.6–1.6	−0.81 (−0.90 to −0.72)			–	
MACE-3 (HR)	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.79 (0.57–1.11)	0.76 (0.62–0.92)	0.82 (0.68–0.98)		0.83 (0.58–1.18)	0.80 (0.72–0.90)	

Table 3: Continued

	T2DM					Ow/Ob, not DM			
	LEADER [54]	SUSTAIN-6 [55]	PIONEER 6 [61, 62]	SUSTAIN-6 + PIONEER 6 [58, 67, 91]	FLOW [13, 68]	SURPASS CVOT [39]	Tirzepatide meta-analysis [92]	SELECT [20, 63]	SURMOUNT-MMO
MACE-3 (HR, in CKD G3+ <60)	0.69 (0.57–0.85)	0.67 (0.48–0.92)	0.74 (0.41–1.33)	0.74 (0.46–1.19)				0.69 (0.52–0.90)	
MACE-3 (HR in eGFR ≥60)	0.94 (0.83–1.07)	0.84 (0.57–1.25)	0.81 (0.54–1.22)	0.72 (0.56–0.93)				0.82 (0.72–0.92)	
Cardiovascular death (HR)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.49 (0.27–0.92)	0.78 (0.56–1.10)	0.71 (0.56–0.89)		0.90 (0.50–1.61)	0.85 (0.71–1.01)	
Fatal or non-fatal myocardial infarction (HR)	0.86 (0.73–1.00)	0.81 (0.57–1.16)	1.18 (0.73–1.90)	0.88 (0.66-1.18)	0.80 (0.55–1.15)		0.76 (0.45–1.28)	0.72 (0.61–0.85)	
Fatal or non-fatal stroke (HR)	0.86 (0.71–1.06)	0.65 (0.41–1.03)	0.74 (0.35–1.57)	0.65 (0.43–0.97)	1.22 (0.84–1.77		0.81 (0.39–1.68)	0.93 (0.74–1.15)	
All-cause mortality (HR)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.51 (0.31–0.84)		0.80 (0.67–0.95)		0.80 (0.51–1.25)	0.81 (0.71–0.93)	
Hospital admission for heart failure (HR)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.86 (0.48–1.44)				0.67 (0.26–1.70)	0.82 (0.71–0.96)	
Composite kidney outcome including macroalbuminuria (HR)	0.78 (0.67–0.92)	0.64 (0.46–0.88)	–	–	0.76 (0.66–0.88)	–	–	0.78 (0.63–0.96)[c]	
Worsening of kidney function (HR)	0.89 (0.67–1.19)	0.98 (0.7–1.37)	0.91 (0.58–1.42)	0.73 (0.51–1.07)	0.73 (0.59–0.89)	–	–	0.57 (0.27–1.14)	

Data expressed as mean ± SD, median (IQR), mean (95% confidence interval) or % as presented in the references cited.
[a]Pre-specified meta-analysis.
[b]None listed in clinicaltrials.gov.
[c]Five-component composite of death from renal causes, initiation of long-term renal replacement therapy (dialysis or transplantation), onset of a persistent eGFR <15 ml/min/1.73 m^2, persistent 50% reduction in eGFR relative to baseline or onset of persistent macroalbuminuria (UACR >300 mg/g).
MACE3: cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke; MACE4: cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospitalized unstable angina; sc: subcutaneously.

