Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

Hiddo J L Heerspink, Naveed Sattar, Imre Pavo, Axel Haupt, Kevin L Duffin, Zhengyu Yang, Russell J Wiese, Katherine R Tuttle, David Z I Cherney

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Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands (Prof H J L Heerspink PhD); **The George Institute for Global Health, Sydney, NSW, Australia** (Prof H J L Heerspink); **School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK** (Prof N Sattar PhD); **Eli Lilly and Company, Indianapolis, IN, USA** (I Pavo MD, A Haupt MD, K L Duffin PhD, Z Yang PhD, R J Wiese PhD); **Providence Health Care, University of Washington, Spokane, WA, USA** (K R Tuttle MD); **Division of Nephrology, Department of Medicine, Toronto General Hospital, University Health Network, University of Toronto, Toronto, ON, Canada** (Prof D Z I Cherney MD)

Correspondence to: Prof H J L Heerspink, Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, 9700 AD Groningen, Netherlands **h.j.lambers.heerspink@umcg.nl**

Summary

Background In the SURPASS-4 trial, the dual GIP and GLP-1 receptor agonist tirzepatide reduced HbA_{1c} concentrations, bodyweight, and blood pressure more than titrated daily insulin glargine in people with type 2 diabetes inadequately controlled on oral diabetes treatments and with high cardiovascular risk. We aimed to compare the effects of tirzepatide and insulin glargine on kidney parameters and outcomes in people with type 2 diabetes.

Methods We did a post-hoc analysis of data from SURPASS-4, a randomised, open-label, parallel-group, phase 3 study at 187 sites (including private practice, research institutes, and hospitals) in 14 countries. Eligible participants were adults (age ≥18 years), with type 2 diabetes treated with any combination of metformin, sulfonylurea, or SGLT2 inhibitor, and with baseline HbA_{1c} of 7·5–10·5% (58–91 mmol/mol), BMI of 25 kg/m² or greater, and established cardiovascular disease or a high risk of cardiovascular events. Randomisation via an interactive web-response system was 1:1:1:3 to a once-weekly subcutaneous injection of tirzepatide (5 mg, 10 mg, or 15 mg) or a once-daily subcutaneous injection of titrated insulin glargine (100 U/mL). The study included up to 104 weeks of treatment, with a median treatment duration of 85 weeks. We compared the rates of estimated glomerular filtration rate (eGFR) decline and the urine albumin–creatinine ratio (UACR) between the combined tirzepatide groups and the insulin glargine group in the modified intention-to-treat population. The kidney composite outcome was time to first occurrence of eGFR decline of at least 40% from baseline, end-stage kidney disease, death owing to kidney failure, or new-onset macroalbuminuria. This study is registered with ClinicalTrials.gov, NCT03730662.

Findings Between Nov 20, 2018, and Dec 30, 2019, we screened 3045 people, of whom 1043 (34%) were ineligible, and 2002 (66%) were randomly assigned to a study drug (997 to tirzepatide and 1005 to insulin glargine). 1995 (>99%) of 2002 received at least one dose of tirzepatide (n=995) or insulin glargine (n=1000). At baseline, participants had a mean eGFR of 81·3 (SD 21·11) mL/min per 1·73 m² and a median UACR of 15·0 mg/g (IQR 5·0–55·8). The mean rate of eGFR decline was –1·4 (SE 0·2) mL/min per 1·73 m² per year in the combined tirzepatide groups and –3·6 (0·2) mL/min per 1·73 m² per year in the insulin group (between-group difference 2·2 [95% CI 1·6 to 2·8]). Compared with insulin glargine, the reduction in the annual rate of eGFR decline induced by tirzepatide was more pronounced in participants with eGFR less than 60 mL/min per 1·73 m² than in those with eGFR 60 mL/min per 1·73 m² or higher (between-group difference 3·7 [95% CI 2·4 to 5·1]). UACR increased from baseline to follow-up with insulin glargine (36·9% [95% CI 26·0 to 48·7]) but not with tirzepatide (–6·8% [–14·1 to 1·1]; between-group difference –31·9% [–37·7 to –25·7]). Participants who received tirzepatide showed a significantly lower occurrence of the composite kidney endpoint compared with those who received insulin glargine (hazard ratio 0·58 [95% CI 0·43 to 0·80]).

Interpretation Our analysis suggests that in people with type 2 diabetes and high cardiovascular risk, tirzepatide slowed the rate of eGFR decline and reduced UACR in clinically meaningful ways compared with insulin glargine.

Funding Eli Lilly and Company.

Introduction

GLP-1 and GIP are incretin hormones released from the gut that regulate insulin response to a meal. GLP-1 receptor agonists are recommended by clinical practice guidelines[1–3] for the treatment of type 2 diabetes and obesity, and to reduce cardiovascular risk in people with type 2 diabetes. In terms of the kidneys, GLP-1 receptor agonists reduce albuminuria and can slow progression of kidney function decline in people with type 2 diabetes with established cardiovascular disease or at increased cardiovascular risk.[4] Data from large cardiovascular outcome trials[5,6] and a glycaemic-control trial[7] suggest that the effects of GLP-1 receptor agonists on kidney function are greater in people with pre-existing kidney disease, defined by a reduced estimated glomerular filtration rate (eGFR), increased albuminuria, or both, than in people without.

Like GLP-1, GIP also promotes insulin secretion after a meal and reduces bodyweight by enhancing satiety. Unlike GLP-1, GIP exerts glucagonotropic effects and

Research in context

Evidence before this study

We searched PubMed on March 30, 2021, with no restrictions other than publications had to be in English, using the search terms "albiglutide", "dulaglutide", "exenatide", "liraglutide", "lixisenatide", "semaglutide", "efpeglenatide", "tirzepatide", "glucagon-like peptide-1 receptor agonist", "GLP-1 receptor agonist", "glucose-dependent insulinotropic polypeptide", "GIP", "basal insulin", "insulin degludec", "insulin glargine", "empagliflozin", "canagliflozin", "dapagliflozin", "sodium-glucose co-transporter-2 inhibitor", "SGLT2 inhibitor", "type 2 diabetes", and "kidney outcome". GLP-1 receptor agonists and SGLT2 inhibitors are glucose-lowering agents with favourable effects on kidney parameters and outcomes. Tirzepatide is a novel once-per-week dual GIP and GLP-1 receptor agonist representing a first-in-class medication for the treatment of type 2 diabetes. Tirzepatide has shown clinically meaningful improvements in HbA_{1c} and bodyweight in various background therapies and is not associated with excess cardiovascular risk. No data are available on its effect on kidney function and outcomes. SURPASS-4 compared the efficacy and safety of tirzepatide with glargine in patients with type 2 diabetes and high risk for cardiovascular events. A portion of the study population had various degrees of chronic kidney disease (CKD).

Added value of this study

To our knowledge, this is the first study to compare the effects of tirzepatide treatment with a basal insulin on kidney parameters and outcomes in people with type 2 diabetes. In SURPASS-4, 342 (17%) of 1995 participants had moderate or severe CKD and 707 (35%) of 1995 had microalbuminuria or macroalbuminuria at baseline. In the full cohort, tirzepatide compared with insulin glargine reduced the annual rate of estimated glomerular filtration rate (eGFR) decline from baseline (2·2 mL/min per 1·73 m^2 [95% CI 1·6, 2·8]). This effect was more pronounced in participants with eGFR lower than 60 mL/min per 1·73 m^2 than with eGFR 60 mL/min per 1·73 m^2 or higher. Urine albumin–creatinine ratio (UACR) increased over time with insulin glargine (36·9% [95% CI 26·0 to 48·7]) but not with tirzepatide (–6·8% [–14·1 to 1·1]; between-group difference –31·9% [–37·7 to –25·7]). Participants who received tirzepatide had a significantly lower occurrence of the composite kidney endpoint compared with insulin glargine (hazard ratio 0·58 [95% CI 0·43 to 0·80]).

