Clinical Kidney Journal, 2023, vol. 16, no. 5, 797–808

https://doi.org/10.1093/ckj/sfac274
Advance Access Publication Date: 23 December 2022
CKJ Review

CKJ REVIEW

Tirzepatide and prevention of chronic kidney disease

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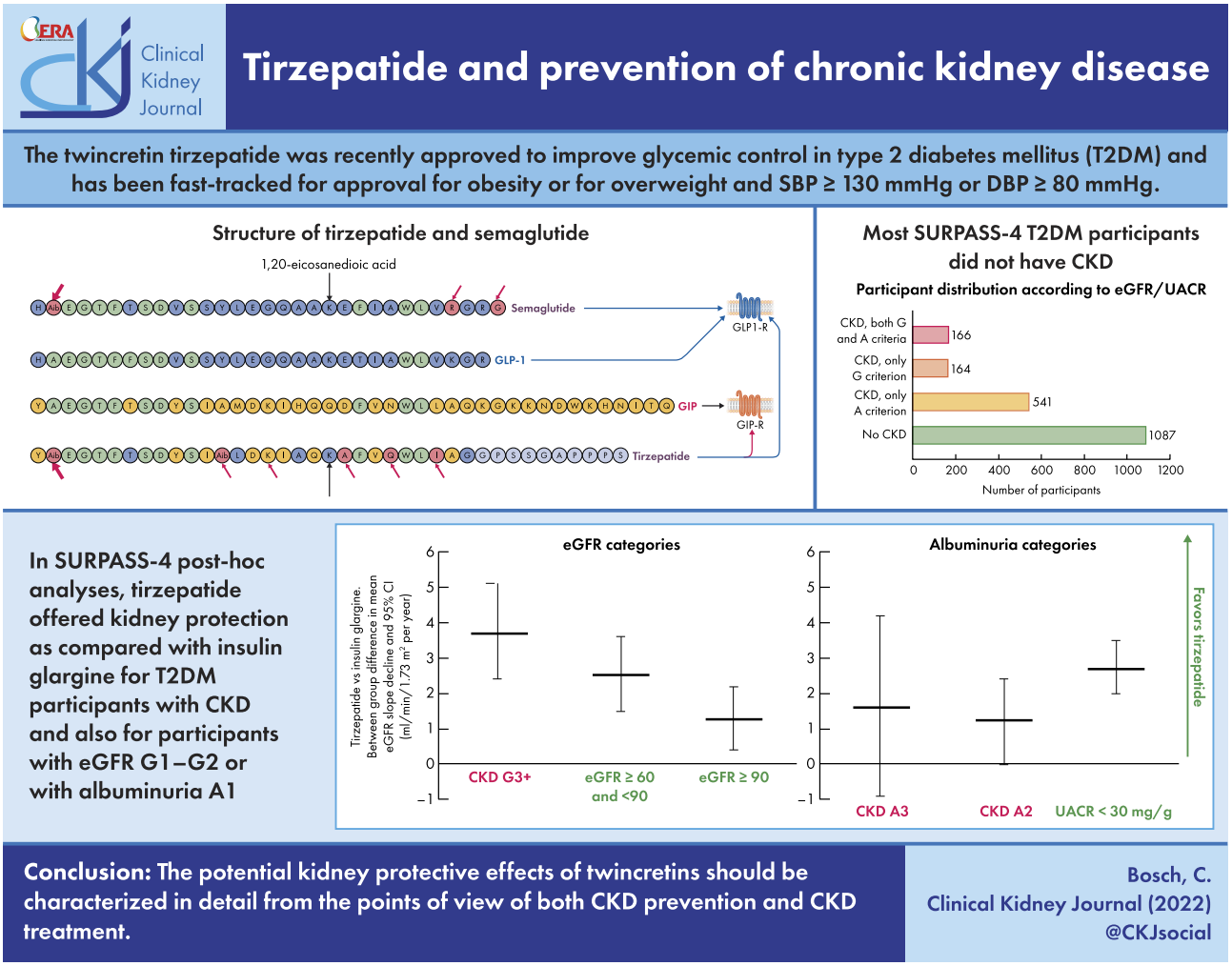
ABSTRACT

Tirzepatide is a twincretin recently approved to improve glycemic control in type 2 diabetes mellitus (T2DM). More specifically, tirzepatide is an agonist of both the glucose-dependent insulinotropic polypeptide (GIP) and the glucagon-like peptide-1 (GLP1) receptors. In recent clinical trials in persons with obesity or overweight with associated conditions, tirzepatide decreased body weight and other cardiorenal risk factors (blood pressure, low-density lipoprotein cholesterol, glycated hemoglobin and albuminuria). Moreover, in a *post hoc* analysis of the SURPASS-4 randomized clinical trial, tirzepatide decreased albuminuria and total estimated glomerular filtration rate (eGFR) slopes and nearly halved the risk of a pre-specified composite kidney endpoint (eGFR decline ≥40%, renal death, kidney failure or new-onset macroalbuminuria) in participants with T2DM and high cardiovascular risk when compared with insulin glargine. Similar to other kidney-protective drugs, tirzepatide, alone or combined with sodium-glucose co-transporter 2 inhibitors, caused an early dip in eGFR. Moreover, tirzepatide also decreased eGFR slopes in participants with eGFR >60 mL/min/1.73 m^2 or with normoalbuminuria. We now review the potential kidney health implications of tirzepatide, addressing its structure and function, relationship to current GLP1 receptor agonists, impact of recent results for the treatment and prevention of kidney disease, and expectations for the future.

Received: 5.10.2022; Editorial decision: 7.12.2022

GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, diabetes mellitus, incretin, obesity, tirzepatide

BACKGROUND

Tirzepatide is a twincretin approved in May 2022 by the United States Food and Drug Administration (FDA) and in November 2022 by the European Medicines Agency (EMA) to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) [1]. Twincretins are dual agonists of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1) receptors. In recent randomized clinical trials (RCTs) in persons with obesity or overweight and associated conditions, tirzepatide decreased body weight and improved other cardiorenal risk factors [blood pressure, glycated hemoglobin, low-density lipoprotein (LDL) cholesterol and albuminuria] [2]. Moreover, in the SURPASS-4 RCT in participants with T2DM and high cardiovascular risk, tirzepatide improved a pre-specified secondary composite kidney endpoint [estimated glomerular filtration rate (eGFR) decline ≥40% from baseline, renal death, kidney failure or new-onset macroalbuminuria] when compared with insulin glargine, although the reduced risk was mainly driven by macroalbuminuria. Tirzepatide also slowed the loss of eGFR, including participants that did not meet either the eGFR or the albuminuria KDIGO criterion for chronic kidney disease (CKD) [3]. We now review the potential kidney health implications of tirzepatide, addressing its structure and function, relationship to current GLP1 receptor agonists (GLP1RA), impact of recent results for the treatment and prevention of kidney disease, and expectations for the future.

