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Tirzepatide Associated With Reduced Albuminuria in Participants With Type 2 Diabetes: Pooled Post Hoc Analysis From the Randomized Active- and Placebo-Controlled SURPASS-1–5 Clinical Trials

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Objective

To assess the **change from baseline in UACR** for **tirzepatide** (GIP/GLP-1 RA) compared with active and placebo treatment in a broad population with **type 2 diabetes**, including people with **CKD**.

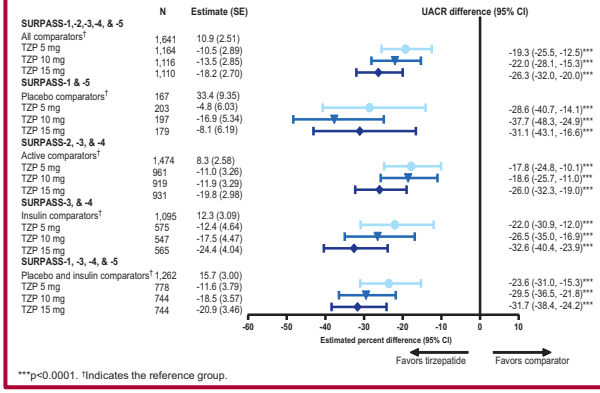
Design & Methods

Post hoc analysis of **pooled SURPASS-1–5 trials**, overall and subgroup analysis (UACR≥30mg/g)

SURPASS trials			
	N	Comparator	Background medication
1	478	Placebo	Diet + exercise
2	1878	Semaglutide 1 mg once weekly	Metformin
3	1437	Insulin degludec	Metformin ± SGLT2i
4	1995	Insulin glargine	1-3 of metformin, SGLT2i, SU
5	475	Placebo	Insulin glargine ± metformin

Results

Relationship between UACR and tirzepatide versus comparators in SURPASS



***p<0.0001. †Indicates the reference group.

Conclusion: In this post hoc analysis in people with type 2 diabetes, including those with CKD, tirzepatide was associated with a clinically relevant decreased UACR versus comparators, suggesting a potential kidney-protective effect.

CKD, chronic kidney disease; GIP/GLP-1 RA, glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonist; SGLT2i, sodium–glucose contransporter 2 inhibitor; SU, sulfonylurea; TZP, tirzepatide; UACR, urine albumin-to-creatinine ratio.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  In a post hoc analysis in people with type 2 diabetes and high cardiovascular risk (SURPASS-4 trial), tirzepatide was associated with a slowed rate of eGFR decline and reduced UACR versus insulin glargine.
- **What is the specific question we wanted to answer?**
  We assessed change from baseline in UACR with tirzepatide versus comparators in a broad population in SURPASS-1–5.
- **What did we find?**
  Tirzepatide was associated with a greater decrease in UACR versus insulin, semaglutide 1 mg, and placebo. This observation was dose-dependent and potentially explained by both a direct effect on the kidney and indirect effects mediated by glycemia and body weight reductions.
- **What are the implications of our findings?**
  These pooled post hoc analyses suggest a potential kidney-protective effect of tirzepatide.

ORIGINAL ARTICLE

Tirzepatide Associated With Reduced Albuminuria in Participants With Type 2 Diabetes: Pooled Post Hoc Analysis From the Randomized Active- and Placebo-Controlled SURPASS-1–5 Clinical Trials

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OBJECTIVE

Tirzepatide, a long-acting, glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonist, reduced urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) decline in people with type 2 diabetes and high cardiovascular risk in the SURPASS-4 trial. To examine the generalizability of these findings, we assessed change from baseline in UACR for tirzepatide (5, 10, and 15 mg) compared with active and placebo treatment in a broad population from the SURPASS-1–5 trials.

RESEARCH DESIGN AND METHODS

This post hoc analysis examined data from the overall pooled SURPASS-1–5 population and subgroups defined by baseline UACR ≥30 mg/g. A mixed model for repeated measures was used to analyze on-treatment data from baseline to the end-of-treatment visit. Study identifier was included in the model as a covariate.

RESULTS

The adjusted mean percent change from baseline in UACR for tirzepatide 5, 10, or 15 mg compared with all pooled comparators was −19.3% (95% CI −25.5, −12.5), −22.0% (−28.1, −15.3), and −26.3 (−32.0, −20.0), respectively, at week 40/42. Results were similar across pooled placebo, active, and insulin comparator studies. UACR lowering appeared more pronounced in subgroups with UACR ≥30 mg/g. Mediation analysis findings suggested that approximately one-half of the reduction in albuminuria associated with tirzepatide may be weight loss related. There was no difference in eGFR between tirzepatide and pooled comparators at week 40/42.