Implications of all the available evidence

In participants with type 2 diabetes who had high cardiovascular risk and varying degrees of CKD, once-weekly tirzepatide was associated with a meaningful improvement in eGFR decline and reduced UACR and risk of kidney outcomes, with a low risk of clinically relevant hypoglycaemia, compared with insulin glargine treatment. These data support doing long-term clinical trials to assess the effect of dual GIP and GLP-1 receptor agonist therapies on kidney protection in people at risk of progressive kidney function loss, including those with type 2 diabetes.

favourably effects lipid homoeostasis.[8] These complimentary properties of GLP-1 and GIP stimulated the development of the dual GIP and GLP-1 receptor agonist tirzepatide. In phase 2 and 3 clinical studies[9–13] of people with type 2 diabetes, tirzepatide has shown clinically meaningful dose-dependent reductions in HbA_{1c} and bodyweight when compared with placebo, semaglutide, dulaglutide, or insulin degludec. Furthermore, in people at high cardiovascular risk, including those with established chronic kidney disease (CKD), who participated in the SURPASS-4 trial and were followed up for a median of 85 weeks, tirzepatide resulted in a clinically meaningful reduction in HbA_{1c} and bodyweight compared with insulin glargine.[14] These effects were accompanied by improvements in blood pressure and lipid profile in the tirzepatide group.[14,15] Tirzepatide did not increase the risk of cardiovascular events, a finding now extended in an analysis of seven trials comparing tirzepatide with different comparators.[16]

CKD is a well known complication of type 2 diabetes. The incidence of CKD is further increased among people in whom traditional cardiovascular risk factors are insufficiently controlled with treatment recommended by guidelines, which include the use of renin–angiotensin–aldosterone-system inhibitors and SGLT2 inhibitors. Additional therapies to reduce the risk of progressive kidney function loss in people with type 2 diabetes and cardiovascular risk factors are therefore desired. We did an exploratory analysis of the SURPASS-4 trial to assess if tirzepatide reduces albuminuria and slows kidney function decline compared with insulin glargine in people with type 2 diabetes, high cardiovascular risk, and varying degrees of CKD.

Methods

Study design

This study is a post-hoc analysis of data from SURPASS-4, a randomised, open-label, active-controlled, multicentre study done at 187 sites in 14 countries (appendix p 10). The protocol was approved by institutional review boards for each site and the trial was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. SURPASS-4 is registered at ClinicalTrials.gov (NCT03730662) and the protocol[14] for SURPASS-4 has been published previously.

Participants

Adults (aged ≥18 years) were eligible for inclusion if they had type 2 diabetes (HbA_{1c} 7·5–10·5% [58–91 mmol/mol]) that was inadequately controlled with any combination of metformin, sulfonylurea, or SGLT-2 inhibitor, a BMI of 25 kg/m^2 or higher, and a stable weight during the

previous 3 months. Participants were at increased risk of cardiovascular events (defined as known coronary, peripheral arterial, or cerebrovascular disease, or aged 50 years or older with either a history of CKD or an eGFR of less than 60 mL/min per 1·73 m², or a history of congestive heart failure New York Heart Association Classification class II or III). Exclusion criteria[14] included type 1 diabetes, a history of pancreatitis, and elevated serum calcitonin concentrations. All participants provided written informed consent before they entered the study.

For the **New York Heart Association Classification** see https://www.havhrt.com/heartfailureclassification

Randomisation and masking

Participants were randomised (1:1:1:3) to receive tirzepatide 5 mg, 10 mg, or 15 mg, or insulin glargine.[14] Randomisation was completed by the Eli Lilly and Company computer-generated random sequence using an interactive web-response system, with stratification based on country, baseline HbA_{1c} (≤8·5% or >8·5% [69 mmol/mol]), and baseline SGLT-2 inhibitor use (yes or no). Because of the differences in dosing schedule, titration, and devices between once-per-week tirzepatide and once-per-day insulin glargine, the study was open label.

Procedures

Participants received tirzepatide (Eli Lilly and Company, Indianapolis, IN, USA) as a once-weekly subcutaneous injection via a prefilled syringe. Treatment was initiated at 2·5 mg and increased by 2·5 mg every 4 weeks until the randomly assigned dose of 5 mg, 10 mg, or 15 mg was achieved and maintained for the study duration. Dose de-escalation (to 5 mg or 10 mg) was allowed once during the dose escalation period if there were intolerable gastrointestinal symptoms or events.

Participants received insulin glargine (basaglar, Eli Lilly and Company, Indianapolis, IN, USA) as a once-daily subcutaneous injection with a prefilled pen containing 3 mL (U100/mL). Treatment was initiated at 10 U/day and titrated to a fasting blood glucose of less than 100 mg/dL, with dose adjustment based on self-monitored fasting blood glucose values.[14,17]

The primary efficacy endpoint was HbA_{1c} change from baseline to week 52. After 52 weeks, to facilitate additional cardiovascular outcome data collection, there was a variable treatment period of no longer than an additional 52 weeks. An off-treatment visit occurred 4 weeks after the participants' last treatment visit.

Urinary albumin and creatinine tests and serum creatinine tests were done by a central laboratory (IQVIA Clinical Analytics, Durham, NC, USA). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[18]

Outcomes

Prespecified analyses included calculations for mean change in eGFR from baseline, the rate of change in eGFR (eGFR slope), and percentage change from baseline in geometric mean urine albumin–creatinine ratio (UACR) between tirzepatide and insulin glargine (appendix p 3). Progression to two composite kidney outcomes, and the individual components of each, were also prespecified analyses. The first of these two composite endpoints consisted of time to first occurrence of eGFR decline of at least 40% from baseline, death due to kidney failure, progression to end-stage kidney disease, or new-onset macroalbuminuria. The second composite endpoint was time to first occurrence of an eGFR decline of at least 40% from baseline, death due to kidney failure, or progression to end-stage kidney disease (appendix p 3). We also did subgroup analyses of eGFR slope and UACR changes between treatment groups as post-hoc analyses.

The overall study population, and a subgroup of participants at high risk for kidney-related outcomes, were prespecified populations for analyses. High risk for kidney-related outcomes was defined as baseline eGFR of less than 75 mL/min per 1·73 m² and macroalbuminuria (UACR >300 mg/g), or eGFR less than 45 mL/min per 1·73 m². The subgroups of participants with increased UACR (≥30 mg/g), and reduced kidney function (eGFR <60 mL/min per 1·73 m²) were prespecified for analyses of mean change in eGFR and mean percentage change in UACR, whereas the analyses of the progression to the composite kidney outcomes and their individual components in these subgroups were defined post hoc. The subgroups of participants categorised by baseline SGLT2 inhibitor use (yes *vs* no) were defined post hoc for all analyses.

Death due to kidney failure was adjudicated by an independent clinical endpoint committee. Progression to end-stage kidney disease was defined as any of: chronic dialysis, kidney transplantation, or an eGFR of less than 15 mL/min per 1·73 m². New-onset macroalbuminuria was defined as the development of a UACR greater than 300 mg/g after randomisation. Sustained UACR progression (either from between ≥30 mg/g and <300 mg/g to ≥300 mg/g, or from <30 mg/g to ≥30 mg/g) or UACR regression (either from between ≥30 mg/g and <300 mg/g to <30 mg/g, or from ≥300 mg/g to <300 mg/g) in albuminuria categories (normoalbuminuria, microalbuminuria, or macroalbuminuria) required respective changes at a minimum of two consecutive study visits.

Statistical analysis

The sample size calculation for SURPASS-4 has been reported previously.[14] The study was not powered for analyses of kidney parameters or outcomes and, therefore, all analyses should be considered exploratory, even though some were prespecified. All randomly assigned participants who took at least one dose of study medication (modified intention-to-treat population) were included in the analyses. Efficacy analyses were based on the efficacy analysis dataset, which included on-treatment data before

the use of rescue therapy unless specified otherwise. Six participants who discontinued study medication due to inadvertent enrolment despite meeting exclusion criteria (four with diabetic retinopathy and two with malignancy) were excluded from the efficacy analyses. Tirzepatide 5 mg, 10 mg, and 15 mg groups were pooled for analyses and the pooled group was compared with insulin glargine.