TIRZEPATIDE

Tirzepatide is a 39 amino acid synthetic peptide that shares features with the amino acid sequence of GIP, GLP1 and exendin-4 (Fig. 1). Its structure results in a half-life of approximately 5 days (116.7 h), supporting once-weekly dosing, as compared with approximately 5 and 2 min for GIP and GLP1, respectively [1]. Renal or hepatic impairment do not impact the pharmacokinetics of tirzepatide, which can be prescribed to patients with any level of kidney function.

Tirzepatide activation of both GIPR and GLP1R differs from current GLP1RA, such as semaglutide, liraglutide, dulaglutide and others, which only activate GLP1R (Fig. 1) [4].

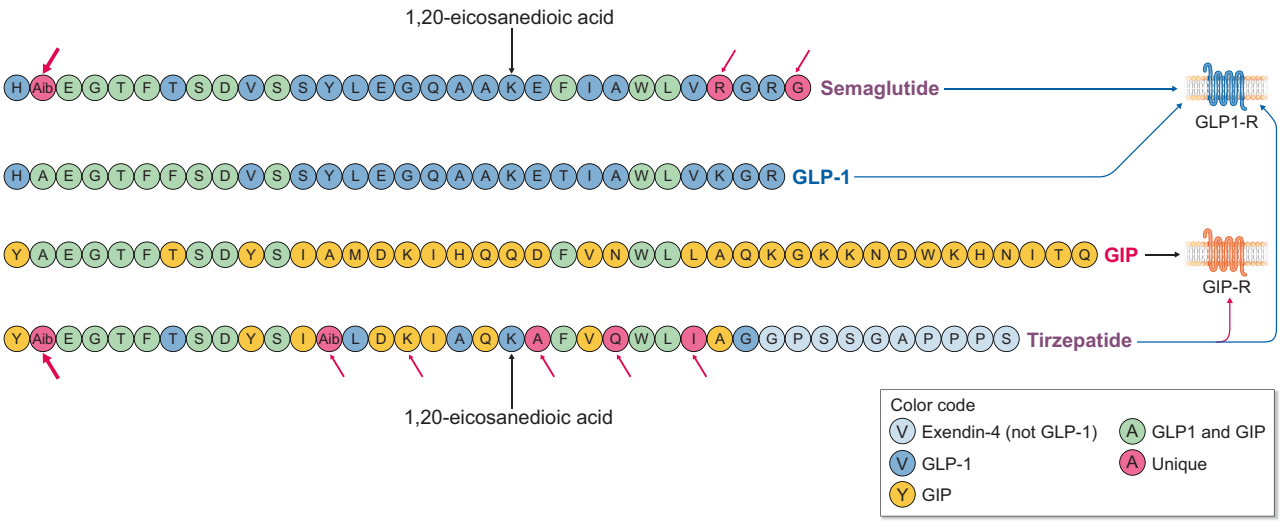


Figure 1: Structure of GLP1, the GLP1 receptor agonist semaglutide, GIP and the dual GLP1 and GIP receptor agonist tirzepatide. Amino acids are color-coded reflecting shared or unique amino acids. Arrows identify amino acids that are unique for the synthetic agonists. The thick arrow indicates aminoisobutyric acid (Aib) residues in positions 2 and 13 which is shared by semaglutide and tirzepatide. Tirzepatide has a C-terminal amide, and a lysine residue at position 20 attached to 1,20-eicosanedioic acid via a linker. The GLP1 receptor and GIP receptors are also shown (adapted from [4]).

Semaglutide and liraglutide are currently approved for the treatment of either T2DM, overweight [body mass index (BMI) $\geq$27 kg/m^2 to $<$30 kg/m^2] when there is at least one associated condition (prediabetes, hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease) or obesity (BMI $>$30 kg/m^2) [2, 5] (Table 1), but only semaglutide and dulaglutide have been compared head-to-head with tirzepatide (Table 2).

Tirzepatide closely resembles native GIP in how it activates the GIPR, but it differs from GLP1 in GLP1R activation, resulting in less agonist-induced receptor desensitization [6]. In live-cell assessments, tirzepatide induced unique spatiotemporal GLP1 and GIP receptor signaling, trafficking and recycling dynamics relative to native peptides, semaglutide and matched mono-agonist controls, potentially conferring a biased agonism that modulates receptor trafficking and decreases ligand-induced internalization of both receptors [4].

GIP and GLP1 are incretin hormones secreted by gut neuroendocrine cells upon food intake that increase insulin secretion (Fig. 2) [7, 8]. They have additional actions, some of which are shared by both incretins while others are specific for each of them (Fig. 3). Both decrease appetite, favoring weight loss. Weight loss improves the metabolic control of T2DM and is the basis for the indication of GLP1RAs such as liraglutide and semaglutide for overweight and obesity. However, GIP lowers gastric acid secretion and promotes glucagon secretion while GLP1 reduces gastric emptying and glucagon secretion. Retention of glucagon function is required to achieve an advantage of tirzepatide over GLP1 monotherapy [9]. GIP receptor agonism in adipocytes increases adipose tissue blood flow and promotes adipose tissue lipid uptake, thus regulating postprandial lipid clearance and, potentially, overall lipid homeostasis [10]. In addition, tirzepatide dose-dependently decreases apoC-III levels, contributing to decrease triglycerides, independently of weight loss [10].

Overall, the combined effect of both incretins may potentiate the beneficial effect over obesity and T2DM [11]. In this regard, in an open-label, 40-week, phase 3 trial (SURPASS-2) tirzepatide (5, 10 or 15 mg s.c. per week) was superior to 1 mg s.c. per week semaglutide for both weight loss and glycemic control in patients with T2DM [12]. The dose range of semaglutide for T2DM is 0.25 to 2 mg s.c. per week while that of tirzepatide is 2.5 to 15 mg s.c. per week. In human studies, the glycemic efficacy of tirzepatide in T2DM resulted from concurrent improvements in β-cell function, insulin sensitivity and glucagon secretion [13]. In obese mice, tirzepatide improved insulin sensitivity to a greater extent than GLP1R agonists due to GIPR activation [14]. Tirzepatide improvement of insulin sensitivity was observed in the absence of GLP1R-induced weight loss in GLP1r-null mice and was dependent on enhanced glucose disposal in white adipose tissue, an action shared by other GIPR agonists [14]. This effect on insulin sensitivity was associated with reduced branched-chain amino acids (BCAAs) and ketoacids in the circulation and with upregulation of genes associated with the catabolism of glucose, lipids and BCAAs in brown adipose tissue [14]. BCAAs are known to promote endothelial dysfunction [15].