CONCLUSIONS

In this post hoc analysis in people with type 2 diabetes, including those with chronic kidney disease, tirzepatide was associated with a clinically relevant decreased UACR versus comparators, suggesting a potential kidney-protective effect.

Chronic kidney disease (CKD), a common complication of type 2 diabetes, is associated with a reduced quality of life and an increased risk of cardiovascular disease and mortality (1). New therapies to slow the progression of CKD have been shown

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to improve the prognosis of CKD; however, the risks of kidney failure and cardiovascular disease remain high (2). Therefore, additional therapies that reduce the rate of kidney function decline are desired. Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 receptor agonist (GLP-1RA). GLP-1 and GIP are incretin gut hormones that promote insulin secretion after food intake and reduce body weight by enhancing satiety (3). Clinical studies have shown more pronounced beneficial effects of tirzepatide compared with GLP-1RAs in reducing hyperglycemia and body weight (4–8). Specifically, in people with type 2 diabetes participating in the SURPASS clinical trials, tirzepatide showed clinically meaningful improvements in glycemic control and body weight compared with placebo, semaglutide, and insulin degludec or glargine, as well as beneficial effects on blood pressure and lipoprotein profile (8–12).

A post hoc analysis from the SURPASS-4 trial suggested that tirzepatide may confer kidney protection (13). Tirzepatide compared with insulin glargine was dose-dependently associated with reduced albuminuria and estimated glomerular filtration rate (eGFR) decline in adults with type 2 diabetes at high cardiovascular risk. While the active control in the SURPASS-4 trial enabled a head-to-head comparison against insulin glargine, no definitive conclusions could be drawn regarding whether tirzepatide is nephroprotective. We therefore performed a pooled post hoc exploratory analysis in a larger sample size using individual patient data from the SURPASS-1–5 trials to determine the potential relationship between tirzepatide compared with placebo and various active comparators with albuminuria (a reasonably likely surrogate kidney outcome) and eGFR decline.

RESEARCH DESIGN AND METHODS

Study Design and Patient Population

The SURPASS trials were randomized, multicenter studies (8–12). Adults (aged ≥18 years) were eligible for inclusion if they had type 2 diabetes and a glycated hemoglobin (HbA_{1c}) level of 7.0% (≥53.0 mmol/mol) to 9.5% (≤80.3 mmol/mol) in SURPASS-1; 7.0% (≥53.0 mmol/mol) to 10.5% (≤91.3 mmol/mol) in SURPASS-2, 3, and 5; and 7.5% (≥58.5 mmol/mol) to 10.5% (≤91.3 mmol/mol) in SURPASS-4. Furthermore, participants needed to have a BMI of ≥23 kg/m^2 (SURPASS-1 and -5) or BMI ≥25 kg/m^2 (SURPASS-2, -3, and -4) and stable weight in the 3 months prior to enrollment. Participants were excluded for type 1 diabetes; history of pancreatitis, proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy requiring treatment; and eGFR <30 mL/min/1.73 m^2 (SURPASS-1 and -5) or <45 mL/min/1.73 m^2 (SURPASS-2 and -3 and participants in SURPASS-5 receiving metformin).

In the SURPASS program, tirzepatide was used at doses of 5, 10, and 15 mg administered as weekly subcutaneous injections. In SURPASS-1 (*N* = 478) tirzepatide was compared with placebo in participants with type 2 diabetes inadequately controlled with diet and exercise alone and who were naive to injectable diabetes therapy. In SURPASS-2 (*N* = 1,878), tirzepatide was compared with the GLP-1RA semaglutide 1 mg administered once weekly in participants using stable metformin monotherapy. In SURPASS-3 (*N* = 1,437), tirzepatide was compared with daily insulin degludec in participants who received stable treatment with metformin with or without a sodium–glucose cotransporter 2 inhibitor (SGLT2i). In SURPASS-4 (*N* = 1,995), tirzepatide was compared with insulin glargine in participants receiving any combination of metformin, sulfonylurea, or SGLT2i. In SURPASS-5 (*N* = 475), tirzepatide was compared with placebo as an adjunct to insulin glargine with or without metformin. Participants were randomized in a 1:1:1:1 ratio in all trials except SURPASS-4, in which the randomization ratio was 1:1:1:3 to tirzepatide 5, 10, 15 mg, or insulin glargine. SURPASS-2, -3, and -4 were open label in design, while SURPASS-1 and -5 used double-blind study designs.

Outcomes

The main outcome of the current post hoc analysis was the percent change in urine albumin-to-creatinine ratio (UACR) from baseline to week 40 or week 42 (SURPASS-4 only, as UACR was not measured at week 40). UACR was measured in single spot urine samples at baseline and follow-up in each study at a central laboratory (IQVIA Clinical Analytics, Durham, NC) using an immunoturbidity assay for albumin and a Jaffe colorimetric method for creatinine. eGFR change over time, estimated using the Chronic Kidney Disease Epidemiology Collaboration creatinine 2009 equation (14), was another outcome of this analysis measured at week 40/42.

