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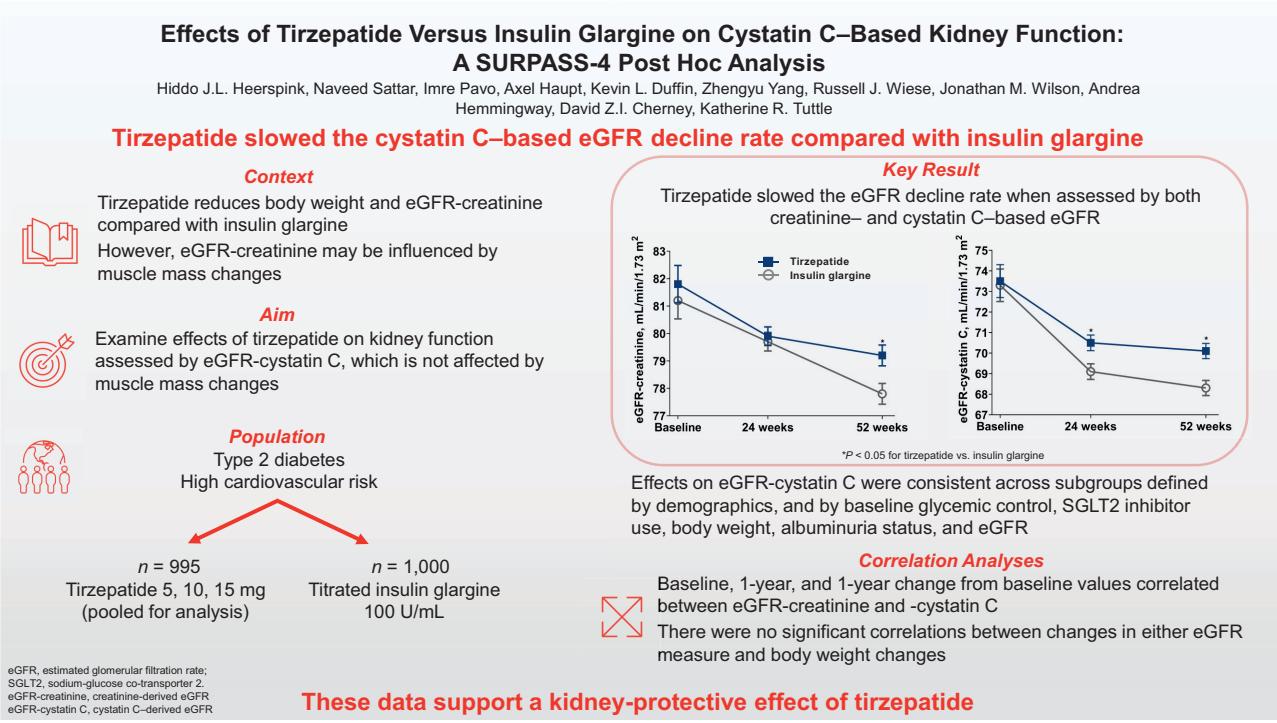

ARTICLE HIGHLIGHTS

- Tirzepatide reduces body weight and the creatinine-based estimated glomerular filtration (eGFR-creatinine) decline rate in people with type 2 diabetes and high cardiovascular risk.
- Although eGFR-creatinine may be affected by muscle mass changes, cystatin C–derived eGFR (eGFR-cystatin C) is not.
- We examined effects of tirzepatide on kidney function in the SURPASS-4 study when assessed using eGFR-cystatin C.
- After 52 weeks, the eGFR decline was lower with tirzepatide versus insulin glargine consistently with eGFR-creatinine and eGFR-cystatin C.
- Although changes in the eGFR measures were significantly correlated, changes in either eGFR measure did not correlate with body weight changes.
- The findings support a kidney-protective effect of tirzepatide.

Effects of Tirzepatide Versus Insulin Glargine on Cystatin C–Based Kidney Function: A SURPASS-4 Post Hoc Analysis

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OBJECTIVE

Tirzepatide reduces HbA_{1c} and body weight, and creatinine-based estimated glomerular filtration rate (eGFR) decline. Unlike creatine-derived eGFR (eGFR-creatinine), cystatin C–derived eGFR (eGFR-cystatin C) is unaffected by muscle mass changes. We assessed effects of tirzepatide on eGFR-creatinine and eGFR-cystatin C.