TIRZEPATIDE AND T2DM

Tirzepatide is approved for the treatment of T2DM in adults in the USA and the European Union [1]. Three different doses of tirzepatide (5, 10 and 15 mg s.c. per week) were evaluated in seven clinical trials as either a stand-alone therapy or as an add-on to other antidiabetic medications (SURPASS program, Table 2) [3, 12, 16–21]. For some analyses reported below, all tirzepatide doses were combined into a single group.

In T2DM patients, the maximum recommended dose of tirzepatide (15 mg once weekly) lowered HbA1c levels by 1.5%–1.6% more than placebo when used in combination with a long-acting insulin or as stand-alone therapy [18, 19], by 0.5% more than 1 mg per week semaglutide, 0.9% more than insulin degludec and 1.0% more than insulin glargine [12, 20, 21].

Obesity was common among participants with T2DM in tirzepatide trials (average BMI 32–34 kg/m^2) [12, 18–22] (Supplementary data, Table S1). In the efficacy measures estimand, the average weight loss in 40 weeks among patients randomized to 15 mg once weekly tirzepatidewas 8.8 kg (10.2%) more than placebo in the absence of insulin and 12.6 kg (13.2%) more when insulin was used. Additionally, the average weight

Table 1: Clinical conditions that may be treated currently with either semaglutide or tirzepatide; conditions that may be treated in the near future based on results from recent clinical trials and conditions that are under advanced clinical development (i.e. ongoing phase 2 or 3 trial).

Drug	T2DM	CVD in T2DM	Overweight[a]	Obesity[b]	CVD in obesity	T2DM and CKD	Obstructive sleep apnea	NASH	Early Alzheimer
Semaglutide	FDA, EMA	Phase 3 RCT to be completed in 2024 (NCT03914326) and 2048 (NCT05441267)	FDA, EMA	FDA, EMA	Phase 3 RCT to be completed in 2023 (NCT03574597)	FLOW phase 3 RCT to be completed in 2024 (NCT03819153)[c]	No trial	Phase 3 RCT to be completed in 2028 (NCT04822181)	Phase 3 RCT to be completed in 2026 (NCT04777409, NCT04777396)
Tirzepatide	FDA, EMA	Phase 3 RCT to be completed in 2024 (NCT04255433)	Phase 3 RCT [2], ongoing fast-track evaluation by FDA	Phase 3 RCT [2], ongoing fast-track evaluation by FDA	Phase 3 RCT to be completed in 2023: heart failure (NCT04847557)	No ongoing RCT	Phase 3 RCT to be completed in 2024 (NCT05412004)	Phase 2 RCT to be completed in 2023 (NCT04166773)	No trial

For conditions that already have an indication, the agency that granted the approval (EMA or FDA) is indicated. For conditions with recent positive result from clinical trial, the reference is provided. For conditions under advanced clinical development, the NCT ID and expected date of completion are shown. Other GLP1RA are not shown. Among them, liraglutide also has an indication for obesity, but it has not been compared with tirzepatide, while dulaglutide has been compared with tirzepatide in clinical trials but lacks an indication for obesity. Neither liraglutide nor dulaglutide have ongoing clinical development programs of the magnitude shown in the table for semaglutide and tirzepatide, except for the phase 3 SURPASS-CVOT trial comparing dulaglutide and tirzepatide inT2DM as shown in Table 3.

[a]BMI $\geq$27 kg/m^2 to <30 kg/m^2 in the presence of at least one associated condition such as prediabetes, hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease.

[b]BMI >30 kg/m^2.

[c]A research study to see how semaglutide works compared with placebo in people with T2DM and CKD.

Table 2: Completed phase 3 RCT that tested tirzepatide in T2DM.

NCT number [Ref]	Title	Acronym	Comparator	Enrollment	Key result
NCT03861039 [16]	A long-term safety study of tirzepatide in participants with T2DM	SURPASS-J-combo	Oral antihyperglycemic medication	443	Tirzepatide well tolerated as an add-on to oral monotherapy. Mean HbA1c decreased 1.5%, 3% and 3% with tirzepatide 5, 10 and 15 mg, respectively. Significant reduction in body weight in all groups.
NCT03861052 [17]	A study of tirzepatide compared to dulaglutide in participants with T2DM	SURPASS-J-mono	Dulaglutide	636	Mean HbA1c decreased from baseline by 2.55% and 2.88% with tirzepatide 10 and 15 mg vs 1.29% with dulaglutide 0.75 mg ($P < .001$).
NCT03954834 [18]	A study of tirzepatide in participants with T2DM not controlled with diet and exercise alone	SURPASS-1	Placebo	478	Mean HbA1c decreased 1.87%, 1.89% and 2.07% with tirzepatide 5, 10 and 15 mg, respectively, versus + 0.04% with placebo. Significant weight loss.
NCT04039503 [19]	A study of tirzepatide versus placebo in participants with T2DM inadequately controlled on insulin glargine with or without metformin	SURPASS-5	Placebo	475	Mean HbA1c decreased by 2.4% and 2.34% with tirzepatide 10 and 15 mg, respectively, versus 0.86% with placebo. Significant weight loss.
NCT03987919 [12]	A study of tirzepatide versus semaglutide once weekly as add-on therapy to metformin in participants with T2DM	SURPASS-2	Semaglutide	1879	Mean HbA1c decreased by 2.01%, 2.24% and 2.3% with tirzepatide 5, 10 and 15 mg, respectively, vs 1.87% with semaglutide 1 mg ($P < .05$ for all comparisons). Tirzepatide was noninferior and superior to semaglutide. Weight loss was greater with tirzepatide.
NCT04093752	A study of tirzepatide in participants with T2DM on metformin with or without sulfonylurea	SURPASS-AP-Combo	Insulin glargine	917	Not results available yet.
NCT03730662 [3, 20]	A study of tirzepatide once a week versus insulin glargine once a day in participants with T2DM and increased cardiovascular risk	SURPASS-4	Insulin glargine	2002	Mean HbA1c decreased by 2.43% and 2.58% with tirzepatide 10 and 15 mg, respectively, vs 1.44% with glargine ($P < .001$). MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina) were not increased in tirzepatide group. Decreased composite kidney endpoint (eGFR decline ≥40% from baseline, renal death, progression to kidney failure or new-onset macroalbuminuria) with tirzepatide.
NCT038882970 [21]	A study of tirzepatide versus insulin degludec in participants with T2DM	SURPASS-3	Insulin degludec	1444	Mean HbA1c decreased by 1.93%, 2.2% and 2.37% with tirzepatide 5, 10and 15 mg, respectively, vs 1.34% with degludec ($P < .001$). Weight loss in tirzepatide groups, while degludec increased bodyweight.