Statistical Analysis

Baseline characteristics of the pooled SURPASS-1–5 population were summarized using mean (SD), frequency (%), or median (minimum, maximum) for non-normally distributed variables. The main outcome of on-treatment percent change from baseline in UACR was calculated using a mixed model for repeated measures. The model included treatment and visit as factors, a treatment-visit interaction term, and log-transformed baseline UACR and study identifier as covariates. Subgroup analyses of the association of tirzepatide with UACR changes stratified by SGLT2i use, renin-angiotensin system inhibitor (RASi) use, or CKD status (baseline CKD defined as yes if UACR ≥30 mg/g and/or eGFR <60 mL/min/1.73 m^2) were also conducted. Changes over time in eGFR, HbA_{1c}, and weight in pooled groups treated with tirzepatide versus comparators were each calculated using a mixed model for repeated measures with study identifier and baseline eGFR, HbA_{1c}, or weight, respectively, as covariates and treatment, visit, and treatment-visit interaction as factors. Data were examined in all participants in each pooled population and in subgroups defined by baseline UACR ≥30 mg/g and eGFR <60 mL/min/1.73 m^2.

To assess whether concomitant effects of tirzepatide on HbA_{1c} and body weight could explain the observed changes in UACR in the pooled population treated with tirzepatide, we performed causal multiple mediation analyses. The SURPASS-2 trial was excluded from these analyses as semaglutide 1 mg, a GLP-1RA already demonstrated to have positive effects on kidney outcomes, was the comparator in that study (15). These analyses break down the relationship between tirzepatide and UACR into potential direct (the potential independent effect of tirzepatide on UACR) and indirect (the potential effect of tirzepatide on UACR explained by prior changes in other cardiometabolic variables) effects, while adjusting for known covariates. Changes in body weight, HbA_{1c}, eGFR, and systolic blood pressure were explored as potential mediators in single-mediator models, with change in body weight and HbA_{1c} being carried forward to multiple mediation analysis as they contributed the largest mediation and offer a clinically plausible direction

of causation. The hypothesis for this analysis was that reductions in weight and HbA_{1c} may explain changes in UACR and not the other way around. eGFR did not indicate any mediation potential, and while systolic blood pressure was found to potentially have a small mediating effect, the addition of this as a third mediator in the multiple mediation model necessitated too many assumptions about directions of causality among the three mediators. Therefore, the two largest mediators, weight and HbA_{1c}, were alone retained. Mediation analyses were conducted using structural equation modeling methods and the lavaan package of R 4.2.2, using a maximum likelihood estimate, robust Huber-White SEs, and nonlinear minimization with box constraints optimization (16,17). Each path model was adjusted for covariates comprising the baseline value of the outcome being modeled, sex, country, and study identifier. Mediation effects for each pathway were calculated as the product of all model coefficients inscribing that path from independent variable (treatment) to dependent variable (change in UACR).

In models or summaries where pooled data from SURPASS studies, including SURPASS-4, were analyzed or tabulated, adjusted estimates of means, SDs, proportions, and model coefficients were obtained by weighting observations with the inverse probability of randomization to each treatment to account for the differing randomization ratios between SURPASS-4 and the other trials. The inverse probability of treatment weights were calculated separately for analyses involving separate doses of tirzepatide and those that pooled tirzepatide doses. No weighting was used in analyses that did not include SURPASS-4 (Supplementary Material). All models were applied to participants with nonmissing week 40/42 data for the modeled outcome, and missingness in covariates was handled by listwise deletion.

RESULTS

Baseline demographics and clinical characteristics for the pooled population from the SURPASS-1–5 trials (N = 5,299 participants with nonmissing postbaseline UACR data) are summarized in Table 1 and were generally balanced among treatment groups. The median UACR in the tirzepatide 5, 10, and 15 mg and the pooled comparator groups was 11.0, 11.0, 11.0, and 12.0 mg/g, respectively. Mean baseline eGFR was 96.3, 95.6, 96.5, and 89.6 mL/min/1.73 m^2, respectively, indicating that most participants had preserved kidney function. Mean HbA_{1c} was 8.3% (67 mmol/mol) in all tirzepatide groups and 8.4% in pooled comparators, and the mean duration of diabetes ranged from 9.0 to 10.8 years. Use of an RASi was reported by 65–66% of tirzepatide-treated participants and 71% of comparator-treated participants. In SURPASS-3, 458 participants (32%) were being treated with metformin plus an SGLT2i, and in SURPASS-4, 501 participants (25%) used an SGLT2i. Baseline characteristics for the pooled population excluding SURPASS-2 are presented in Supplementary Tables 1 and 2. Participants without available postbaseline data (n = 1,215) did not differ demonstrably from those with data who were included in analyses in terms of treatment group distribution, baseline demographics, or baseline clinical characteristics.