Time from first dose to the first occurrence of the composite kidney outcome was analysed using the Kaplan–Meier method. Cox proportional-hazard regression was used to determine the between-group difference in the risk of composite kidney outcome. Subgroup analyses were done by adding the subgroup variable of interest and an interaction term between treatment group and the subgroup to the relevant Cox proportional-hazard model. Time to the first sustained UACR progression or regression was analysed using the Kaplan–Meier method and Cox proportional-hazard regression. Kaplan–Meier curves were used to visualise the time to the first occurrence of these endpoints.

We analysed the effects of tirzepatide on the rate of eGFR decline by fitting a random effect mixed effects model with random intercepts and slopes for each participant over time. Fixed effects included baseline eGFR, treatment group, stratification factors (country, baseline HbA_{1c} [≤8·5% or >8·5% (69 mmol/mol)]), and baseline SGLT-2 inhibitor use [yes or no]), time as a continuous variable, and the interactions of treatment with time. To visualise trajectories of mean eGFR over time, a mixed model for repeated measures was done with on-treatment data from baseline up to the 104-week visit with restricted maximum likelihood method. The model included change from baseline in eGFR as a dependent variable, and continuous baseline eGFR value, stratification factors, categorical fixed effects of treatment, visit, and treatment by visit interaction as covariates. For UACR, the log-transformed ratios ($\log[UACR_{visit}/UACR_{baseline}]$) were used as the response variable, and the log-transformed baseline UACR value was used as the continuous fixed effect. To evaluate the effect of tirzepatide compared with insulin glargine on UACR across the treatment period, we used the mean coefficient of treatment to estimate the tirzepatide effect on the geometric mean UACR across all visits. In an additional post-hoc analysis, we estimated eGFR slope and UACR effect of the three separate tirzepatide doses versus insulin glargine.

We used an unstructured covariance structure in the mixed models. In subgroup analyses, all possible two-way and three-way interactions between the treatment group, subgroup variable, and time were added to the model. We avoided including redundant terms for the stratification factor and subgroup variable when the two correlated highly.

The main random effect mixed effects model was repeated, with adjustment for concomitant last on-treatment changes in HbA_{1c} and bodyweight from baseline, to determine post hoc if the differences between tirzepatide and insulin glargine in the effects on eGFR and the UACR could be explained by concomitant changes in HbA_{1c} or bodyweight.

The safety analyses included all data from the start of treatment to the end of safety follow-up.

In an additional post-hoc analysis, we assessed the effect of 40 weeks of treatment with tirzepatide 5 mg, 10 mg, or 15 mg once weekly on UACR in the SURPASS-1,[10] SURPASS-2,[11] SURPASS-3,[12] and SURPASS-5[13] trials. The design of these trials and patient characteristics are described in the appendix (p 2). In these trials, analyses were based on the efficacy analysis dataset, including on-treatment data before the use of rescue therapy. Participants who discontinued study medication due to inadvertent enrolment were excluded from the efficacy analyses. Log-transformed UACR ratios were used as the response variable in a mixed model for repeated measures. The model included treatment and the patient visit number (eg, 1, 2, or 3) as factors and the original stratification factors from each trial as published previously[10–13] as covariates.

See Online for appendix

Two-sided p values of less than 0·05 were considered to indicate statistical significance. All analyses were done using SAS (version 9.4).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

The first patient visit occurred on Nov 20, 2018, recruitment continued until Dec 30, 2019, and the last patient visit was on April 22, 2021. Of 3045 people screened, 1043 were not eligible and 2002 (66%) were randomly assigned to tirzepatide (n=997) or insulin glargine (n=1005), of whom 1995 (>99%) received at least one dose of tirzepatide (n=995) or insulin glargine (n=1000 and were included in the modified intention-to-treat (mITT) population. The median study duration was 85 weeks. At week 52, the minimum follow-up duration per protocol, 1909 (96%) of 1995 patients were still in the study and 1819 (91%) of 1995 patients were using study medication (appendix, p 11). Baseline characteristics in the overall population and kidney-related subgroups were balanced (table; appendix p 4). Mean baseline eGFR was 81·1 (SD 21·44) mL/min per 1·73 m² in the pooled tirzepatide groups and 81·5 (20·78) mL/min per 1·73 m² in the insulin glargine group. The median UACR was 15·9 mg/g (IQR 5·0–59·0) for participants who received tirzepatide and 14·0 mg/g (4·4–53·1) for insulin glargine. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) medication use was reported by 804 (81%) of 995 participants assigned to tirzepatide and 811 (81%) of 1000 those assigned to insulin glargine. SGLT2 inhibitor use was 245 (25%) of

	Tirzepatide (n=995)	Insulin glargine (n=1000)	All (n=1995)
Age, years	63·4 (8·6)	63·8 (8·5)	63·6 (8·6)
Sex			
Male	610 (61%)	636 (64%)	1246 (62%)
Female	385 (39%)	364 (36%)	749 (38%)
Race			
American Indian or Alaska Native	88 (9%)	85 (9%)	173 (9%)
Asian	39 (4%)	31 (3%)	70 (4%)
Black or African American	41 (4%)	32 (3%)	73 (4%)
White	801 (81%)	825 (83%)	1629 (82%)
Duration of diabetes, years	11·5 (7·4)	12·0 (7·7)	11·8 (7·51)
HbA_{1c}, mmol/mol	69·9 (9·97)	69·4 (9·32)	69·7 (9·65)
HbA_{1c}, %	8·54 (0·91)	8·50 (0·85)	8·52 (0·88)
FSG, mmol/L	9·7 (2·87)	9·4 (2·76)	9·5 (2·82)
Weight, kg	90·3 (18·33)	90·2 (19·00)	90·3 (18·66)
BMI, kg/m²	32·6 (5·54)	32·5 (5·55)	32·6 (5·54)
History of cardiovascular disease	864 (87%)	869 (87%)	1733 (87%)
CKD epidemiology, eGFR ml/min per 1·73 m²	81·1 (21·44)	81·5 (20·78)	81·3 (21·11)
<60	176 (18%)	166 (17%)	342 (17%)
≥15 to <30	12 (1%)	10 (1%)	22 (1%)
≥30 to <45	60 (6%)	55 (6%)	115 (6%)
≥45 to <60	104 (10%)	101 (10%)	205 (10%)
≥60 to <90	394 (40%)	400 (40%)	794 (40%)
≥90	425 (43%)	434 (43%)	859 (43%)
Median UACR, mg/g	15·9 (5·0–59·0)	14·0 (4·4–53·1)	15·0 (5·0–55·8)
Normoalbuminuria (UACR <30)	621 (62%)	630 (63%)	1251 (63%)
Microalbuminuria (UACR 30–300)	276 (28%)	270 (27%)	546 (27%)
Macroalbuminuria (UACR >300)	82 (8%)	79 (8%)	161 (8%)
Haemoglobin, g/dL	14·1 (1·41)	14·1 (1·47)	14·1 (1·44)
Potassium, mEq/L	4·6 (0·43)	4·6 (0·42)	4·6 (0·43)
Systolic blood pressure, mm Hg	134·2 (15·12)	134·6 (15·7)	134·4 (15·40)
Diastolic blood pressure, mm Hg	78·4 (9·13)	78·4 (9·62)	78·4 (9·38)
Pulse rate, beats per min	72·7 (10·65)	72·8 (10·34)	72·8 (10·49)
SGLT2 inhibitor use			
Yes	245 (25%)	256 (26%)	501 (25%)
No	750 (75%)	744 (74%)	1494 (75%)
ACE inhibitor or angiotensin II receptor blocker use			
Yes	804 (81%)	811 (81%)	1615 (81%)
No	191 (19%)	189 (19%)	380 (19%)
ACE inhibitor use			
Yes	415 (42%)	425 (43%)	840 (42%)
No	580 (58%)	575 (57%)	1155 (58%)
Angiotensin II receptor blocker use			
Yes	402 (40%)	390 (39%)	792 (40%)
No	593 (60%)	610 (61%)	1203 (60%)
Mineralocorticoid receptor antagonist use			
Yes	89 (9%)	79 (8%)	168 (8%)
No	906 (91%)	921 (92%)	1827 (92%)

Data are mean (SD), n (%), or median (IQR). The median UACR was 6·2 (IQR 3·0–13·3) mg/g among patients with normoalbuminuria, 66·7 (44·0–116·8) mg/g with microalbuminuria, and 708 (433–1375) mg/g with macroalbuminuria. ACE=angiotensin-converting enzyme. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. FSG=fasting serum glucose. UACR=urine albumin–creatinine ratio.