All trials tested 5, 10 and 15 mg per week of tirzepatide. Only key results are shown. MACE-4: cardiovascular death, myocardial infarction, stroke and hospitalized unstable angina.

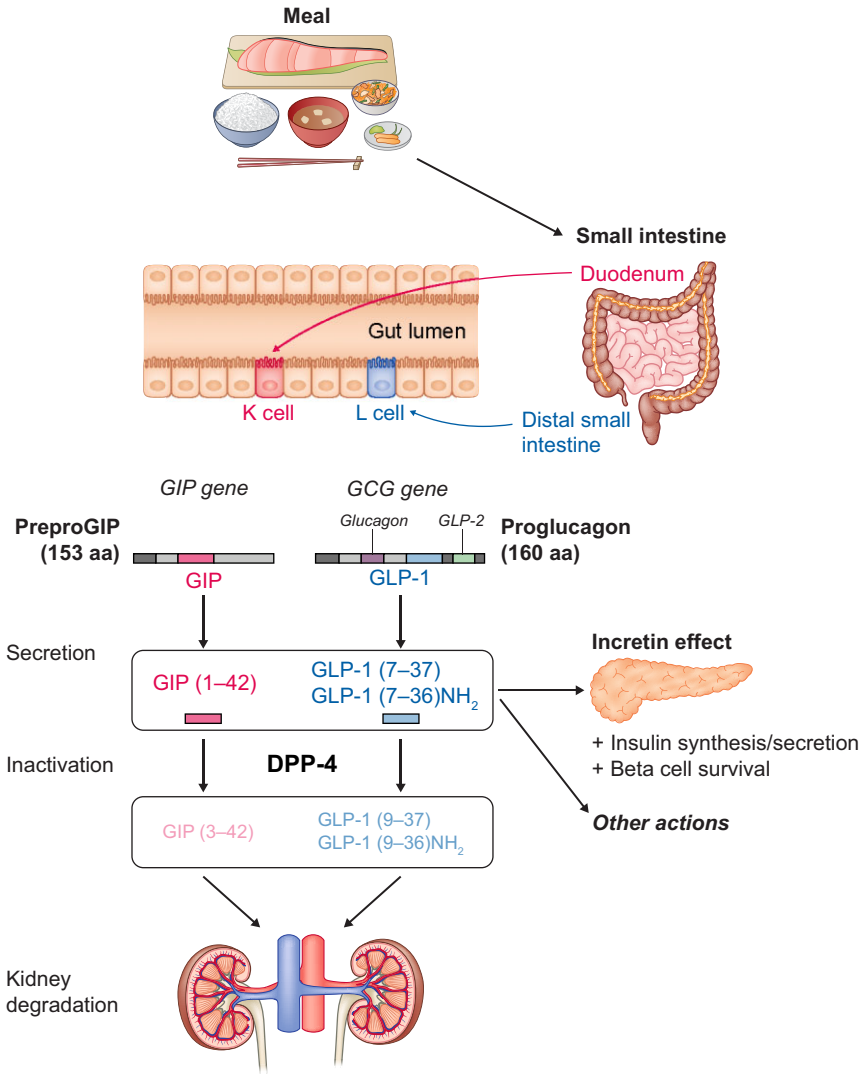


Figure 2: Physiology of GIP and GLP1. Food ingestion triggers the release of incretins from gut neuroepithelial cells. GIP is encoded by the GIP gene and is generated by proteolysis of a precursor peptide (PreproGIP) by K cells in the duodenum. GLP1 is encoded by the GCG gene that also encodes glucagon and GLP-2. GLP1 is generated by proteolysis of a precursor peptide (proglucagon) by L cells from the distal small intestine. Both GIP and GLP1 have incretin effects (i.e. promote insulin release from pancreatic beta cells) and have additional shared and unique actions as reflected in Fig. 3. Both have short half-life (approximately 5 and 2 min for GIP and GLP1, 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 GLP1R agonists or dual GLP1R/GIPR agonists. Adapted from [8].

loss in 40 weeks was 6.2 kg (6.6%) more than for 1 mg per week semaglutide and in 52 weeks, 13.6–15.2 kg (15.1%–16.1%) more than for insulin glargine or degludec, respectively. Corresponding values were somewhat lower for the treatment regimen estimand that evaluated the full analysis dataset.

WHAT IS NEW ABOUT TIRZEPATIDE?

The results of RCTs testing tirzepatide in overweight/obesity were recently reported [2]. They are part of a wider clinical development program (Table 3). Additional ongoing RCTs are exploring the role of tirzepatide in obstructive sleep apnea or nonalcoholic steatohepatitis (NASH). The cardiovascular impact is being assessed in patients with obesity and heart failure with preserved ejection fraction, and in participants with T2DM. While no specific trial is yet exploring tirzepatide in patients with CKD, and kidney-specific endpoints were investigated as secondary outcomes, some pre-specified CKD outcomes have been or are being explored in overweight/obesity and T2DM trials that enrolled patients with CKD, defined as eGFR <60 mL/min/1.73 m^2 or urinary albumin:creatinine ratio (UACR) ≥30 mg/g, as well as patients not meeting these criteria to diagnose CKD.

Overweight/obesity

Tirzepatide decreased body weight in non-diabetic overweight or obese participants in the phase 3 RCT SURMOUNT-1 (NCT04184622) [2]. SURMOUNT-1 randomized 2539 participants with BMI ≥30 kg/m^2 or ≥27 kg/m^2 and at least one weight-related complication (e.g. hypertension, dyslipidemia, obstructive sleep

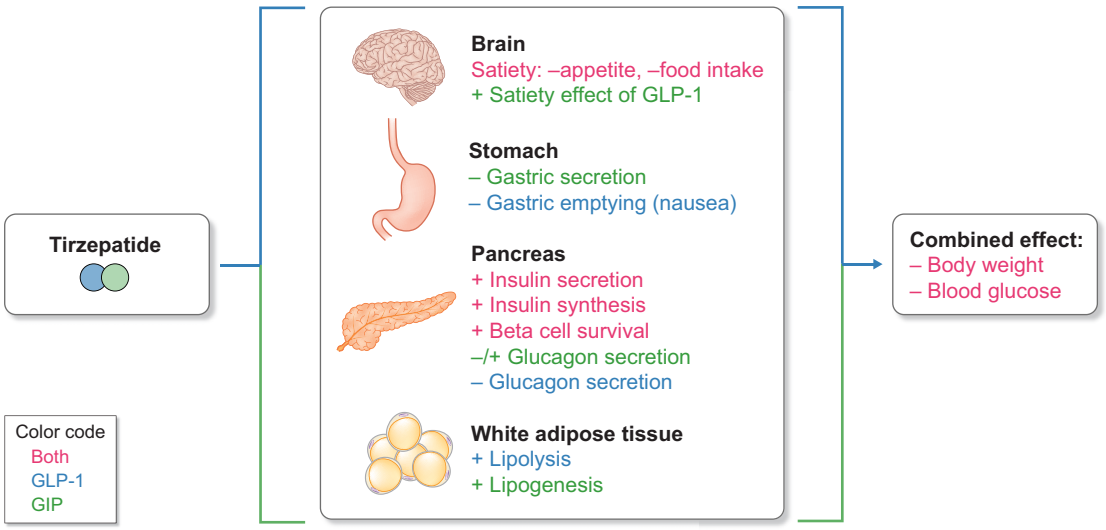


Figure 3: Shared and unique actions by GIP and GLP1 in key target organs that may be reproduced by tirzepatide.