Table 1—Baseline characteristics of participants in the pooled SURPASS-1–5 trials

	Comparator (n = 1,748)	Tirzepatide 5 mg (n = 1,218)	Tirzepatide 10 mg (n = 1,173)	Tirzepatide 15 mg (n = 1,160)
Sex, male	1,010 (57.8)	627 (51.5)	664 (56.6)	611 (52.7)
Age (years)	61.3 ± 6.0	57.7 ± 4.9	58.1 ± 4.9	57.2 ± 5.1
Race, White	1,445 (82.8)	951 (78.1)	926 (78.9)	941 (81.1)
Ethnicity, Hispanic or Latino	831 (47.5)	573 (47.0)	562 (47.9)	555 (47.8)
Duration of diabetes (years)	10.78 ± 4.58	9.37 ± 3.42	8.97 ± 3.21	9.16 ± 3.36
Weight (kg)	91.18 ± 11.91	92.31 ± 9.58	93.98 ± 10.09	93.76 ± 9.84
BMI (kg/m^2)	32.80 ± 3.61	33.35 ± 3.04	33.77 ± 3.08	33.83 ± 3.02
HbA_{1c} (%)	8.4 ± 0.54	8.3 ± 0.46	8.3 ± 0.46	8.3 ± 0.48
UACR (mg/g)	12.0 (1.0, 6,985.0)	11.0 (1.0, 7,548.0)	11.0 (1.0, 4,338.0)	11.0 (1.0, 7,307.0)
UACR category				
Macroalbuminuria	95 (5.5)	60 (5.0)	79 (6.8)	57 (4.9)
Microalbuminuria	416 (24.0)	288 (23.8)	270 (23.2)	282 (24.4)
Normal	1,220 (70.5)	862 (71.2)	815 (70.0)	819 (70.7)
eGFR (mL/min/1.73 m^2)†	89.64 ± 12.38	96.28 ± 8.86	95.56 ± 8.36	96.47 ± 8.43
eGFR category (mL/min/1.73 m^2)				
<60	146 (8.4)	78 (6.4)	59 (5.0)	55 (4.7)
≥60	1,602 (91.6)	1,140 (93.6)	1,114 (95.0)	1,105 (95.3)
RASi use	1,239 (70.9)	793 (65.1)	769 (65.6)	768 (66.2)
SGLT2i use	321 (18.4)	173 (14.2)	165 (14.1)	163 (14.1)

Data are n (%), mean ± SD, or median (minimum, maximum) from the modified intention-to-treat population (efficacy analysis set), including participants with nonmissing postbaseline UACR data, and weighted using inverse probability of treatment weights. Comparators were placebo in SURPASS-1 and -5, semaglutide 1 mg in SURPASS-2, insulin degludec in SURPASS-3, and insulin glargine in SURPASS-4. †By Chronic Kidney Disease Epidemiology Collaboration equation.

Association of Tirzepatide With Kidney Parameters

Overall, the adjusted mean percent change from baseline in UACR for tirzepatide 5, 10, or 15 mg compared with all pooled comparators was −19.3% (95% CI −25.5, −12.5), −22.0% (−28.1, −15.3), and −26.3% (−32.0, −20.0), respectively, at week 40/42 (Fig. 1). Results were similar when SURPASS-2 was excluded from the analysis and in studies with insulin comparators (Fig. 1). The reduction in UACR was somewhat larger when comparing tirzepatide with placebo in the pooled SURPASS-1 and SURPASS-5 trials (Fig. 1). Tirzepatide compared with semaglutide 1 mg (SURPASS-2) was associated with adjusted mean percent changes from baseline in UACR of −4.8% (−15.6, 7.3), 2.8% (−8.9, 16.1), and −11.1% (−21.3, 0.4) for the 5, 10, and 15 mg tirzepatide doses, respectively, indicating no significant differences in UACR changes between tirzepatide and semaglutide (13). Subgroup analyses of the association of tirzepatide with UACR changes stratified by SGLT2i or RASi use showed consistent results irrespective of baseline SGLT2i or RASi use (Supplementary Figs. 1 and 2).