Table: **Baseline characteristics**

995 in the tirzepatide group and 256 (26%) of 1000 in the insulin glargine group.

An initial decrease in eGFR was observed in the tirzepatide group (figure 1A); at week 12, the between-group difference for change from baseline in mean eGFR was –2·1 (95% CI –3·0 to –1·2) mL/min per 1·73 m² for the tirzepatide group compared with the insulin glargine group. However, after week 12, eGFR values were higher in the tirzepatide group than in the insulin glargine group. Overall, during the 104 weeks follow-up, the mean eGFR slope was –1·4 (SE 0·2) mL/min per 1·73 m² per year in the tirzepatide group and –3·6 (0·2) mL/min per 1·73 m² per year in the insulin group (between-group difference 2·2 [95% CI 1·6 to 2·8]). 4 weeks after study drug discontinuation, eGFR increased in the tirzepatide group but not in the insulin glargine group (between-group difference 0·9 [95% CI 0·1 to 1·6]; figure 1A). The beneficial effects of tirzepatide compared with insulin glargine on eGFR slope were consistent across baseline ACE inhibitor or ARB use and SGLT2 inhibitor use, but were more pronounced in participants with eGFR less than 60 mL/min per 1·73 m² at baseline compared with those with eGFR of at least 60 mL/min per 1·73 m² ($p_{interaction}$=0·016; figure 2, appendix p 12). The mean eGFR slope was –1·8 (SE 0·4) mL/min per 1·73 m² per year in the 5 mg tirzepatide group, –1·5 (0·4) mL/min per 1·73 m2 per year in the 10 mg tirzepatide group, and –1·1 (0·4) mL/min per 1·73 m2 per year in the 15 mg tirzepatide group. The between-group differences versus insulin glargine were 1·8 (95% CI 1·0–2·7) for 5 mg tirzepatide, 2·2 (1·3–3·1) for 10 mg tirzepatide, and 2·6 (1·7–3·5) for 15 mg tirzepatide (appendix p 14).

Figure 1B shows the albuminuria changes over time. UACR concentrations in the tirzepatide group remained reasonably stable, whereas those in the insulin glargine group increased progressively over time. At week 52, the mean percentage change from baseline in UACR was –6·4% (SE 3·3) with tirzepatide and 24·1% (4·3) with insulin glargine (between-group difference –24·6% [95% CI –31·5 to –17·0]; p<0·0001). This difference in UACR was sustained until week 104, at which point the mean percentage change in UACR was –4·4% (SE 7·1) with tirzepatide and 56·7% (12·2) with insulin glargine (between-group difference –39·0% [95% CI –50·6 to –24·6]; p<0·0001). 4 weeks after discontinuation of tirzepatide, UACR had increased compared with concentrations during the treatment period, with a greater percentage increase with tirzepatide than insulin glargine, but the geometric mean UACR remained significantly different between the treatment groups (figure 1B). The proportion of participants with at least 30% reduction in UACR at 52 weeks was 341 (41%) of 833 in the tirzepatide groups versus 248 (29%) of 859 in the insulin glargine group (odds ratio 1·7 [95% CI 1·4 to 2·1]).

The effect of tirzepatide versus insulin glargine on UACR in subgroups of participants with variable degrees

of CKD or by medication use at baseline is shown in figure 3 and the appendix (p 15). Overall, the least square mean percentage change from baseline in UACR was –6·8 (95% CI –14·1 to 1·1) with tirzepatide and 36·9 (95% CI 26·0 to 48·7) with insulin glargine (between-group difference –31·9 [95% CI –37·7 to –25·7]). The difference in effect between tirzepatide and insulin glargine was generally consistent among patient subgroups. The mean percentage change from baseline to 52 weeks in UACR was 3·7 (95% CI –8·1 to 17·0; between-group difference *vs* insulin glargine –24·5 [–33·3 to –14·4]) in the 5 mg tirzepatide group, –10·4 (–20·7 to 1·2; –34·7 [–42·5 to –25·9]), in the 10 mg tirzepatide group, and –11·9 (–21·9 to –0·6; –35·8 [–43·4 to –27·3]) in the 15 mg tirzepatide group (appendix p 14).

Treatment with tirzepatide significantly decreased the likelihood of progression to increasingly severe stages of albuminuria (figure 4A). The hazard ratio (HR) for worsening UACR stage (defined as sustained progression, either from a baseline UACR of <30 mg/g to ≥30 mg/g [microalbuminuria or macroalbuminuria], or from a baseline UACR of 30–300 mg/g [microalbuminuria] to at least 300 mg/g [macroalbuminuria]) for tirzepatide versus insulin glargine was 0·43 (95% CI 0·27–0·71). In parallel, among participants with baseline UACR of at least 30 mg/g (microalbuminuria or macroalbuminuria), participants who were assigned tirzepatide were more likely to regress to a less severe albuminuria stage (from microalbuminuria to normoalbuminuria, or from macroalbuminuria to either microalbuminuria or normoalbuminuria) than participants who were assigned insulin glargine (HR 1·97 [95% CI 1·51–2·57]; figure 4B).

The effect of tirzepatide on clinical kidney outcomes is shown in appendix (p 6) and figure 4C–D. In the overall cohort, tirzepatide compared with insulin glargine reduced the risk of the composite kidney endpoint of new-onset macroalbuminuria, eGFR decline of at least 40%, end-stage kidney disease, or death due to kidney failure by 42% (HR 0·58 [95% CI 0·43–0·80]). This effect was driven by new-onset macroalbuminuria component of the composite endpoint and was generally consistent across participant subgroups.

To assess whether the effect of tirzepatide on UACR and eGFR was mediated by changes in HbA_{1c} or bodyweight, the main analyses were repeated with adjustment for concomitant changes in HbA_{1c} and bodyweight. Effects of tirzepatide compared with insulin glargine on UACR and eGFR slope were essentially similar after taking into account HbA_{1c} and bodyweight changes (appendix p 7).

To assess the generalisability of our findings, we assessed the effect of tirzepatide in four other phase 3 clinical trials from the SURPASS programme, in different patient cohorts and using different comparators. In SURPASS-1[10] (5 mg, 10 mg, and 15 mg doses) and SURPASS-5[13] (10 mg and 15 mg doses), tirzepatide compared with placebo significantly reduced UACR after 40 weeks of treatment with effect sizes of similar magnitude as compared with SURPASS-4 (appendix p 8). In SURPASS-3,[12] both tirzepatide 10 mg and tirzepatide 15 mg once-weekly significantly reduced UACR compared with insulin degludec. In SURPASS-1,[10] SURPASS-3,[12] and SURPASS-5,[13] tirzepatide also reduced UACR among participants with baseline UACR of at least 30 mg/g