RESEARCH DESIGN AND METHODS

Our primary outcome was eGFR change from baseline at 52 weeks with pooled tirzepatide (5, 10, and 15 mg) and titrated insulin glargine in adults with type 2 diabetes and high cardiovascular risk (SURPASS-4).

RESULTS

Least squares mean (SE) eGFR-creatinine (mL/min/1.73 m^2) changes from baseline with tirzepatide and insulin glargine were −2.5 (0.38) and −3.9 (0.38) (between-group difference, 1.4 [95% CI 0.3–2.4]) and −3.5 (0.37) and −5.3 (0.37) (between-group difference, 1.8 [95% CI 0.8–2.8]) for eGFR-cystatin C. Baseline, 1-year, and 1-year change from baseline values significantly correlated between eGFR-cystatin C and eGFR-creatinine. Measures of eGFR changes did not correlate with body weight changes.

CONCLUSIONS

Tirzepatide slows the eGFR decline rate, supporting a kidney-protective effect.

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide 1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes. Tirzepatide reduces glycated hemoglobin (HbA_{1c}) and provides durable and clinically relevant body weight reductions in people with type 2 diabetes and those with overweight or obesity without type 2 diabetes (1).

In the SURPASS-4 study of people with type 2 diabetes and established cardiovascular disease, tirzepatide reduced the annual rate of estimated glomerular filtration rate (eGFR) decline from baseline by 2.2 mL/min/1.73 m^2 compared with insulin glargine (2). Tirzepatide also reduced body weight by up to 13.5 kg (3). Because the weight loss effect of tirzepatide could conceivably reduce muscle mass, serum creatinine could change unrelated to kidney function and thereby bias eGFR measurements to the high (4). Cystatin C is an endogenous filtration marker that is not dependent on

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muscle mass and may be more robustly associated with cardiovascular outcomes and mortality than creatinine-based eGFR (eGFR-creatinine) (5).

In this post hoc analysis, we compared the effects of tirzepatide on cystatin C-derived eGFR (eGFR-cystatin C) versus eGFR-creatinine to ascertain the validity of use of eGFR-creatinine to characterize the effects of tirzepatide on kidney function.

RESEARCH DESIGN AND METHODS

Study Design, Participants, and Procedures

SURPASS-4 was a randomized, open-label, active-controlled study, with primary study end point at 52 weeks (3). Participants had type 2 diabetes with inadequate glycemic control (HbA_{1c} 7.5–10.5%) with any combination of metformin, sulfonylurea agent, or sodium–glucose cotransporter-2 inhibitors, a BMI $\geq$25 kg/m^2, and high risk of atherosclerotic cardiovascular disease. Participants were randomized 1:1:1:3 to received tirzepatide 5, 10, or 15 mg once weekly or to receive titrated insulin glargine (100 U/mL). For these analyses, we pooled eGFR data from the three tirzepatide doses, similar to previous work (2). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent to enter the study.

Measurements and Outcomes

Serum creatinine measurements were performed during the study in a central laboratory. EDTA plasma samples for cystatin C were collected at baseline and at weeks 24 and 52 and were measured in duplicate at the end of the study at Eli Lilly and Company (Supplemental Additional Methods). The duplicate values were averaged for eGFR. eGFR was calculated using the 2009 (creatinine) and 2012 (cystatin C) Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equations, as well as the 2021 equations for eGFR-creatinine and eGFR-creatinine/cystatin C (6–8). The primary outcome was the effect of tirzepatide versus insulin glargine on eGFR using creatinine versus cystatin C.

Statistical Analysis

All randomly assigned participants who took at least one dose of study treatment were included in analyses. We analyzed the treatment effect on eGFR by using a mixed model for repeated measures. On-treatment eGFR values were used in the mixed-effects model. The model included change from baseline in eGFR as the dependent variable, and baseline eGFR value, stratification factors (namely, country, baseline HbA_{1c} [$\leq$8.5% or >8.5%], and baseline sodium–glucose cotransporter-2 inhibitor use [yes or no]), and categorical fixed effects of treatment, visit, and treatment-by-visit interaction as covariates. Unstructured covariance structure was used in the mixed model for repeated measures. In subgroup analyses, all