The UACR analyses were also conducted in participants with CKD defined by UACR ≥30 mg/g or eGFR <60 mL/min/1.73 m^2. At baseline, 1,846 participants (30%) had a UACR ≥30 mg/g, and 537 participants (9%) had an eGFR <60 mL/min/1.73 m^2. Among participants with UACR ≥30 mg/g, the adjusted mean percent UACR change for tirzepatide 5, 10, and 15 mg compared with all pooled comparators was −31.3% (95% CI −42.0, −18.6), −42.2% (−51.2, −31.6), and −47.3% (−55.5, −37.5), respectively (Fig. 2). These observations were similar when tirzepatide was compared with placebo or active comparators and when SURPASS-2 was excluded (Fig. 2). In participants with UACR ≥30 mg/g from the SURPASS-2 trial, tirzepatide 5, 10, and 15 mg compared with semaglutide 1 mg reduced UACR by −13.2% (−36.0, 17.9), −15.7% (−38.3, 15.1), and −28.7% (−48.0, −2.2), respectively, with a significant difference observed for tirzepatide 15 mg compared with semaglutide only.

Among participants from the pooled population with baseline eGFR <60 mL/min/1.73 m^2, the adjusted mean percent UACR change for tirzepatide 5, 10, and 15 mg compared with the pooled comparator group was −26.6% (95% CI −49.4, 6.3), −23.6% (−49.4, 15.2), and −49.2% (−66.6, −22.5), with similar observations when the placebo and active comparators were considered separately (Supplementary Fig. 3). When considering the baseline CKD population, defined as the union of these baseline UACR and eGFR conditions, tirzepatide was consistently associated with greater reductions in UACR relative to comparator, regardless of CKD status (Supplementary Fig. 4).

In SURPASS-1, -3, -4, and -5, adjusted mean eGFR changed by −2.4 mL/min/1.73 m^2 from baseline to week 40/42 among participants who received tirzepatide compared with −2.8 mL/min/1.73 m^2 for participants in the pooled comparator group (between-group difference 0.3 [95% CI −0.5, 1.2]) (Supplementary Fig. 5). eGFR changes over time for SURPASS-2 are presented in Supplementary Fig. 5.

Relationship Between Tirzepatide Treatment and UACR May Be Explained by Metabolic Effects

Populations treated with tirzepatide versus pooled comparators were examined to determine potential mediators for inclusion in the mediation analyses. The adjusted mean change in HbA_{1c} from baseline to week 40/42 was −2.3% in the pooled tirzepatide group and −1.3% in the comparator group, resulting in a between-group difference of −1.0% (95% CI −1.0, −0.9)