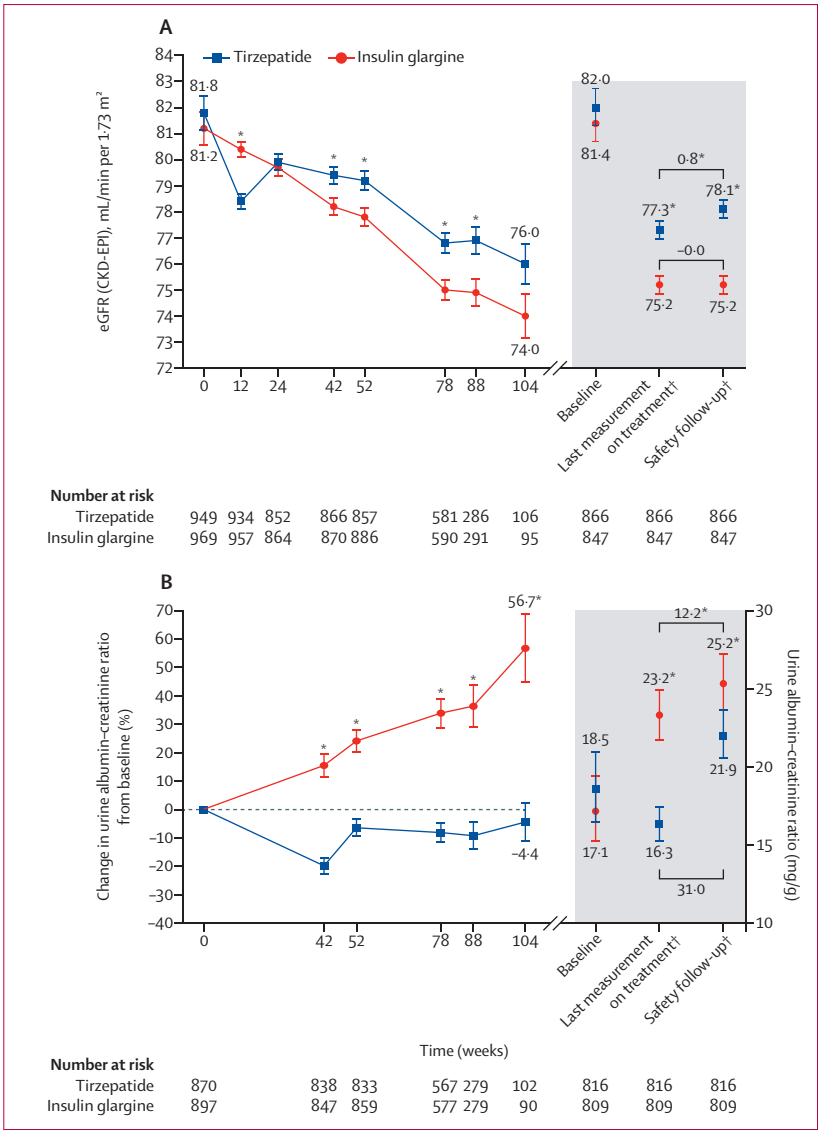


Figure 1: **eGFR and mean percentage changes from baseline in urine albumin–creatinine ratio during treatment and at safety follow-up**

For the grey shaded areas on the right of each panel, only patients who were measured at all three time points (ie, at baseline, last measurement on treatment, and safety follow up) were included in the analysis. (A) Least squares mean (SE) eGFR (CKD-EPI) over time and adjusted least squares mean (SE) at baseline, last measurement during treatment and safety follow-up. (B) Least squares mean (SE) percentage change from baseline in urine albumin–creatinine ratio over time and adjusted geometric mean (95% CI) urine albumin–creatinine ratio at baseline, last measurement during treatment and safety follow-up. Adjusted mean eGFR and adjusted geometric mean urine albumin–creatinine ratio were calculated from the analysis of a covariance model. eGFR=estimated glomerular filtration rate. CKD-EPI=chronic kidney disease epidemiology. *p<0·05 versus insulin glargine for between-group difference and between group change from last measurement during treatment to safety follow-up. †Median time from baseline to last measurement on treatment was 79 (IQR 69–88) weeks; the safety follow-up visit was 30 days after the last measurement during treatment.

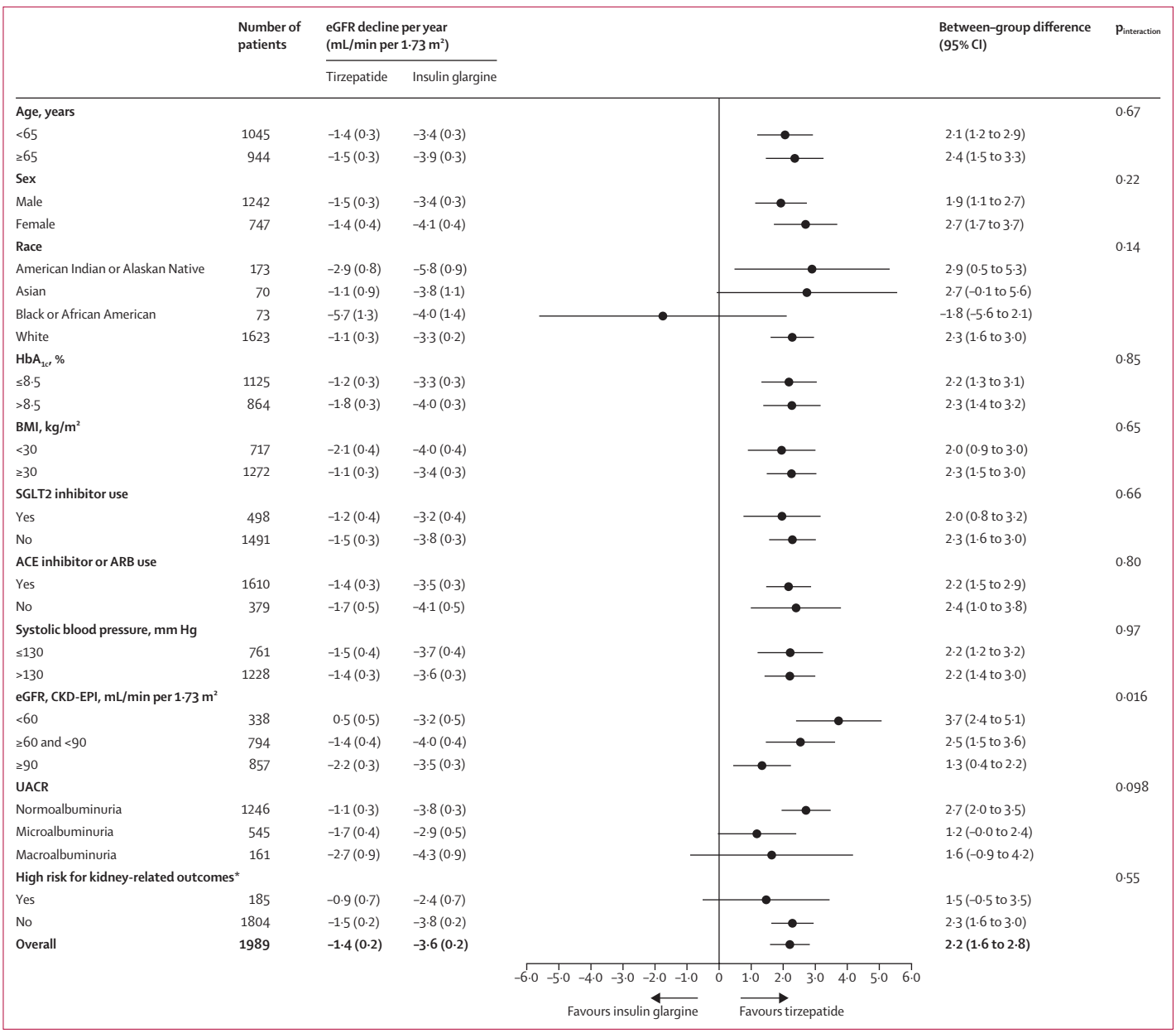


Figure 2: **eGFR (CKD-EPI) changes between baseline and end of treatment for the tirzepatide versus insulin glargine groups**
Slope data are mean decline (SE) per year and differences between tirzepatide and insulin glargine are with 95% CI. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blockers. CKD-EPI=chronic kidney disease epidemiology. eGFR=estimated glomerular filtration rate. UACR=urine albumin–creatinine ratio. *eGFR <75 CKD-EPI mL/min per 1·73 m² and macroalbuminuria, or eGFR <45 CKD-EPI mL/min per 1·73 m².

(appendix p 8). Finally, in SURPASS-2,[11] which compared semaglutide 1 mg once weekly with tirzepatide 5 mg, 10 mg, and 15 mg once weekly, the change in UACR was not significantly different between semaglutide and any of the three tirzepatide doses after 40 weeks. Among participants with a baseline UACR of at least 30 mg/g in SURPASS-2,[11] tirzepatide 15 mg (but not 10 mg or 5 mg) once weekly significantly reduced UACR compared with semaglutide 1 mg once weekly (between-group difference –28·7% [95% CI –48·0 to –2·2]).