Table 1—Baseline characteristics

	Tirzepatide (*n* = 995)	Insulin glargine (*n* = 1,000)
Age, years	63 (8.6)	64 (8.5)
Sex, male, *n* (%)	610 (61)	636 (64)
Race, *n* (%)		
American Indian or Alaska Native	88 (9)	85 (9)
Asian	39 (4)	31 (3)
Black or African American	41 (4)	32 (3)
White	804 (81)	825 (83)
Duration of diabetes, years	12 (7.4)	12 (7.7)
HbA_{1c}, %	8.5 (0.9)	8.5 (0.9)
FSG, mmol/L	9.7 (2.9)	9.4 (2.8)
History of CVD, *n* (%)	864 (87)	869 (87)
Weight, kg	90.3 (18.3)	90.2 (19.0)
BMI, kg/m^2	32.6 (5.5)	32.5 (5.6)
BMI <30 kg/m^2, *n* (%)	339 (34)	379 (38)
BMI $\geq$30 kg/m^2, *n* (%)	656 (66)	621 (62)
Smoking status, yes, *n* (%)	540 (54)	542 (54)
SGLT2 inhibitor use, yes, *n* (%)	245 (25)	256 (26)
ACE inhibitors or ARB use, yes, *n* (%)	804 (80)	811 (81)
UACR, mg/g	15.9 (5.0, 59.0)	14.0 (4.4, 53.1)
No albuminuria (UACR <30), *n* (%)	621 (63)	630 (64)
Microalbuminuria (UACR 30–300), *n* (%)	276 (28)	270 (28)
Macroalbuminuria (UACR >300), *n* (%)	82 (8)	79 (8)
eGFR-creatinine, mL/min/1.73 m^2*	81.1 (21.4)	81.5 (20.8)
eGFR ranges, mL/min/1.73 m^2 (%)		
<60	176 (18)	166 (17)
$\geq$15 to <30	12 (1)	10 (1)
$\geq$30 to <45	60 (6)	55 (6)
$\geq$45 to <60	104 (11)	101 (10)
$\geq$60 to <90	394 (40)	400 (40)
$\geq$90	425 (43)	434 (43)
eGFR-cystatin C, mL/min/1.73 m^2†	72.9 (23.5)	73.5 (23.8)
eGFR ranges, mL/min/1.73 m^2 (%)		
<60	283 (31)	281 (30)
$\geq$15 to <30	23 (3)	24 (3)
$\geq$30 to <45	99 (11)	92 (10)
$\geq$45 to <60	161 (18)	165 (18)
$\geq$60 to <90	397 (43)	388 (42)
$\geq$90	239 (26)	261 (28)

Data are mean (SD), median (Q1, Q3), or *n* (%). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CV, cardiovascular; FSG, fasting serum glucose; Q, quartile; SGLT2, sodium–glucose cotransporter 2; UACR, urine albumin-to-creatinine ratio. *eGFR-creatinine was estimated using the 2009 CKD-EPI equation. †eGFR-cystatin C was estimated using the 2012 CKD-EPI equation.

possible two-way and three-way interactions among the treatment, subgroup variable, and visit were added to the model. We analyzed the bivariate linear relationships among eGFR, body weight, HbA_{1c}, BMI, and waist circumference using Pearson correlation coefficients. A two-sided *P* value of <0.05 was considered statistically significant. All analyses were done using SAS, version 9.4.

RESULTS

Of 1,995 participants, the mean eGFR-creatinine was 81 mL/min/1.73 m^2 and mean eGFR-cystatin C was 73 mL/min/1.73 m^2 (Table 1). Overall, 342 (17%) and 564 (31%) participants had eGFR <60 mL/min/1.73 m^2 when estimated from creatinine and cystatin C, respectively, and 707 (36%) had high levels of albuminuria (urine albumin-to-creatinine ratio ≥ 30 mg/g). Baseline characteristics were well balanced between randomized groups (Table 1). Supplementary Table 1 presents baseline eGFR measured using the 2021 CKD-EPI equations.

Mean body weight at baseline was 90.3 kg in the pooled tirzepatide group and 90.2 kg in the insulin glargine group. At week 52, mean (SE) body weight changes were −7.1 (0.34) kg with tirzepatide 5 mg, −9.5 (0.34) kg with tirzepatide 10 mg, −11.7 (0.33) kg with tirzepatide 15 mg, and 1.9 (0.19) kg with insulin glargine (between-group differences [95% CI], −9.0 kg [−9.8 to −8.3], −11.4 kg [−12.1 to −10.6], and −13.5 kg [−14.3 to −12.8], respectively). Supplementary Table 2 shows body weight changes at week 24.