apnea or cardiovascular disease) to once weekly s.c. tirzepatide (5 mg, 10 mg or 15 mg) or placebo for 72 weeks, with a 20-week dose scalation adjustment period. Of interest for the future clinical use of tirzepatide, hypertension was defined as previously recorded and treated with drugs, or systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg. In this regard, SBP ≥130 mmHg or DBP ≥80 mmHg are not diagnostic of hypertension according to the 2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension. Persons with CKD G4–G5 (eGFR <30 mL/min/1.73 m^2) were excluded but there was no exclusion based on UACR. Mean baseline BMI was 38 kg/m^2, mean eGFR 98.1 ± 18.0 mL/min/1.73 m^2, UACR 7.6–8.0 mg/g, 32% of patients had hypertension and 30% had dyslipidemia. At 72 weeks, UACR had decreased –9.3 ± 2.69% to –12.3 ± 2.63% in the tirzepatide groups and to –3.2 ± 3.05% in the placebo group.

Regarding the co-primary endpoints, mean % change in weight at the end of the study ranged from –15.0% [95% confidence interval (CI) –15.9 to –14.2%] with 5 mg/week tirzepatide to –20.9% (95% CI –21.8 to –19.9%) with 15 mg/week tirzepatide, which was more than with placebo [–3.1% (95% CI –4.3 to –1.9%), $P < .001$ vs tirzepatide]. Additionally, 85% (95% CI 82%–89%) to 91% (95% CI 88%–94%) of tirzepatide patients achieved a 5% or more decrease in weight from baseline vs 35% (95% CI 30%–39%) with placebo. In the 10 and 15 mg/week tirzepatide groups, at least 50% of participants had more than 20% of weight reduction compared with 3% of participants in the placebo group ($P < .001$ for all comparisons with placebo).

SBP progressively decreased over the first 6 months of the study and then remained 7–8 mmHg lower than baseline and 6–7 mmHg lower than placebo for the next year. Tirzepatide additionally lowered glycated hemoglobin, triglycerides, total, LDL and very-LDL cholesterol, free fatty acids and fasting insulin levels and increased high-density lipoprotein cholesterol when compared with placebo. Thus, tirzepatide provided a holistic improvement in cardiovascular and kidney risk factors in non-diabetic participants with overweight or obesity.

Cardiovascular outcomes

A pre-specified cardiovascular meta-analysis explored the time to first occurrence of major atherosclerotic cardiovascular events (MACE-4) in pooled tirzepatide ($n = 4887$) and control groups ($n = 2328$) from the SURPASS RCTs in T2DM with a duration of at least 26 weeks [23]. Among MACE-4 (cardiovascular death, myocardial infarction, stroke and hospitalized unstable angina) events, 109/142 occurred in a single trial that enrolled participants at high cardiovascular risk. The analysis combined all tirzepatide doses (5–15 mg/week) into one group. The hazard ratios (HRs) comparing tirzepatide versus controls were 0.80 (95% CI 0.57–1.11) for MACE-4, 0.90 (95% CI 0.50–1.61) for cardiovascular death and 0.80 (95% CI 0.51–1.25) for all-cause death. In summary, tirzepatide did not increase the risk of MACE in participants with T2DM versus controls. The hypothesis that tirzepatide may provide benefit on cardiovascular outcomes is currently being explored. In obese participants with heart failure with preserved ejection fraction, SUMMIT (NCT04847557) is evaluating the impact of tirzepatide on all-cause mortality and heart failure events (Table 3). In T2DM, SURPASS-CVOT (NCT04255433) is comparing tirzepatide and dulaglutide with a primary endpoint of MACE-3 (death from cardiovascular causes, myocardial infarction or stroke). In this regard, in participants with T2DM and high cardiovascular risk or prior cardiovascular events, dulaglutide was previously shown to reduce MACE-3 [HR 0.88 (95% CI 0.79–0.99); $P = .026$] and, in an exploratory analysis, to decrease the renal component of the composite microvascular outcome (new macroalbuminuria, a sustained decline in eGFR of 30% or more from baseline, or kidney renal replacement therapy) [24, 25]. These results are aligned with those obtained for MACE-3 with semaglutide or liraglutide in a similar population:

Table 3: Ongoing RCT testing tirzepatide.

NCT Number	Title	Acronym	Status	Conditions	Interventions	Primary/key outcome measures	Kidney outcome	Phase	Enrollment	Completion
NCT05024032	A study of tirzepatide in Chinese participants without T2DM who have obesity or overweight	SURMOUNT-CN	Active, not recruiting	Obesity, overweight	Tirzepatide, placebo	Body weight	No	3	210	December 2022
NCT04844918	A study of tirzepatide in participants with obesity disease	SURMOUNT-J	Active, not recruiting	Obesity	Tirzepatide, placebo	Body weight	No	3	261	2023
NCT04657003	A study of tirzepatide in participants with T2DM who have obesity or are overweight	SURMOUNT-2	Active, not recruiting	T2DM, overweight, obesity	Tirzepatide, placebo	Body weight	No	3	900	2023
NCT04660643	A study of tirzepatide in participants with obesity or overweight for the maintenance of weight loss	SURMOUNT-4	Active, not recruiting	Obesity, overweight	Tirzepatide, placebo	Body Weight	No	3	750	2023
NCT04657016	A study of tirzepatide in participants after a lifestyle weight loss program	SURMOUNT-3	Active, not recruiting	Obesity, overweight	Tirzepatide, placebo	Body weight	No	3	800	2023
NCT04184622	A study of tirzepatide in participants with obesity or overweight	SURMOUNT-1	Active, not recruiting	Overweight, obesity	Tirzepatide, placebo	Body weight	No	3	2539	2024
NCT05412004	Obstructive sleep apnea master protocol GPIF: a study of tirzepatide in participants with obstructive sleep apnea	SURMOUNT-OSA	Not yet recruiting	Sleep apnea, obesity	Tirzepatide, placebo	Apnea-Hypopnea Index	No	3	412	2024
NCT04847557	A study of tirzepatide in participants with heart failure with preserved ejection fraction and obesity	SUMMIT	Recruiting	Obesity, heart failure with preserved ejection fraction	Tirzepatide, placebo	All-cause mortality, heart failure events	No	3	700	2023
NCT04255433	A study of tirzepatide compared with dulaglutide on major cardiovascular events in participants with T2DM	SURPASS-CVOT	Recruiting	T2DM	Tirzepatide, dulaglutide	MACE-3	Secondary endpoint: UACR, new or worsening nephropathy	3	12 500	2024
NCT05260021	A study to evaluate tirzepatide in pediatric and adolescent participants with T2DM mellitus inadequately controlled with metformin or basal insulin or both	SURPASS-PEDS	Recruiting	T2DM	Tirzepatide, placebo	HbA1c	No	3	90	2027
NCT04166773	A study of tirzepatide in participants with NASH	SYNERGY-NASH	Recruiting	NASH	Tirzepatide, placebo	NASH, liver fibrosis	No	2	196	2023