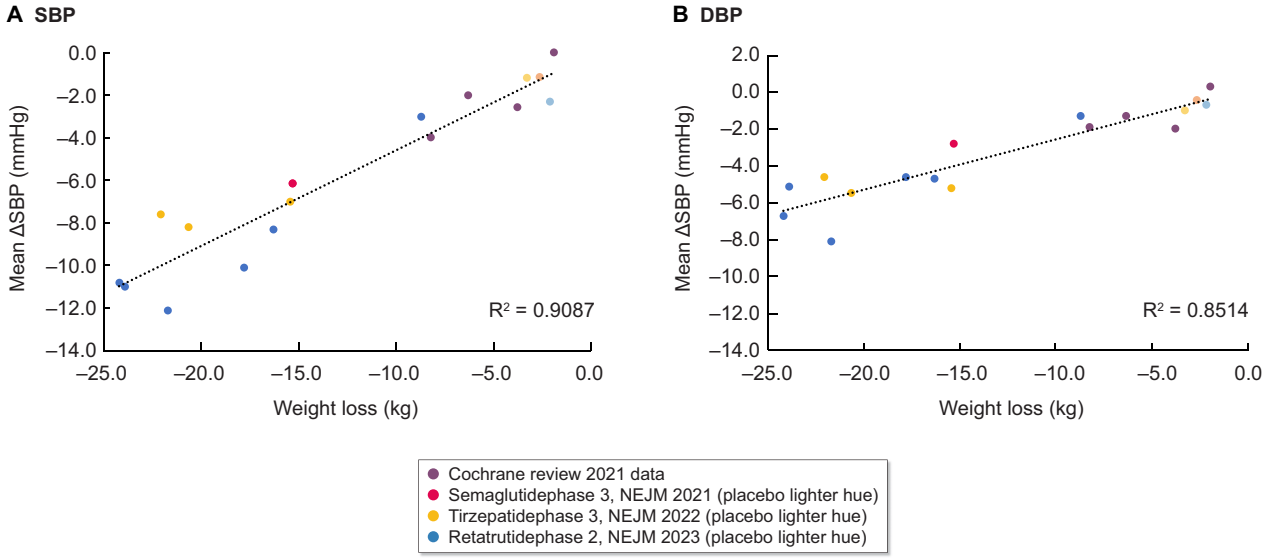


Figure 6: Relationship between decrease in body weight and change in **(A)** SBP and **(B)** diastolic BP in recent clinical trials for weight loss drugs and in data from a 2021 Cochrane review on the topic [49–52].

related to decreased GFR when GLP-1 RAs were tested for T2DM (enrolling a majority of participants with overweight/obesity) or overweight/obesity without T2DM, as discussed below [26, 41, 48] (Table 3). Additionally, there is observational information for >1000 individuals with kidney failure (eGFR <15 ml/min/1.73 m^2), with or without dialysis therapy, who were treated for T2DM with GLP-1 RAs [59]. In the largest study, from a National Health Insurance database, GLP-1 RAs were associated with lower all-cause mortality [HR 0.79 (95% CI 0.63–0.98)] and sepsis- and infection-related mortality [HR 0.61 (95% CI 0.40–0.91)] among people with T2DM and kidney failure than DPP-4 inhibitors [60].

The kidney impact of semaglutide has been characterized in the greatest detail so far. We next summarize key results for liraglutide, semaglutide and tirzepatide on CKD outcomes obtained in patients with T2DM (mostly with overweight/obesity) or with overweight/obesity but without T2DM. Of note, liraglutide and semaglutide decreased all-cause mortality in patients with T2DM at high CVD risk and semaglutide also decreased all-cause mortality in patients with T2DM and CKD and in patients with overweight/obesity and CVD without T2DM (Table 3) [13, 54, 61–63].

LIRAGLUTIDE

Liraglutide and semaglutide are products of the same manufacturer. In the T2DM LEADER CVOT, liraglutide decreased the risk of MACE [HR 0.74 (95% CI 0.58–0.95)], cardiovascular death [HR 0.78 (95% CI 0.66–0.93)] and a composite kidney outcome that included A3 albuminuria [HR 0.78 (95% CI 0.67–0.92)]. The HR for worsening kidney function was more modest, at 0.89 (95% CI 0.67–1.19) [41]. However, an in-depth clinical development program convincingly showed the superiority of semaglutide over liraglutide in terms of dosing (weekly subcutaneous or oral versus daily subcutaneous), magnitude of weight loss (15.8% versus 6.4%), tolerability and safety profile (treatment discontinuation 13.5% versus 27.6%) and value for money for weight reduction in head-to-head comparisons [45, 64, 65], so liraglutide will not be discussed further.

SEMAGLUTIDE

Most participants in the T2DM clinical development program for semaglutide were overweight/obese and FLOW tested primary kidney outcomes in CKD (Table 3). Additionally, semaglutide has been tested in overweight/obesity without T2DM [STEP program (NCT03548935), SELECT] and there is secondary outcome information in CKD and on kidney outcomes [48, 66].