At week 52, mean eGFR-creatinine (mL/min/1.73 m^2) change from baseline was −2.5 (0.38) with tirzepatide and −3.9 (0.38) with insulin glargine (between-group difference, 1.4 [95% CI 0.3–2.4]) (Fig. 1). Mean eGFR-cystatin C (mL/min/1.73 m^2) change from baseline in these groups were −3.5 (0.37) and −5.3 (0.37), respectively (between-group difference, 1.8 [95% CI 0.8–2.8]) (Fig. 1). The respective changes when assessed using eGFR-creatinine/cystatin C were −3.1 (0.36) and −4.9 (0.35) mL/min/1.73 m^2 (between-group difference, 1.8 [95% CI, 0.8–2.7]). There was no evidence the effect of tirzepatide versus insulin glargine on eGFR-cystatin C varied in various participant subgroups (Fig. 2). Baseline (r = 0.765), 1-year (r = 0.771), and 1-year change from baseline (r = 0.326) values correlated significantly between eGFR-cystatin C and eGFR-creatinine (all $P <$ 0.0001; Supplementary Fig. 1). Between-group differences (95% CI) for tirzepatide versus insulin glargine in reducing eGFR-cystatin C decline from baseline at 1 year were 1.2 (−0.2 to 2.7), 2.1 (0.7–3.6), and