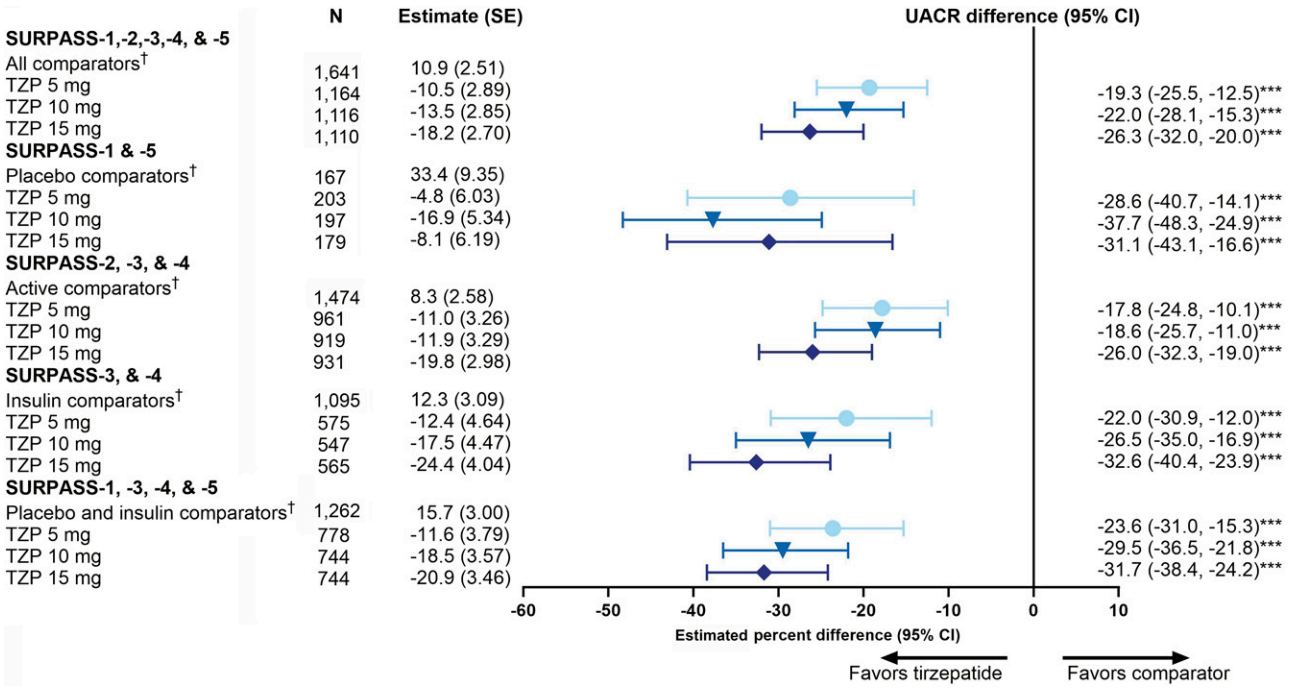

Figure 1—Relationship between UACR and tirzepatide (TZP) vs. comparators in the SURPASS-1–5 trials. Data are percent change from baseline estimate (SE) and estimated difference (95% CI) for UACR at 40 weeks from the modified intention-to-treat population (efficacy analysis set). Data were measured at week 40 (week 42 for SURPASS-4). Comparators were placebo in SURPASS-1 and -5, semaglutide 1 mg in SURPASS-2, insulin degludec in SURPASS-3, and insulin glargine in SURPASS-4. Trials were pooled as SURPASS-1–5; those with placebo; active; and insulin comparators; and placebo and insulin comparators (excluding SURPASS-2). †Reference group. ***$P < 0.001$.

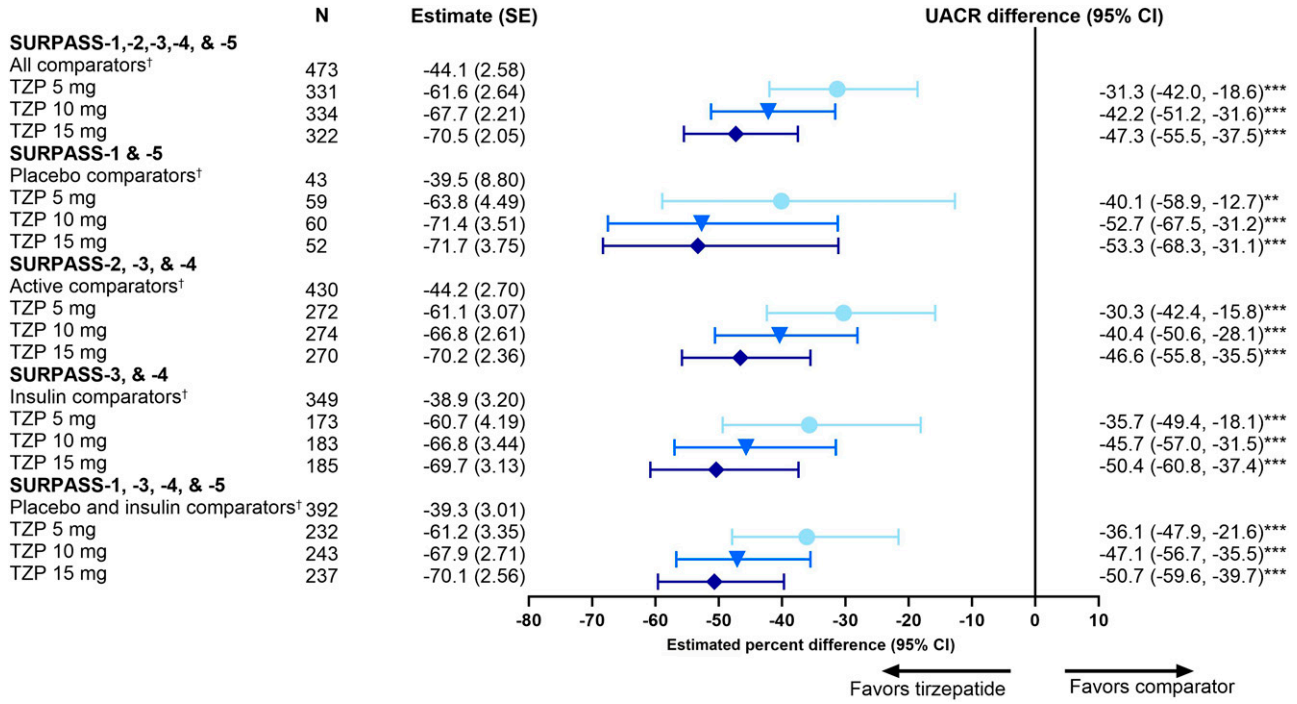

Figure 2—Relationship between UACR and tirzepatide (TZP) vs. comparators among participants with UACR ≥30 mg/g in the SURPASS-1–5 trials. Data are percent change from baseline estimate (SE) and estimated difference (95% CI) for UACR at 40 weeks from the modified intention-to-treat population (efficacy analysis set). Data were measured at week 40 (week 42 for SURPASS-4). Comparators were placebo in SURPASS-1 and -5, semaglutide 1 mg in SURPASS-2, insulin degludec in SURPASS-3, and insulin glargine in SURPASS-4. Trials were pooled as SURPASS-1–5; those with placebo; active; and insulin comparators; and those with placebo and insulin comparators (excluding SURPASS-2). †Reference group. ***$P < 0.001$.

at week 40/42 in favor of tirzepatide (Supplementary Table 3). Participants treated with tirzepatide also experienced an adjusted mean change in body weight of −10.1% compared with 2.1% in participants in the pooled comparator group (between-group difference −11.0% [−11.5, −10.5]) (Supplementary Table 3).