In the T2DM CVOT SUSTAIN-6, subcutaneous semaglutide reduced the risk of a secondary composite kidney outcome that included A3 albuminuria[(HR 0.64 (95% CI 0.46–0.88)] [41]. In a combined analysis of SUSTAIN-6 and the oral semaglutide T2DM CVOT PIONEER 6 trial, semaglutide was associated with 0.59 ml/min/1.73 m^2 (95% CI 0.29–0.89) lower annual eGFR slopes and eGFR subgroup analysis was consistent with these results [67]. Interestingly, weight loss was 43% greater in patients with CKD G3–G4 than in those without CKD [58].

FLOW was the first GLP-1 RA trial with a primary renal endpoint in patients with CKD. It enrolled 3534 participants with T2DM, eGFR 25–75 ml/min/1.73 m^2 and albuminuria 300–5000 mg/g [38]. More than 88% of participants had overweight/obesity. After a median follow-up of 3.4 years, it was prematurely stopped after the prespecified interim analysis showed a 24% relative risk reduction in the combined primary endpoint of cardiovascular or kidney death or CKD progression (kidney failure or 50% decrease in eGFR) for semaglutide 1 mg/week [HR 0.76 (95% CI 0.66–0.88)] [13]. Benefit was also observed for a composite of the kidney-specific components of the primary outcome [HR 0.79 (95% CI 0.66–0.94)], cardiovascular death [HR 0.71 (95% CI 0.56–0.89)], MACE [HR 0.82 (95% CI 0.68–0.98)] and all-cause death [HR 0.80 (95% CI 0.67–0.95)]. The mean annual eGFR slope was 35% lower in the semaglutide group (difference 1.16 ml/min/1.73 m^2, $P < .001$). A key unanswered question relates to the beneficial impact of semaglutide on kidney outcomes for T2DM patients already on SGLT2i, as they

represented just 15% of FLOW participants: despite non-significant *P*-values for heterogeneity for the primary outcome, HR values were consistently >1.00 for most kidney outcomes (the sole exception was kidney replacement therapy: HR 0.98), with evidence for heterogeneity for onset of a persistent ≥50% reduction in eGFR [semaglutide versus placebo: HR 1.30 (95% CI 0.76–2.26) for participants on SGLT2i and HR 0.66 (95% CI 0.53–0.83) for participants not on SGLT2i; *P* for interaction = .023), while the HR for MACE or all cause-death was consistent across SGLT2i subgroups [68]. In contrast, in a metanalysis of 12 randomized, double-blind, placebo-controlled trials comprising 3065 of 73 238 participants (4.2%) with diabetes who were using GLP-1 RAs at baseline, SGLT2i reduced the risk of CKD progression in participants both receiving and not receiving GLP-1 RAs [HR 0.65 (95% CI 0.46–0.94) versus HR 0.67 (95% CI 0.62–0.72); *P* for heterogeneity = .81] [69]. Participants receiving GLP-1 RAs had a higher BMI (e.g. for those participating in CKD trials, mean BMI 35.4–35.7 kg/m^2 versus 31.2 kg/m^2 in those not on GLP-1 RAs).

In STEP-2 (NCT03552757), semaglutide (1.0–2.4 mg/week subcutaneously) reduced albuminuria by 25% versus placebo in normoalbuminuric patients with overweight/obesity but not T2DM and by 41–57% in 166 participants with A2/A3 albuminuria [70]. In STEP-4 (NCT03548987), maintenance semaglutide after 20 weeks for another 48 weeks led to a further 7.9% bodyweight loss for a total 17.4% weight loss over the whole trial, whereas those who switched to placebo regained an average 6.9% (total weight loss of 5.0%) [66]. In STEP 5 (NCT03693430), semaglutide (2.4 mg/week subcutaneously) resulted in sustained weight loss for 2 years versus placebo in people with overweight/obesity without diabetes (−15.2% versus −2.6%) [71]. The incidence of prediabetes or T2DM was 10-fold lower (14.3% versus 1.4%) and 3-fold more participants stopped antihypertensive medication (26.0% versus 8.2%) in the semaglutide arm. STEP UP (NCT05646706) is exploring the efficacy on weight loss and cardiometabolic impact of higher dose subcutaneous semaglutide (up to 7.2 mg/week) in >1400 people with obesity without T2DM.