With respect to safety, gastrointestinal adverse event rates were more common with tirzepatide than with insulin glargine and, in the tirzepatide groups, were similar between participants with and without CKD (eGFR <60 or ≥60 mL/min per 1·73 m²). Most of these events were reported as being mild or moderate. Hypoglycaemia was more common in the insulin glargine group, both in those with eGFR above or below 60 mL/min per 1·73 m², compared with those in the tirzepatide groups. Acute renal failure or CKDs based on

	Number of patients	UACR percentage change from baseline		Between-group difference (95% CI)	$p_{interaction}$
		Tirzepatide	Insulin glargine		
Age, years					0·80
<65	1044	−10·4 (−19·6 to −0·1)	25·3 (12·3 to 39·8)	−28·5 (−36·4 to −19·7)	
≥65	942	−1·9 (−13·4 to 11·3)	52·2 (34·0 to 72·8)	−35·5 (−43·6 to −26·2)	
Sex					0·28
Male	1239	−14·8 (−23·2 to −5·5)	35·7 (22·6 to 50·2)	−37·2 (−43·9 to −29·8)	
Female	747	7·5 (−7·6 to 24·9)	37·4 (17·3 to 60·9)	−21·8 (−32·1 to −9·8)	
Race					0·13
American Indian or Alaskan Native	173	7·1 (−28·5 to 60·3)	26·0 (−13·8 to 84·1)	−15·0 (−42·7 to 26·1)	
Asian	70	−37·2 (−64·7 to 11·7)	62·7 (−7·2 to 185·3)	−61·4 (−78·4 to −30·9)	
Black or African American	73	−11·1 (−50·6 to 60·0)	−11·1 (−50·6 to 60·0)	−19·8 (−53·7 to 38·9)	
White	1620	−12·4 (−25·8 to 3·6)	−12·4 (−25·8 to 3·6)	−32·2 (−38·3 to −25·4)	
HbA_{1c}, %					0·16
≤8·5	1124	2·5 (−7·9 to 14·0)	54·7 (39·3 to 71·7)	−33·8 (−41·1 to −25·5)	
>8·5	862	−18·3 (−28·4 to −6·7)	16·4 (1·3 to 33·7)	−29·8 (−38·5 to −19·7)	
BMI, kg/m²					0·33
<30	717	−5·3 (−18·4 to 9·8)	34·9 (16·9 to 55·6)	−29·8 (−39·9 to −18·0)	
≥30	1269	−8·9 (−18·3 to 1·5)	34·5 (20·3 to 50·3)	−32·3 (−39·2 to −24·5)	
SGLT2 inhibitor use					0·86
Yes	498	−7·6 (−19·4 to 5·9)	54·5 (34·2 to 78·0)	−40·2 (−49·4 to −29·4)	
No	1488	−10·4 (−19·6 to −0·0)	26·6 (13·5 to 41·2)	−29·2 (−36·2 to −21·5)	
ACE inhibitor or ARB use					0·55
Yes	1609	−5·3 (−13·8 to 4·0)	42·0 (28·9 to 56·3)	−33·3 (−39·6 to −26·4)	
No	377	−10·9 (−25·9 to 7·1)	22·1 (1·9 to 46·3)	−27·0 (−40·3 to −10·7)	
Systolic blood pressure, mm Hg					0·84
≤130	760	13·1 (−1·1 to 29·4)	55·7 (35·5 to 79·0)	−27·4 (−37·0 to −16·2)	
>130	1226	−16·6 (−25·2 to −7·0)	28·7 (15·3 to 43·7)	−35·2 (−42·2 to −27·4)	
eGFR, CKD-EPI, mL/min per 1·73 m²					0·66
<60	335	−5·3 (−23·6 to 17·4)	62·8 (30·8 to 102·5)	−41·8 (−54·1 to −26·1)	
≥60 and <90	794	−5·6 (−18·0 to 8·7)	49·9 (30·5 to 72·2)	−37·0 (−45·4 to −27·4)	
≥90	857	−5·8 (−16·2 to 5·9)	20·5 (6·9 to 35·7)	−21·8 (−30·8 to −11·6)	
UACR					0·40
Normoalbuminuria	1246	47·5 (35·3 to 60·8)	89·7 (74·0 to 106·7)	−22·2 (−28·6 to −15·3)	
Microalbuminuria	545	−56·7 (−62·8 to −49·6)	−19·3 (−31·1 to −5·4)	−46·4 (−55·3 to −35·6)	
Macroalbuminuria	161	−70·7 (−81·3 to −54·1)	−47·0 (−66·8 to −15·4)	−44·8 (−64·5 to −14·2)	
High risk for kidney-related outcomes*					0·99
Yes	184	−22·5 (−44·2 to 7·5)	42·1 (5·5 to 91·4)	−45·5 (−61·0 to −23·8)	
No	1802	−3·5 (−11·1 to 4·7)	34·5 (23·8 to 46·2)	−28·3 (−34·3 to −21·7)	
Overall	**1986**	**−6·8 (−14·1 to 1·1)**	**36·9 (26·0 to 48·7)**	**−31·9 (−37·7 to −25·7)**	

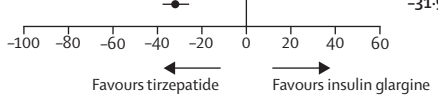


Figure 3: **Differences in UACR percentage changes from baseline to end of treatment for tirzepatide versus insulin glargine groups**
Data are percentage change (95% CI) and group difference (95% CI) between tirzepatide and insulin glargine. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blockers. CKD-EPI=chronic kidney disease epidemiology. eGFR=estimated glomerular filtration rate. UACR=urine albumin–creatinine ratio. *eGFR <75 CKD-EPI mL/min per 1·73 m² and macroalbuminuria, or eGFR <45 CKD-EPI mL/min per 1·73 m².

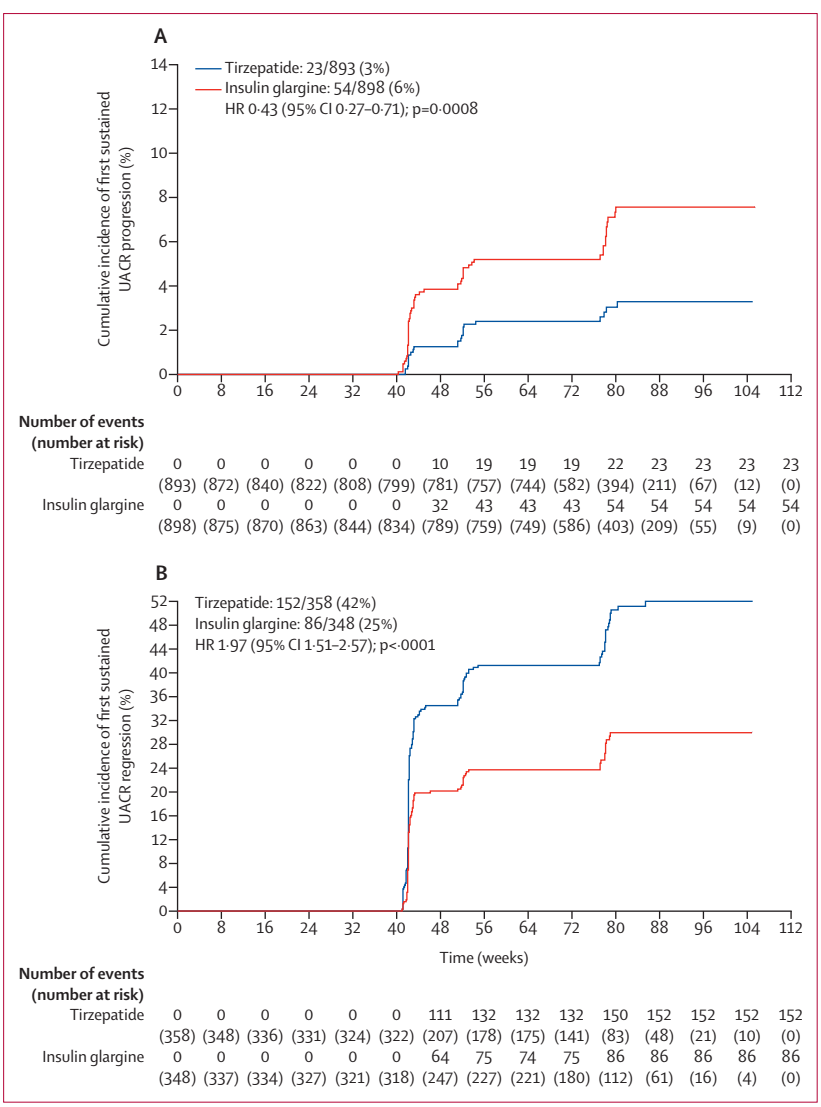
standardised MedDRA queries were not different between treatment groups (appendix p 9).