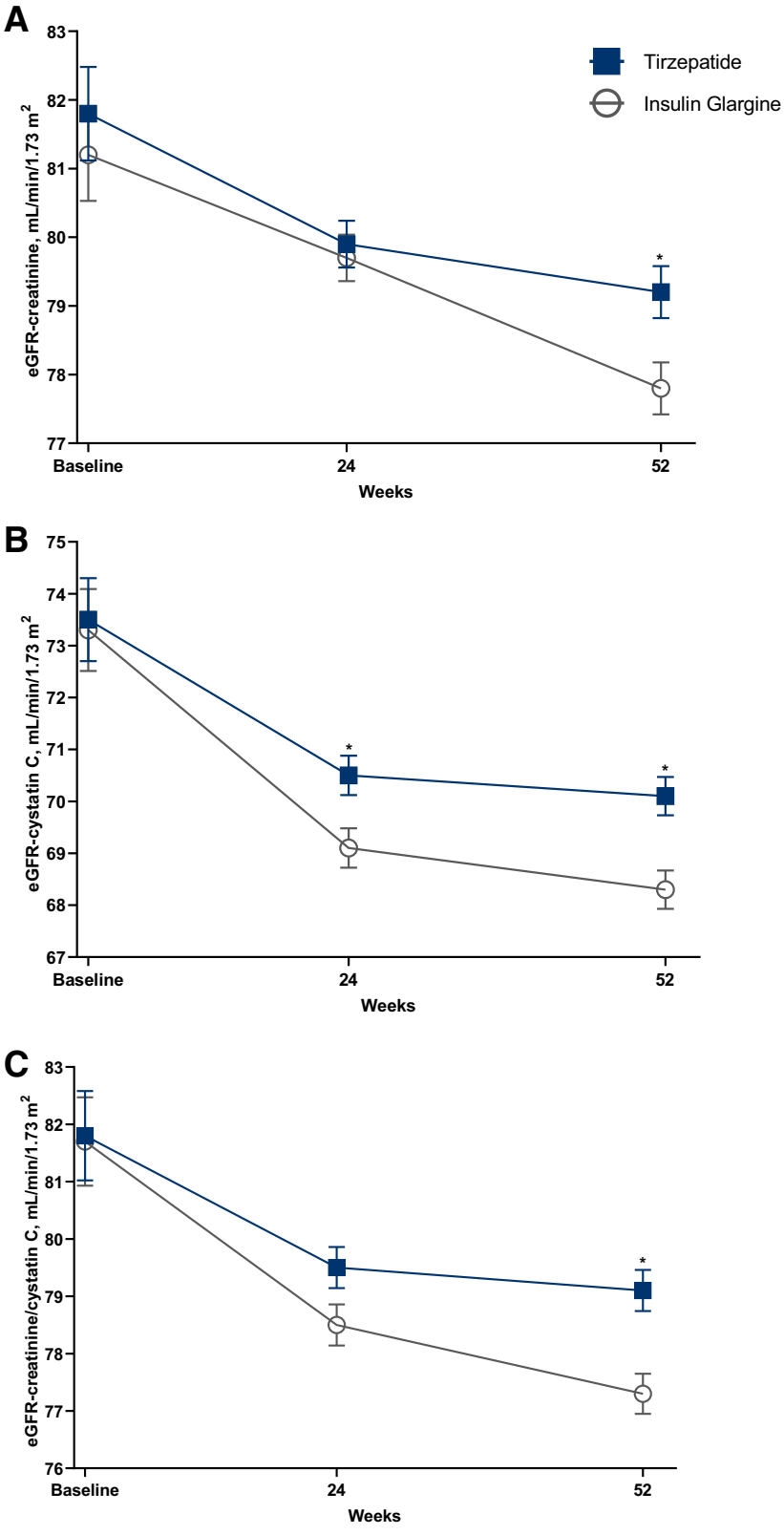

Figure 1—Creatinine-, cystatin C–, and creatinine/cystatin C–based eGFR over time. *A*: eGFR-creatinine (estimated using the 2009 CKD-EPI equation). *B*: eGFR-cystatin C (estimated using the 2012 CKD-EPI equation). *C*: eGFR-creatinine/cystatin C (estimated using the CKD-EPI 2021 equation). Data are least squares mean (SE). *$P < 0.05$ for tirzepatide versus insulin glargine.