SELECT, the CVOT for subcutaneous semaglutide 2.4 mg/week in overweight/obesity without T2DM followed 17 604 participants for 39.8 ± 9.4 months [20, 48]. Semaglutide decreased the risk of a five-item secondary composite kidney outcome comprising decreased eGFR and A3 albuminuria [HR 0.78 (95% CI 0.63–0.96)] and a five-item composite outcome based on decreased eGFR and cardiovascular death [HR 0.82 (95% CI 0.69–0.97)]. The HR for a four-item kidney function endpoint was 0.62 (95% CI 0.33–1.14) [20, 48]. Additionally, a kidney benefit was observed for eGFR at 104 weeks (difference 0.75 ml/min/1.73 m^2; *P* < .001, over a loss of 1.61 ml/min/1.73 m^2 on placebo) and the chronic eGFR slope was 0.29 ml/min/1.73 m^2 (95% CI 0.18–0.40) lower on semaglutide. Interestingly, the HR for the five-item (A3 albuminuria included) composite kidney outcome was 1.00, 0.77, 0.68 and 0.46 for increasing baseline BMI, with wide CIs (*P* for heterogeneity = .27). Overall, 2292 participants potentially had CKD as diagnosed by albuminuria >30 mg/g and 1908 as diagnosed by eGFR <60 ml/min/1.73 m^2. Kidney protection was consistent across albuminuria and eGFR categories. However, for participants with eGFR <60 ml/min/1.73 m^2 the HR for the five-item composite kidney outcome that included A3 albuminuria was 0.97 (95% CI 0.70–1.34; *P* for heterogeneity = 0.06) and surprisingly, eGFR increased in both arms, but more so for semaglutide (difference 2.19 ml/min/1.73 m^2; *P* < .001) [20].

Ongoing randomized controlled trials (RCTs) are exploring in-depth the benefits of semaglutide for weight-related conditions (Supplementary Table S1).

TIRZEPATIDE

Tirzepatide led to more weight loss than semaglutide 2.4 mg/week subcutaneously in overweight/obese patients without T2DM (15.0–20.9% depending on the dose up to 15 mg/week versus 14.9%) [51, 52].

In obesity and T2DM, the SURPASS-4 trial (NCT03730662) [72] demonstrated a lower risk of the prespecified secondary composite kidney endpoint (eGFR decline ≥40% from baseline, renal death, kidney failure or new-onset macroalbuminuria) compared with insulin glargine, mainly driven by decreased albuminuria, although eGFR slopes were also lower. The phase 2 TREASURE-CKD (NCT05536804) trial is currently exploring its impact on kidney oxygenation as assessed by BOLD MRI (NCT05536804). The SURPASS CVOT is comparing tirzepatide with dulaglutide for T2DM and will be completed later this year, while SURMOUNT-MMO (NCT05556512) is an overweight/obesity, no T2DM CVOT to be completed in 2027. Both have secondary kidney outcomes.

Ongoing RCTs are exploring in-depth the benefits of tirzepatide for weight-related conditions (Supplementary Table S2).

THE PIPELINE OF GLP-1 RA AND CKD

Two GLP-1 RAs in the clinical pipeline for overweight/obesity merit comment, as they are being evaluated for kidney protection in ongoing RCTs [73, 74] (Supplementary Tables S1 and S3).