Discussion

In previous studies, the GIP and GLP-1 receptor agonist tirzepatide improved clinical risk factors known to promote cardiorenal risk, including glycaemic control, weight loss, and blood pressure.[9–15,19] In this kidney-specific exploratory analysis of 1995 patients with type 2 diabetes participating in the SURPASS-4 trial, our prespecified and post-hoc findings suggest that tirzepatide has kidney-protective effects. Compared with insulin glargine, tirzepatide slowed eGFR decline, reduced albuminuria, and reduced the risk of substantial loss of kidney function or new-onset microalbuminuria or macroalbuminuria. These kidney-related beneficial effects appear to be greater in people with pre-existing kidney disease, as defined by a lower eGFR.

Our first novel observation was that tirzepatide treatment resulted in a lower eGFR slope decrease per year compared

with insulin glargine. The point estimate for the reduction in annual eGFR loss achieved with tirzepatide was more pronounced at higher tirzepatide doses and clinically meaningful, since therapies that slow eGFR decline by 0·5–1·0 mL/min per 1·73 m² per year are highly likely to infer clinical benefit, including reducing the risk of kidney failure.[20] This notion is supported by clinical trials[21,22] that showed SGLT2 inhibitors reduced annual eGFR loss by at least 0·75 ml/min per 1·73 m² across subgroups of people with various degrees of CKD progression and also reduced the risk of kidney clinical outcomes. For the eGFR profile over time, tirzepatide treatment acutely reduced eGFR at 12 weeks in the overall cohort and in those with UACR of at least 30 mg/g, an effect that was also similar in SGLT2 inhibitor users versus non-users. This initial dip in eGFR was partly reversed after discontinuation of tirzepatide, which suggests that the initial dip in eGFR does not reflect structural kidney tissue injury. An acute dip in eGFR has been observed with other classes of kidney-protective therapies, such as renin–angiotensin system (RAS) inhibitors and SGLT2 inhibitors, and has been linked with long-term kidney protection.[23,24] Although it is not possible to define the physiological pathways responsible for this initial dip in eGFR at 12 weeks, several pathways could be involved. First, improved glycaemic control and weight loss can attenuate neurohormonal activation and other factors associated with glomerular hypertension, which can in turn reduce eGFR.[25] Second, GLP-1 receptor activation can induce a proximal tubular natriuresis via inhibition of sodium/hydrogen exchanger 3, an effect proposed to activate tubuloglomerular feedback and thereby reduce hyperfiltration.[26] Consequently, further work is required to understand this effect with tirzepatide, and the effect on the potential long-term benefits reported in this analysis.



(Figure 4 continues on next page)

Our second main finding was that tirzepatide stabilised UACR over time compared with insulin glargine, resulting in a gradual increase over time in the UACR difference between the two treatment groups. The magnitude of this effect was clinically relevant, since treatments that reduce UACR by more than 30% are highly likely to confer significant long-term kidney protection as shown with RAS inhibitors and SGLT2 inhibitors.[27] Furthermore, development of microalbuminuria or macroalbuminuria are hallmarks of the progression of diabetic kidney disease and are associated with poor kidney and cardiovascular survival.[27] Tirzepatide was associated with a reduction in the likelihood of progression to worsening UACR categories. The UACR-stabilising effect of tirzepatide was similar in SGLT2 inhibitor users versus non-users, which is clinically important, as SGLT2 inhibitors are recommended by clinical practice guidelines and are part of the standard of care for kidney protection in addition to RAS inhibition.[28] In SURPASS-4, 25% of patients were using SGLT2 inhibitors, which is a larger proportion than in other clinical trials, illustrating the rapid uptake of this drug class among participants in clinical trials. Yet, despite the use of SGLT2 inhibitors, high UACR concentrations persist in a substantial proportion of patients, and are associated with a high risk of poor kidney and cardiovascular outcomes.[29] Additional therapies that further lower UACR and slow the progression of eGFR decline are therefore desirable. The mechanisms responsible for this clinical effect of tirzepatide are not yet known, but could include indirect factors outside the kidney, such as blood pressure, bodyweight, and blood glucose lowering effects. However, the effects of tirzepatide on UACR and the eGFR slope after adjustment for concomitant changes in HbA_{1c} and bodyweight remained largely similar to the main analyses, which suggests that improvement in these metabolic parameters contribute only moderately to the observed kidney benefits with tirzepatide. It is also possible that the effects of tirzepatide can be attributed to direct intrarenal effects. GIP receptors are found in

adipose tissue that is located surrounding and within organs, including the kidneys.[30] Targeting GIP in perirenal fat and intrarenal fat might favourably effect inflammation that extends into functioning kidney tissue and damage associated with albuminuria.[31] Additionally, as with GLP-1 receptor agonists, tirzepatide could improve endothelial function, suppress the RAS, and exert natriuretic effects, which could lead to kidney protection.[32,33]

Beyond eGFR slope and UACR benefits, tirzepatide treatment also reduced the risks of the composite kidney outcome compared with insulin glargine, although this effect appears to be largely driven by a reduction in new-onset macroalbuminuria. Similar benefits for clinical kidney outcomes have been reported with GLP-1 receptor agonists in cardiovascular safety trials.[7,34–36] In these cardiovascular safety trials, similarly to SURPASS-4, the majority of participants were at low risk of progressive kidney function loss, making it difficult to ascertain accurately the potential benefits regarding kidney failure during the short follow-up of clinical trials. However, post-hoc pooled analyses from cardiovascular safety trials[5–7] published in 2020–22 on GLP-1 receptor agonists have suggested protection against substantial kidney function loss, especially in people with pre-existing kidney disease. Furthermore, in patients with type 2 diabetes and established chronic kidney disease, dulaglutide significantly reduced the risk of kidney failure compared with insulin treatment.[7] In accordance with these findings, in SURPASS-4, the benefits of tirzepatide in slowing eGFR decline were more pronounced in people with reduced kidney function than in those with healthy kidneys. The more pronounced benefit of tirzepatide on kidney function decline in participants with reduced eGFR, who are at increased risk of kidney failure, support future randomised controlled clinical trials in people with pre-existing kidney disease.

In the overall trial population, the adverse event profile of tirzepatide was similar to that for GLP-1 receptor agonists and such events were mainly gastrointestinal in nature, which were reported more frequently with tirzepatide than with insulin glargine. Participants with CKD (eGFR <60 mL/min per 1·73 m²) reported more adverse events than those without CKD, which was true in both the tirzepatide and the insulin glargine groups. Both acute and chronic kidney injury reported by the investigators were more frequent in participants with CKD than in those without, with no with no statistically significant differences between treatment groups, although event numbers were small.