To explore the mechanism by which the relationship between tirzepatide and UACR may be mediated by changes in metabolic parameters, causal multiple mediation analyses were performed among participants in the SURPASS-1, -3, -4, and -5 trials (Fig. 3 and Supplementary Tables 4 and 5). In these analyses, tirzepatide appeared to affect both UACR directly and indirectly via its treatment effects on HbA_{1c} and/or body weight. In this population, the indirect effects, mediated through reductions in HbA_{1c} and body weight, appeared to explain 45.9% (95% CI 20.7, 71.0) of the decrease in UACR associated with tirzepatide relative to the pooled comparator. These indirect effects were driven primarily by improved glycemic control. Of the 45.9% mediated effects, 21.7% appeared to be mediated by the change in HbA_{1c} itself and a further 15.6% by the change in HbA_{1c} associated with prior weight reduction. In contrast, the indirect path mediated only by weight reduction was not statistically significant. Accordingly, 54.1% (29.0, 79.3) appeared to be explained through effects not mediated via HbA_{1c} or weight and assumed to be direct effects of the pooled tirzepatide doses with some potential contribution from unmodeled variables.

CONCLUSIONS

In this pooled post hoc analysis of the SURPASS-1–5 clinical trials involving >5,200 participants, we observed a consistently greater decrease in UACR associated with tirzepatide versus all comparators, including both placebo or active (insulin and semaglutide) comparators. The extent of reductions in UACR appeared more pronounced in participants with preexisting kidney disease, defined as baseline UACR ≥30 mg/g or, in those in the 15 mg tirzepatide group, a baseline eGFR <60 mL/min/1.73 m^2. These clinically relevant outcomes appeared in part to be explained by concomitant reductions in HbA_{1c} and body weight, but tirzepatide also may have a beneficial effect on UACR independent of changes in body weight or HbA_{1c}. Tirzepatide did not appear to affect eGFR over the relatively short observation time (<1 year) in these studies of participants with type 2 diabetes and preserved kidney function.

In prior studies, tirzepatide improved clinical risk factors known to increase cardio-kidney-metabolic risk, including glycemic control, blood pressure, and weight loss (7–12,18,19). Furthermore, a post hoc analysis of the SURPASS-4 trial suggested that tirzepatide may slow CKD progression as evidenced by reduced eGFR decline and a reduced risk of a clinical kidney outcome (13). This post hoc analysis provides further support for a potential kidney-protective effect of tirzepatide. In this broad population of participants with type 2 diabetes, the reduction in UACR (−26.3% change from baseline with tirzepatide 15 mg in the pooled population) is clinically relevant as large meta-analyses have demonstrated that reductions in UACR of at least 25% translate into a long-term benefit of maintaining kidney function (20,21). Among the subgroup of participants with UACR ≥30 mg/g, all tirzepatide doses were associated with reductions in UACR of >40%, a threshold highly predictive of a reduced risk of clinical kidney disease

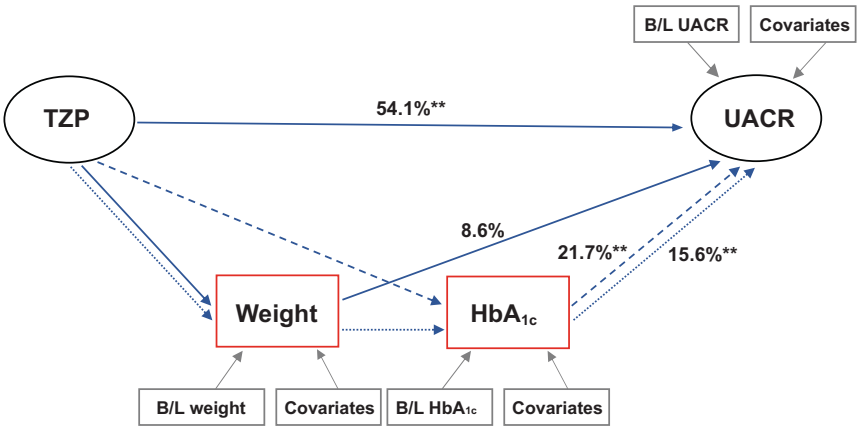

Figure 3—Mediation analysis exploring potential effects of tirzepatide (TZP) on UACR among participants in the pooled SURPASS-1, 3, 4, and 5 trials. The total potential indirect effect of TZP was 45.9%. Indirect paths are denoted by solid, dotted, or dashed lines to depict the full modeled relationship from TZP to change in UACR: Solid lines depict TZP → weight → UACR; dashed lines depict TZP → HbA_{1c} → UACR; and dotted lines depict TZP → weight → HbA_{1c} → UACR. Only participants with nonmissing baseline and week 40/42 value of the response variable were included in analysis (n = 2,978). Each analysis model was adjusted for study identifier, sex, country, treatment, and baseline outcome variable and weighted using inverse probability of treatment weights. $^{**}P < 0.001$. B/L, baseline.