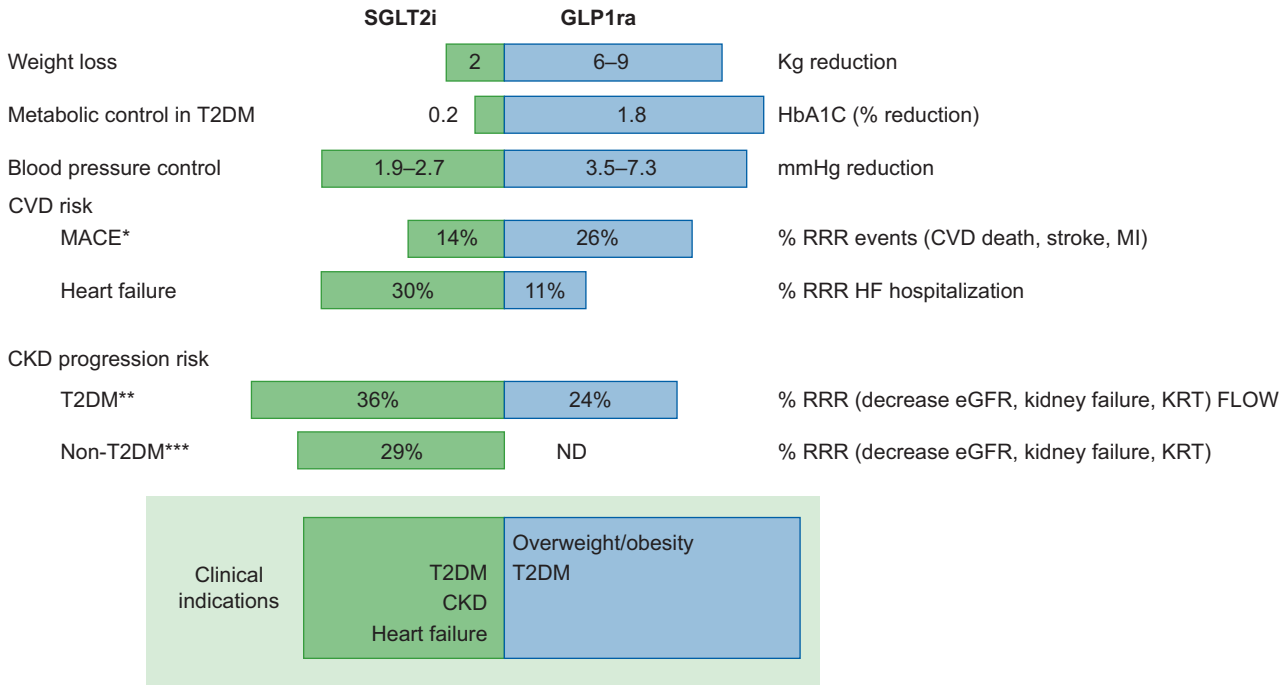
In a phase 2 trial, once weekly retatrutide reduced weight by up to 24.2%, as compared with 2.1% on placebo at 48 weeks in 338 persons with overweight/obesity, no T2DM and eGFR ≥45 ml/min/1.73 m^2 [50]. Retatrutide is undergoing phase 3 trials in T2DM and obesity. Additionally, an ongoing phase 2 trial (NCT05936151) has a primary endpoint of change in measured GFR in participants with overweight/obesity and CKD with or without T2DM.

In a phase 2 RCT, cagrilintide was as safe and as effective for weight loss as liraglutide in overweight/obesity without T2DM [75]. In a T2DM phase 2 trial, cagrisema provided better glycaemic control and more weight loss than semaglutide or cagrilintide alone [34]. A phase 2 RCT (NCT06131372) will randomize 618 participants with CKD (GFR >15 ml/min/1.73 m^2, UACR >100 mg/g), T2DM and overweight/obesity to cagrisema, semaglutide, cagrilintide or placebo, with a primary endpoint of change in UACR in 26 weeks.

The international clinical development of efpeglenatide was stopped, despite being the only exendin derivative that, in a (terminated) phase 3 RCT, showed kidney benefit [HR 0.68 (95% CI 0.57–0.79)] and a reduction in the primary MACE outcome in T2DM patients with a history of CVD or CKD plus at least one other cardiovascular risk factor [57]. However, weight loss was mild (2.6 kg lower than placebo).

GLP-1 RA MECHANISMS OF KIDNEY PROTECTION

The molecular mechanism of kidney protection by GLP-1 RAs is less well understood than for SGLT2is, and comparing their clinical impact may provide insights into differential mechanisms (Fig. 7) (8–12, 48, 76–82). An exploratory mediation analysis of the effects on kidney outcomes (composite of macroalbuminuria, decreased GFR, renal death) with liraglutide and semaglutide in patients with T2DM in the LEADER and SUSTAIN-6 trials observed that HbA1c mediated 25–26% and SBP 9–22% of kidney



* Cardiovascular death or non-lethal stroke or myocardial infarction
** FLOW
*** No primary outcome data on GLP1ra and a CKD-only non-diabetic population

Figure 7: Conceptual representation of the relative impact of SGLT2i and GLP-1 RA on key outcomes across the CKM spectrum. Note that differences in trial design, such as inclusion and exclusion criteria, precise definition of outcomes and follow-up time, may differ and thus results are not directly comparable. However, the conceptual representation provides a gross overview of therapeutic effects. Data obtained from [48, 76–82].