We assessed the effects of tirzepatide on albuminuria in other phase 3 trials of the SURPASS programme, recruiting different patient populations and using different comparators, to assess the generalisability of our findings. Although these trials were not designed to assess the effects of tirzepatide on albuminuria and most patients had albuminuria concentrations in the normal range, the results suggested that, compared with placebo or insulin degludec, tirzepatide reduced albuminuria in the overall population, and in participants with microalbuminuria or macroalbuminuria at baseline. In this subgroup of patients who are at increased risk of kidney function decline, tirzepatide 15 mg once weekly also reduced albuminuria compared with the GLP-1 receptor agonist semaglutide, potentially suggesting superior kidney protective effects. Collectively, these data support the SURPASS-4 findings

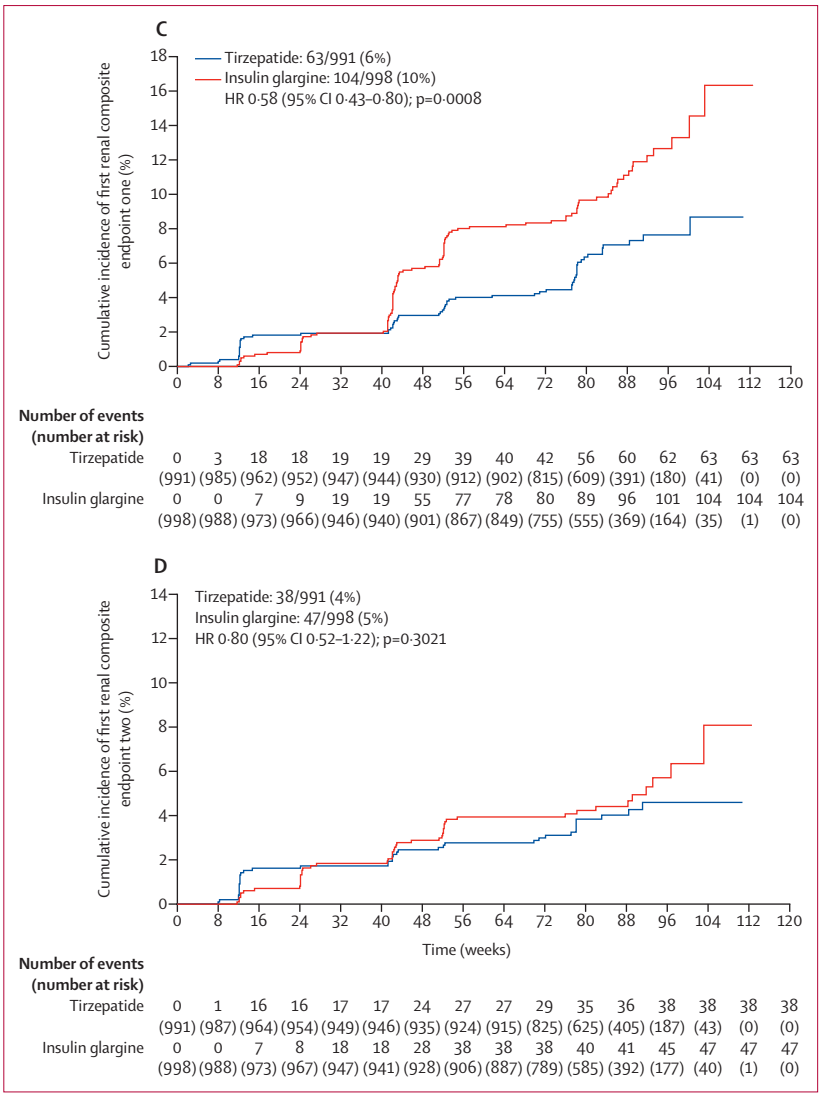


Figure 4: **Kaplan-Meier plots**
HR, 95% CI, and p values are derived from a Cox proportional-hazards model with treatment (tirzepatide *vs* insulin glargine) as a fixed effect. (A) Time to first sustained UACR progression. Sustained was defined as two consecutive measurements fulfilling the condition; for patients with normoalbuminuria at baseline, sustained progression required two consecutive worsening measurements (ie, microalbuminuria or macroalbuminuria), whereas for patients who were in the macroalbuminuria category at baseline, sustained regression required two consecutive improving measurements (ie, normoalbuminuria or microalbuminuria). (B) Time to first sustained UACR regression. (C) Time to first occurrence of renal composite endpoint one (ie, estimated eGFR [chronic kidney disease epidemiology] decline ≥40% from baseline, renal death, or progression to end-stage kidney disease, and new-onset macroalbuminuria). (D) Time to first occurrence of renal composite endpoint two (ie, same as composite endpoint one but without new-onset macroalbuminuria). eGFR=estimated glomerular filtration rate. HR=hazard ratio. UACR=urine albumin–creatinine ratio.

and the generalisability of a potential kidney protective effect of tirzepatide.

This analysis does have limitations. First, the study was an exploratory, partly post-hoc analysis of a randomised controlled trial. Our results can therefore only be regarded as hypothesis generating. Second, we recognise that by design, the SURPASS-4 trial was not a dedicated kidney outcomes trial. Overall, 342 patients had pre-existing kidney disease (defined by an eGFR of less than 60 mL/min per 1·73m²), which is far fewer than in subsequent dedicated kidney outcome trials[37–39] that included more than 4000 people. Nevertheless, phase 3 trials[40–43] that preceded these kidney outcome trials enrolled a similar number of patients with CKD as SURPASS-4 did. Since many SURPASS-4 participants had baseline clinical kidney parameters within the normal range, effects on kidney function preservation and UACR cannot be directly generalised to people with advanced stages of CKD. Similarly, owing to low numbers of clinical kidney outcomes, our analysis had insufficient statistical power to define benefits for clinically relevant patient-oriented outcomes and our results need to be confirmed in a larger well designed kidney outcome trial. Third, the absence of a placebo group in the current study means that no definitive conclusions can be drawn regarding whether tirzepatide is nephroprotective or whether insulin glargine worsens the progression of kidney disease. However, data from the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial[44] showed that the initiation of insulin glargine to lower HbA_{1c} does not accelerate kidney function decline. Finally, not every participant had complete follow-up data available over 104 weeks, because the trial was closed after the collection of protocol-defined number of major cardiovascular events.

In conclusion, in people with type 2 diabetes and high cardiovascular risk, tirzepatide slowed eGFR decline and reduced UACR in comparison with insulin, including in patients on ACE inhibitors, ARB, or SGLT2 inhibitors at baseline. Based on the results of this study, trials examining the effect of dual GIP and GLP-1 receptor agonist therapies on kidney protection in patients at high risk of diabetic kidney disease progression are warranted.

Contributors

HJLH and DZIC drafted the first version of the manuscript edited subsequent drafts, and approved the final version. All authors were involved in developing the kidney analyses, provided critical review and editorial input, and approved the final draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. IP and ZY are the guarantors of this work, directly accessed and verified the underlying data reported, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

HJLH has received grants or contracts from AstraZeneca, Boehringer Ingelheim, Janssen, and NovoNordisk; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Chinook, Dimerix, Eli Lilly, Gilead, Goldfinch Bio, Janssen, Mitsubishi Tanabe Pharma, NovoNordisk, MSD, and Travere Therapeutics; payment or honoraria for speaking from AstraZeneca; and support for attending meetings from Eli Lilly. NS has received grants from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics; and consulting fees from Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceutical, MSD, Novartis, Novo Nordisk, Pfizer, and Sanofi. IP, AH, KLD, ZY, and RJW are employees and shareholders of Eli Lilly and Company. AH is a data monitoring committee board member for tirzepatide (Eli Lilly and Company). KRT has received grants or contracts from Bayer, Goldfinch Bio, and Travere; consulting fees from Eli Lilly, Boehringer Ingelheim, AstraZeneca, Goldfinch Bio, Travere Pharmaceuticals, Bayer, and Novo Nordisk; payment or honoraria for speaking from Eli Lilly, AstraZeneca, Bayer, and Novo Nordisk; has participated on data safety monitoring or advisory boards for the US National Institute of Diabetes and Digestive and Kidney Diseases National Institutes of Health and the George Clinical Institute for Global Health; and reports a leadership or fiduciary role as Chair of the Diabetic Kidney Disease Collaborative Task Force, American Society of Nephrology. DZIC has received grants or contracts from Boehringer Ingelheim–Lilly, Merck, Janssen, Sanofi, AstraZeneca, CSL Behring, and Novo Nordisk; and consulting fees and speaking honoraria from Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, Abbvie, Janssen, Bayer, Prometic, BMS, Maze, Gilead, CSL Behring, Otsuka, Novartis, Yeungene, and NovoNordisk.

Data sharing

Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU, and after primary publication acceptance, whichever is later. No expiry date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For instructions on submitting a data access request, see https://vivli.org/.

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