MACE-3: death from cardiovascular causes, myocardial infarction or stroke.

HR 0.74 (95% CI 0.58–0.95; $P < .001$) for noninferiority and HR 0.87 (95% CI 0.78 to 0.97; $P = .01$) for superiority, respectively [26, 27].

Kidney outcomes

No specific trial is available or ongoing exploring the impact of tirzepatide in patients with CKD. However, a *post hoc* analysis of pre-specified kidney endpoints was reported for SURPASS-4 that compared tirzepatide and insulin glargine during a median follow-up of 85–104 weeks in participants with T2DM, BMI ≥25 kg/m^2 and high cardiovascular risk or cardiovascular disease [3, 20]. From 3045 screened persons, 2002 (66%) were randomized to tirzepatide (997 participants, distributed 1:1:1 between 5, 10 or 15 mg/week) or insulin glargine (1005 participants). There were no exclusion criteria based on eGFR, albuminuria or dialysis but patients with a transplanted organ or awaiting an organ transplant were excluded. Mean eGFR was 81.3 ± 21.1 mL/min/1.73 m^2, 342 (17%) had eGFR <60 mL/min/1.73 m^2, median UACR was 15.0 mg/g (interquartile range 5.0–55.8), 546 (28%) had A2 and 161 (8%) A3 albuminuria categories for a total of 35% participants having albuminuria levels that were diagnostic of CKD (≥30 mg/g). Renin–angiotensin system blockers were used in 81% and sodium-glucose cotransporter 2 (SGLT2) inhibitors in 25% of participants.

Tirzepatide participants presented significantly fewer composite kidney endpoints (eGFR decline ≥40% from baseline, renal death, kidney failure or new-onset macroalbuminuria, i.e. UACR >300 mg/g, A3) [HR 0.59 (95% CI 0.43–0.80); $P < .05$] (Fig. 4). Tirzepatide kidney protection was mainly explained by a reduction in new onset of macroalbuminuria [HR 0.41 (95% CI 0.26–0.66); $P < .05$] in the full population and in patients with A2 albuminuria (Fig. 4A and B). Interestingly, the decrease in new-onset macroalbuminuria (and of the composite outcome that contained it) was apparent in both patients on and off SGLT2 inhibitors, although the difference was only statistically significant for patients off SGLT2 inhibitors, which were the larger group [HR 0.57 (95% CI 0.40–0.81) for the composite endpoint and HR 0.37 (95% CI 0.21–0.65) for new-onset macroalbuminuria]. New-onset macroalbuminuria was decreased both in patients with baseline UACR diagnostic of CKD (≥30 mg/g) and in participants with baseline normoalbuminuria (<30 mg/g). An alternative composite kidney outcome that lacked new-onset macroalbuminuria was not significantly different in the full population [HR 0.80 (95% CI 0.53–1.22)]; however, it approached statistical significance in patients with more advanced CKD [CKD G3+: baseline eGFR <60 mL/min/1.73 m^2; HR 0.37 (95% CI 0.13–1.02)], although the low number of patients (342/1992, 17%) and events (a total of 21 in both groups combined) limits the interpretation of these results. In this regard, in CKD G3+ patients, the decrease in kidney function endpoints carried more weight in the overall statistically significant decrease in kidney endpoints than the decrease in new-onset A3 albuminuria (Fig. 4C).

The total slope of eGFR from baseline to 104 weeks and change in albuminuria were also explored. Tirzepatide benefit on these endpoints was independent of weight or HbA1C changes. The mean total eGFR slope was –1.4 ± 0.2 mL/min/1.73 m^2 per year in the combined tirzepatide groups and –3.6 ± 0.2 mL/min/1.73 m^2 per year in the insulin glargine group [between-group difference 2.2 (95% CI 1.6 to 2.8)]. There was evidence for a tirzepatide dose–response from 5 to 15 mg. Interestingly, an early reversible dip (3 months) in eGFR was noted in patients on tirzepatide, consistent with a decrease in hyperfiltration. The dip in eGFR was also observed, although it was milder, in patients on SGLT2 inhibitors. Upon stopping tirzepatide, eGFR