effects with a negligible contribution of the other parameters studied, such as body weight [15]. Thus >50% of the kidney protective effect of GLP-1 RAs remains unexplained by easy-to-assess clinical variables. The mechanisms involved may also differ between classic GLP-1 RAs and twincretins. While SGLT2is directly target kidney proximal tubular cells, the kidney cell targets for GLP-1 RAs are unclear. GLP-1 RAs induced an early dip in eGFR, suggesting decreased intraglomerular pressure and decreased glomerular hyperfiltration, followed by slower eGFR loss in the overall population of GFR subgroups compared with placebo [13, 20], a feature shared with all currently known nephroprotective drugs ranging from renin–angiotensin blockers to mineralocorticoid receptor antagonists to SGLT2is to tolvaptan [67]. However, the magnitude of the eGFR decrease appears to be milder than for SGLT2is in T2DM patients with similar baseline eGFRs (Fig. 8) [67, 79, 80]. The REMODEL trial (NCT04865770) is exploring the mechanisms of human kidney protection by semaglutide in 105 patients with T2DM and CKD through a combination of multiparametric MRI, histology and single-nucleus RNA sequencing (expected completion: end of 2024). An early transient eGFR decrease associated with a transient decrease in albuminuria was also observed in overweight/obese participants without DM in the SELECT trial [20]. Similar to REMODEL, the SMART trial (NCT04889183), completed in 2024, explored mechanisms of human kidney protection by 2.4 mg subcutaneous semaglutide in 125 overweight/obese participants with A2–A3 albuminuria without T2DM, with a primary endpoint of albuminuria. In addition to well-characterized metabolic effects (Figs. 1 and 4), multiple potential mechanisms of kidney protection have been described experimentally (e.g. natriuretic effect via Na^+/H^+ exchanger 3, angiotensin II, inflammation and oxidative stress), although their clinical relevance in patients treated with multiple other agents that also target similar 'usual suspect' pathways is unclear [83–87].

Safety

GLP-1 RAs were safe and serious adverse effects were generally as common or even less common than in the placebo arms in both T2DM and overweight/obesity trials [48, 54, 88] (13). The main adverse effects leading to drug discontinuation were gastrointestinal disorders. For example, for semaglutide, these occurred in 5.1–5.9% versus 0.9–1.8% of controls in SUSTAIN-6 and PIONEER 6 and in ≈10% versus 2% of placebo patients in SELECT [48, 88]. Safety data on participants with CKD are not usually reported separately. However, in one analysis, severe gastrointestinal adverse effects increased as eGFR decreased in both the semaglutide and placebo arms, but the difference between both arms remained stable [58]. In FLOW, semaglutide was safer than placebo in T2DM with CKD, mostly with overweight/obesity [13]: the incidence rate of serious adverse events per 100 patient-years was 10% lower for semaglutide. Although 4.5% (versus 1.1% with placebo) discontinued the drug because of gastrointestinal disorders, the incidence rate of serious gastrointestinal disorders was similar (2.4 versus 2.1 per 100 patient-years). Among participants with eGFR <60 ml/min/1.73 m^2 in the SELECT trial (overweight/obesity, no DM), serious adverse events were 21% less common among those randomized to semaglutide than to placebo and fatal events and acute kidney injury were halved (4.9% versus 9.8% and 3.5% versus 6.7%, respectively) [20].