outcomes (20). Of note, when comparing tirzepatide with semaglutide 1 mg in participants with baseline UACR ≥30 mg/g, tirzepatide was associated with a greater reduction in UACR, suggesting that GIP activation may contribute to the beneficial effects of tirzepatide on UACR, although our analyses did not exclude the possibility of a more pronounced GLP-1 activation of tirzepatide at the tested doses. Semaglutide 1 mg has been shown to reduce albuminuria and confer kidney protection in a dedicated kidney outcomes trial (15). The current analyses provide further support that the robust and clinically relevant albuminuria-lowering effects of tirzepatide may translate into long-term benefits for kidney function, although a large outcomes trial is needed to confirm this hypothesis.

The underlying mechanisms by which tirzepatide may be associated with decreased UACR are not fully understood. Indirect effects through reductions in HbA_{1c} and body weight are likely involved as suggested by the mediation analyses. However, potential direct effects of tirzepatide on glomerular barrier integrity, podocyte function, or inflammation leading to reductions in UACR cannot be excluded. GIP receptors are located in adipose tissue surrounding the kidney and other organs (22). Targeting these receptors might suppress proinflammatory pathways in the kidney, which can ameliorate endothelial dysfunction and reduce glomerular albumin leakage. Anti-inflammatory properties of tirzepatide may also improve tubular function and increase tubular albumin reabsorption (23). The reduction in albuminuria may also be attributed to reduced intraglomerular pressure. In the SURPASS-4 trial, tirzepatide treatment resulted in an initial reduction of eGFR (13). This effect was partially reversed 4 weeks after discontinuation of tirzepatide, suggesting a potential hemodynamic effect reflecting a reduction in intraglomerular pressure that may reduce glomerular albumin filtration and urinary excretion. The initial dip in eGFR could be attributed, at least in part, to improved glycemic control and weight loss, which can attenuate neurohormonal activation and other factors associated with glomerular hypertension and, in turn, reduce eGFR (24). The ongoing Study of Tirzepatide (LY3298176) in Participants With Overweight or Obesity and CKD With or Without Type 2 Diabetes (TREASURE-CKD; ClinicalTrials.gov identifier NCT05536804) is designed to assess mechanistic effects of tirzepatide on kidney function and will provide more insight into potential mechanisms for UACR-lowering effects (25).

Tirzepatide did not influence eGFR over time compared with all active or placebo comparators. This finding was not unexpected since eGFR at baseline was in the normal range in the large majority of participants, the follow-up was <1 year, and the rate of eGFR decline in the pooled comparator group was negligible, making it very difficult to detect any treatment effect.

A meta-analysis using published data from the SURPASS and SURMOUNT trials reported that tirzepatide reduced albuminuria (26). The key strength of our meta-analysis is the availability of the individual patient data, which leads to more accurate treatment estimates and allows for detailed subgroup analyses and exploration of the underlying mechanisms for the observed reductions in albuminuria through mediation analyses. There are also limitations. First, the SURPASS-1–5 trials were not designed to assess effects on UACR. Accordingly, urine was collected in single urine spot samples, which are known to be highly variable. The random variation in UACR may have decreased precision of the effect estimates. Second, the primary end point of the trials varied between 40 and 52 weeks, with week 40/42 data used for these analyses. Whether UACR effects are sustained for longer follow-up periods and whether tirzepatide slows eGFR decline require longer studies involving participants at higher risk of CKD progression. Regarding mediation analyses, it is acknowledged that the effect of change in blood pressure, and other unmodeled confounders, may potentially contribute to the estimated direct (nonmediated) effect of tirzepatide on change in UACR. Finally, not every participant was using an RASi or SGLT2i, the treatments currently recommended by guidelines for people with increased albuminuria and CKD. Nevertheless, the reduction in albuminuria associated with tirzepatide treatment was consistent regardless of use of these treatments.

In conclusion, this post hoc analysis of the SURPASS-1–5 trials showed that tirzepatide was associated with a greater decrease in UACR versus placebo and insulin. In addition, among individuals with UACR >30 mg/g, the highest dose of tirzepatide was associated with a larger UACR reduction compared with semaglutide. This protective relationship is hypothesized to be explained by both a potential direct effect on the kidney and potential indirect effects of tirzepatide mediated by improvements in glycemic control and body weight reductions.

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