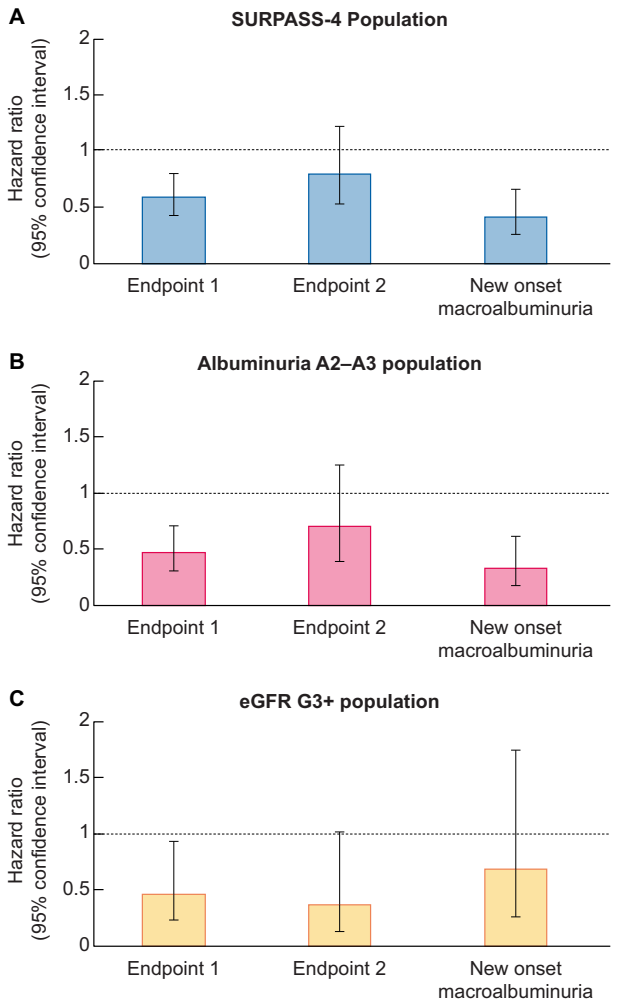


Figure 4: Key pre-specified kidney endpoints reported for SURPASS-4. SURPASS-4 compared tirzepatide 5, 10 or 15 mg/week and insulin glargine during a median follow-up of 85–104 weeks in people with T2DM, BMI ≥25 kg/m^2 and high cardiovascular risk with a primary endpoint of non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus glargine in HbA1c change from baseline to 52 weeks. Kidney outcomes were secondary endpoints and for this analysis, tirzepatide groups were combined [3]. (**A**) Full population ($n = 1995$). (**B**) CKD defined by UACR ≥30 mg/g ($n = 707/1995$, 35% of the full population). (**C**) CKD defined by eGFR <60 mL/min/1.73 m^2 ($n = 342/1992$, 17% of the full population). Endpoint 1: eGFR decline ≥40% from baseline, renal death, progression to kidney failure or new-onset macroalbuminuria. Endpoint 2: eGFR decline ≥40% from baseline, renal death, progression to kidney failure. New-onset macroalbuminuria: UACR >300 mg/g. There were no exclusion criteria based on albuminuria or eGFR but patients who had had a transplanted organ or were awaiting an organ transplant were excluded. Horizontal line indicates HR of 1.0. Figure designed using data reported in reference [3].

increased, suggesting a reversible hemodynamic downmodulation of hyperfiltration while on the drug. In this regard, the total slope up to104 weeks underestimated the impact on eGFR that may have been better represented by chronic slopes from week 12 to 104 or from baseline to off-therapy follow-up. Consistent with the combined endpoint results, the slower total eGFR slope on tirzepatide than on glargine was more pronounced in participants with CKD G3+ [between-group difference 3.7 (95% CI 2.4 to 5.1)] than in those with CKD G1–G2 (Fig. 5A). Preservation of eGFR was more evident in patients with lower eGFR and was also observed in normoalbuminuric patients (Fig. 5A and B).

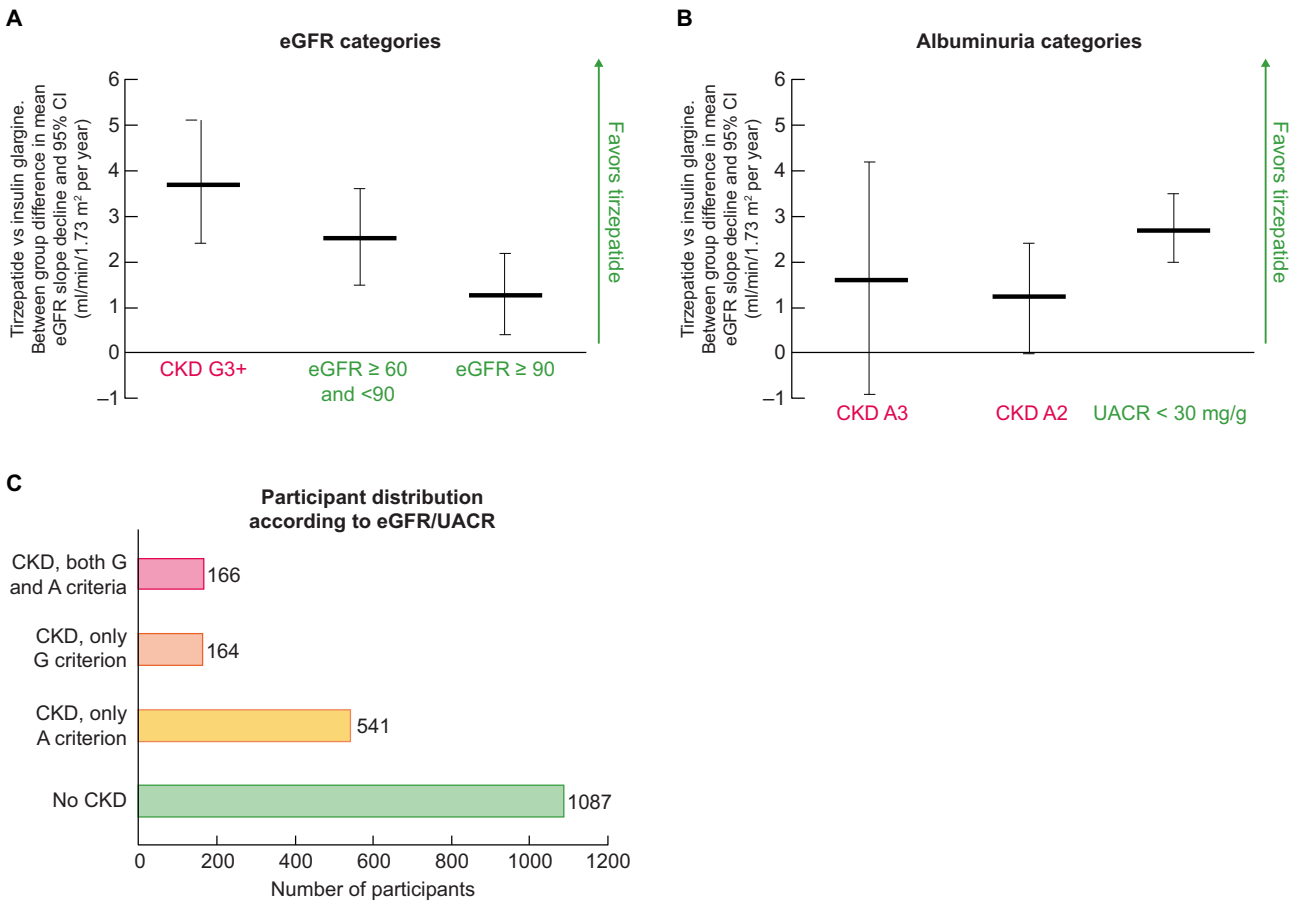


Figure 5: Changes in eGFR between baseline and end of treatment in SURPASS-4. SURPASS-4 compared tirzepatide and insulin glargine during a median follow-up of 85–104 weeks in people with T2DM, BMI ≥25 kg/m^2 and high cardiovascular risk [3]. The primary endpoint was non-inferiority of tirzepatide 10 mg or 15 mg per week, or both, versus glargine in HbA1c change from baseline to 52 weeks. For the analysis of change in eGFR, tirzepatide groups were combined. Between-group differences in mean eGFR slope decline and 95% CI are shown. (**A**) According to baseline eGFR. (**B**) According to baseline UACR. (**C**) Information was not provided for the subgroup of patients without CKD (i.e. eGFR 60 mL/min/1.73 m^{2}and UACR <30 mg/g) which represents the largest subgroup of participants. G and A categories are defined according to KDIGO 2012. Horizontal line at zero indicates no difference and values above zero favor tirzepatide. Figure designed using data reported in reference [3].