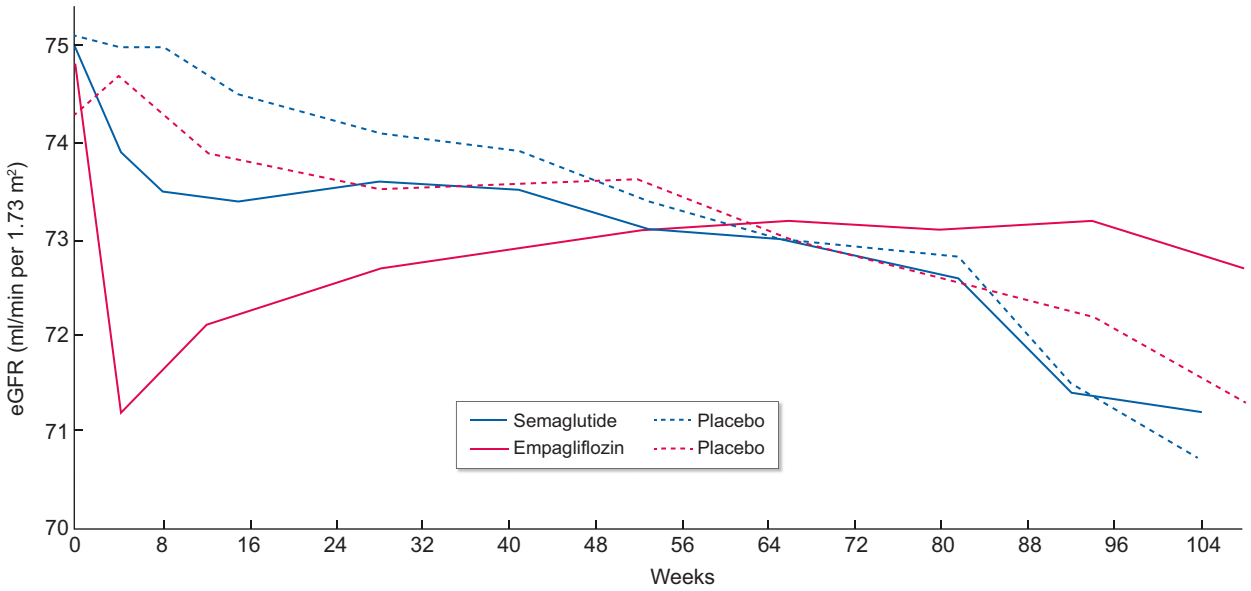


Figure 8: The early decrease in eGFR induced by SGLT2is and GLP-1 RAs appears to differ in magnitude. Results are presented for the EMPA-REG OUTCOME trial (NCT01131676) and SUSTAIN-6 trials performed in people with T2DM who had similar baseline eGFR values [55, 81].

However, nearly 1 in 4 (22.0% versus 13.8% in placebo and 15.9% on semaglutide with preserved kidney function) stopped treatment because of adverse events.

CONCLUSIONS

In conclusion, GLP-1 RAs, and especially twincretins, are the safest and most effective drugs to treat overweight/obesity. They may benefit patients with either overweight/obesity or T2DM through improving dietary habits, decreasing risk or improving control of T2DM, hypertension and CVD and weight loss, all of which may contribute to prevent CKD onset or slow its progression and decrease all-cause mortality, and these benefits are also observed in patients with CKD. Notice the continued reference to both overweight and obesity, since referring only to obesity may contribute to overlooking the risks and therapeutic opportunities associated with overweight. Currently, semaglutide is the best characterized GLP-1 RA in the context of overweight/obesity, CVD risk and kidney disease, but the clinical development program for tirzepatide is expected to be completed with CVD information and preliminary kidney disease results in the next 3 years. Even more potent drugs, such as retatrutide and cagrisema, are in the clinical pipeline. Nephrologists should embrace the holistic CKM approach to chronic disease and be part of the ongoing metabolic revolution by thinking beyond T2DM and becoming familiar with the beneficial effects of GLP-1 RAs on CVD and CKD risk in patients with overweight/obesity independent of the presence of T2DM or CKD. Beyond kidney patients, nephrologists are central players in the CKM syndrome and should become public health advocates of CKM health for society and primary care colleagues. GLP-1 RAs may become first-line kidney protective drugs in overweight/obesity without T2DM or CKD in the near future. Once T2DM or CKD has developed, the practicalities of their integration with other kidney protective drugs such as SGLT2is should be further explored. Finally, the widespread use of GLP-1 RAs is limited by high costs and accessibility issues. Governments and pharmaceutical companies should work together to address these issues.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

Daria Abasheva made substantial contributions in the design of the work, bibliographic research, interpretation and drafted the manuscript, contribute to text and contents of the manuscript including revisions and edits and approve of the content of the manuscript and agree to be held accountable for the work; Beatriz Fernandez-Fernandez made substantial contributions in the design of the work, bibliographic search, drafted the manuscript, reviewed the manuscript, interpretation, discussion

and conclusions, contribute to text and contents of the manuscript including revisions and edits and approve of the content of the manuscript and agree to be held accountable for the work; Alberto Ortiz made substantial contributions in the design of the work, bibliographic search, drafted the manuscript, reviewed the manuscript, interpretation, discussion and conclusions, provided intellectual senior input, contribute to text and contents of the manuscript including revisions and edits and approve of the content of the manuscript and agree to be held accountable for the work.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

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