Albuminuria increased from baseline to follow-up by 37% (95% CI 26%–49%) in patients randomized to insulin glargine, but not in those on with tirzepatide –7% (–14%–1%] [3]. Furthermore, the impact of tirzepatide on albuminuria was additive to that of SGLT2 inhibitors and was also observed in normoalbuminuric patients. Unfortunately, upon stopping tirzepatide, UACR increased by 34%, although it did appear to remain below UACR values in the glargine group.

As it was the case for cardiovascular outcome trials of SGLT2 inhibitors [28, 29], the ongoing SURPASS-CVOT trial pitting tirzepatide against dulaglutide in T2DM also has secondary endpoints of UACR and new or worsening nephropathy that may be informative to develop CKD-focused trials.

SAFETY OF TIRZEPATIDE

Tirzepatide has so far proven safe from a cardiovascular point of view. The main adverse effects were mild gastrointestinal events, mainly on the higher dose (nausea, vomiting, diarrhea, decreased appetite, constipation, and upper abdominal discomfort or pain) [2, 3]. The most common adverse effect was nausea that decreased progressively within the first 6 months. Adverse events were more common in patients with CKD G3+, both in the tirzepatide and the insulin glargine arms. Treatment was discontinued because of adverse events in 4.3%, 7.1%, 6.2% and 2.6% of patients receiving 5 mg, 10 mg and 15 mg/weekly tirzepatide or placebo, respectively [2]. Additionally, based on preclinical observations in rats, the FDA has added a boxed warning contraindication for patients with a personal or family history of medullary thyroid cancer or at high risk of medullary thyroid cancer, such as those with multiple endocrine neoplasia syndrome type 2 due to pathogenic *RET* gene variants [1].

Towards prevention of CKD

Tirzepatide is a novel addition to the therapeutic armamentarium ofT2DM and soon, of treatment of obesity and of overweight with associated conditions of interest to nephrologists such as SBP ≥130 mmHg or DBP ≥80 mmHg. If not implemented already, BMI should be monitored in nephrology visits. Tirzepatide provided weight reduction and T2DM control as effectively or even more effectively that at least some GLP1RAs and improved blood pressure control. Additionally, tirzepatide may improve albuminuria and eGFR outcomes in T2DM, even on top of SGLT2 inhibition. The potential impact on eGFR slopes and kidney outcomes should be confirmed in kidney-focused trials.

Future analysis of SURPASS-4 should report kidney outcomes for participants without baseline CKD as there was evidence of significant eGFR preservation in participants with either eGFR ≥60 mL/min/1.73 m^2 or normoalbuminuria (Fig. 5). These analyses may guide the design of CKD prevention trials that enroll participants without CKD (i.e. with UACR <30 g/g and with eGFR ≥60 mL/min/0.173 m^2) with the aim of slowing eGFR loss and preventing CKD. CKD prevention trials may complement the CKD treatment trials proposed by Heerspink *et al.* [3].

Post hoc analyses have shown kidney protection suggestive of primary prevention of CKD by dapagliflozin or empagliflozin in participants with T2DM that had both eGFR ≥60 mL/min/1.73 m^2 and normoalbuminuriain cardiovascular outcome trials [30, 31]. Given the increasing burden of CKD, its increasing impact on global deaths and the considerable residual risk in patients on the current standard of therapy, preventing CKD should be a major goal. In this regard, the entry criteria for SURPASS-4 may have identified a T2DM population without baseline CKD at relatively high risk of CKD progression, at least while on glargine [3], that may benefit from primary prevention interventions.

CONCLUSION

Tirzepatide may be the first of a new generation of antidiabetic and weight-correcting drugs. Beyond dual agonists of GLP1 and GIP receptors, tri-agonists that combine the ganorectic and insulinotropic activities of GLP1 and GIP with the energy expenditure effect of glucagon are under preclinical development and normalize body weight in obese mice and enhance energy expenditure in a manner superior to that of GLP1R mono-agonists and GLP1R/GIPR dual agonists [32]. The potential kidney protective effects of this new family of drugs should be characterized in detail from the points of view of CKD prevention and treatment.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

FUNDING

FIS/Fondos FEDER (PI18/01366, PI19/00588, PI19/00815, PI20/00744, DTS18/00032, ERA-PerMed-JTC2018 KIDNEY AT390 TACK AC18/00064 and PERSTIGAN AC18/00071, ISCIII-RETIC REDinREN RD016/0009), Sociedad Española de Nefrología, Sociedad Madrileña de Nefrología (SOMANE), FRIAT, Comunidad de Madrid en Biomedicina (B2017/BMD-3686 and CIFRA2-CM). Instituto de Salud Carlos III (ISCIII) RICORS program (RICORS2040-395 , RD21/0005/0001) and SPACKDc PMP21/00109, FEDER funds funded by European Union—Next Generation EU', Mecanismo para la Recuperación y la Resiliencia (MRR) and RD16/0009.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

CONFLICT OF INTEREST STATEMENT

A.O. is the former Editor-in-Chief of *CKJ* and has received grants from Sanofi and consultancy or speaker fees or travel support from Advicciene, Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Mundipharma, Kyowa Kirin, Alexion, Freeline, Idorsia, Chiesi, Otsuka, Novo-Nordisk, Sysmex and Vifor Fresenius Medical Care Renal Pharma and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra AstraZeneca-UAM of chronic kidney disease and electrolytes.

B.F.-F. has received grants from Esteve and consultancy or speaker fees or travel support from AstraZeneca, Bayer, Menarini, Novo-Nordisk Boehringer Ingelheim and Mundipharma. B.F.-F. is Editor for *Nefroplus*.

S.C. has received honoraria for consultancy from Otsuka.

M.J.S. is the Editor-in-Chief of *CKJ* and reports personal fees from NovoNordisk, Jansen, Mundipharma, AstraZeneca, Esteve, Fresenius, Ingelheim Lilly, Vifor, ICU, Pfizer, Bayer, Travere Therapeutics and GE Healthcare, and grants and personal fees from Boehringer Ingelheim, outside the current study.

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