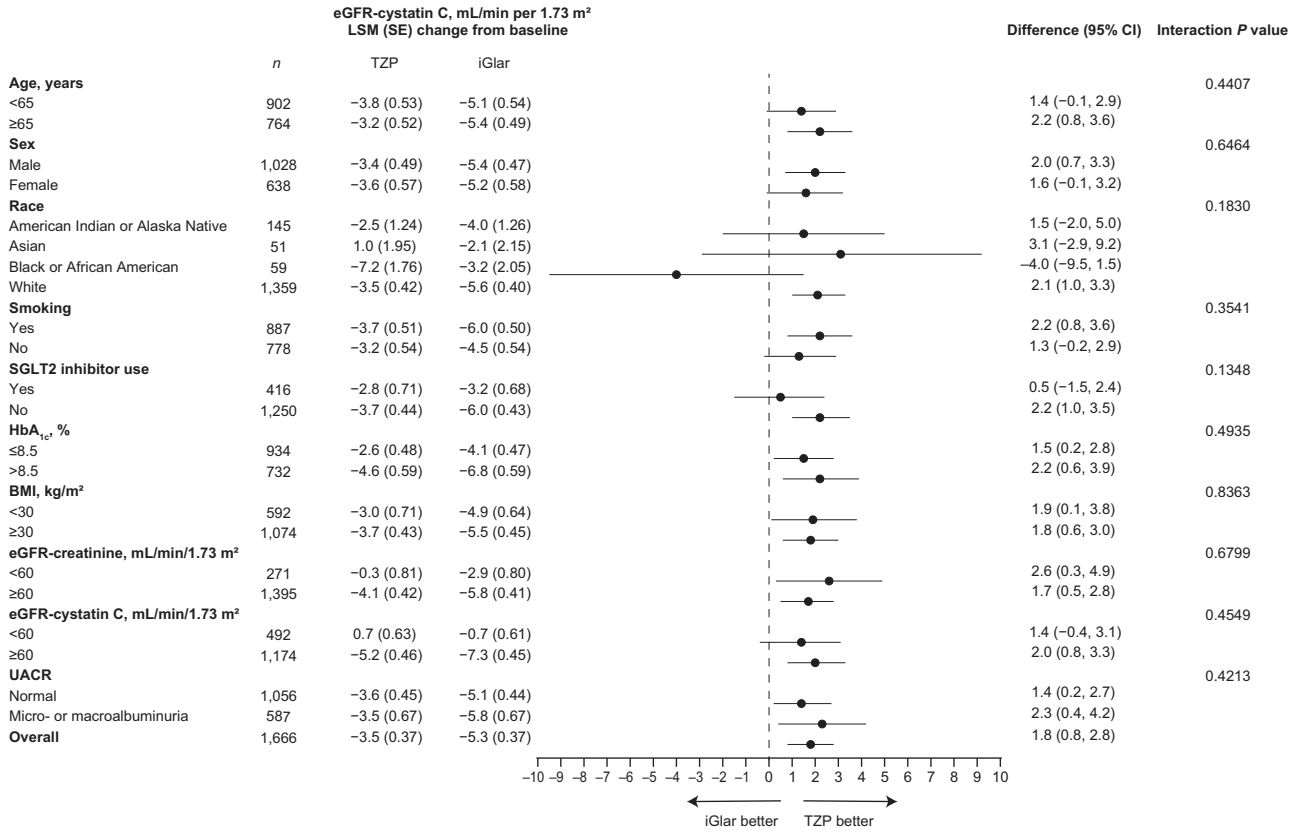

Figure 2—Differences in eGFR-cystatin C change from baseline to 52 weeks between tirzepatide and insulin glargine. Data are LSM (SE) change from baseline and difference (95% CI) at 52 weeks. eGFR-creatinine and eGFR-cystatin C were estimated using the 2009 and 2012 CKD-EPI equations, respectively. iGlar, insulin glargine; LSM, least squares mean; *N* = number of participants in population with baseline value and post-baseline value at week 52; SGLT2, sodium–glucose cotransporter 2; TZP, tirzepatide; UACR, urine albumin-to-creatinine ratio.

2.0 (0.6–3.5) mL/min/1.73 m^2 with the 5, 10, and 15 mg doses, respectively, consistent with more pronounced effects at higher tirzepatide doses (Supplementary Fig. 2). The effects of tirzepatide versus insulin glargine on eGFR changes over time were similar in the overall population and in subgroups when eGFR was calculated using the 2021 CKD-EPI equations (Supplementary Figs. 3 and 4).

Body weight change was not correlated with changes in either eGFR-creatinine or eGFR-cystatin C at 52 weeks (Fig. 3*A* and *B*). HbA_{1c} changes with tirzepatide did not correlate with eGFR-creatinine change (Fig. 3*C*). A small but statistically significant correlation was observed between changes in HbA_{1c} and eGFR-cystatin C with tirzepatide at 52 weeks (Fig. 3*D*). Findings were consistent when eGFR was calculated using the 2021 equations (Supplementary Fig. 5). Similarly, a small but statistically significant correlation was observed between changes in HbA_{1c} and either eGFR-creatinine or eGFR-cystatin C after 52 weeks treatment with insulin glargine (r = 0.087, P = 0.0097; and r = 0.1071, P = 0.0020, respectively). Body weight change with insulin glargine did not correlate with either eGFR-creatinine or eGFR-cystatin C change (r = −0.053, P = 0.1129; and r = −0.042, P = 0.2230, respectively). Findings for insulin glargine were similar when eGFR was calculated using the 2021 equations. In both the tirzepatide and insulin glargine groups, correlations for waist circumference and BMI were generally consistent with the body weight correlations regardless of eGFR equation used (Supplementary Table 3).

CONCLUSIONS

In the SURPASS-4 study, we recently reported potential kidney protective effects of tirzepatide, including a slowed eGFR-creatinine decline with tirzepatide as compared with insulin glargine (2). These post hoc analyses from SURPASS-4 comparing cystatin C–derived eGFR versus creatinine-derived eGFR confirm and extend our earlier findings to show that a marker unaffected by muscle mass produced comparable results, supporting an actual benefit on kidney function. Similar effects of tirzepatide on eGFR were observed whether calculated with serum creatinine- or cystatin C–based equations. The independence of cystatin C–based eGFR from muscle mass imply that the effects of tirzepatide on kidney function are unlikely related to change in muscle mass. Consistent with this concept, in people with type 2 diabetes, tirzepatide treatment significantly reduced visceral adipose tissue and abdominal subcutaneous adipose tissue (1). Moreover, in people with obesity, tirzepatide treatment resulted in a three times greater reduction in fat compared with lean body mass (9). Although showing consistent trends, there were differences in the eGFR values estimated by creatinine and cystatin C, which may reflect characteristics of the study population. eGFR-creatinine is often higher, whereas eGFR-cystatin C is lower, among people with lesser muscle mass such as those who are older with long-term diabetes and comorbidities, as in this study (10). Accordingly, within-individual differences between eGFR-creatinine- and eGFR-cystatin C have been reported, and the difference

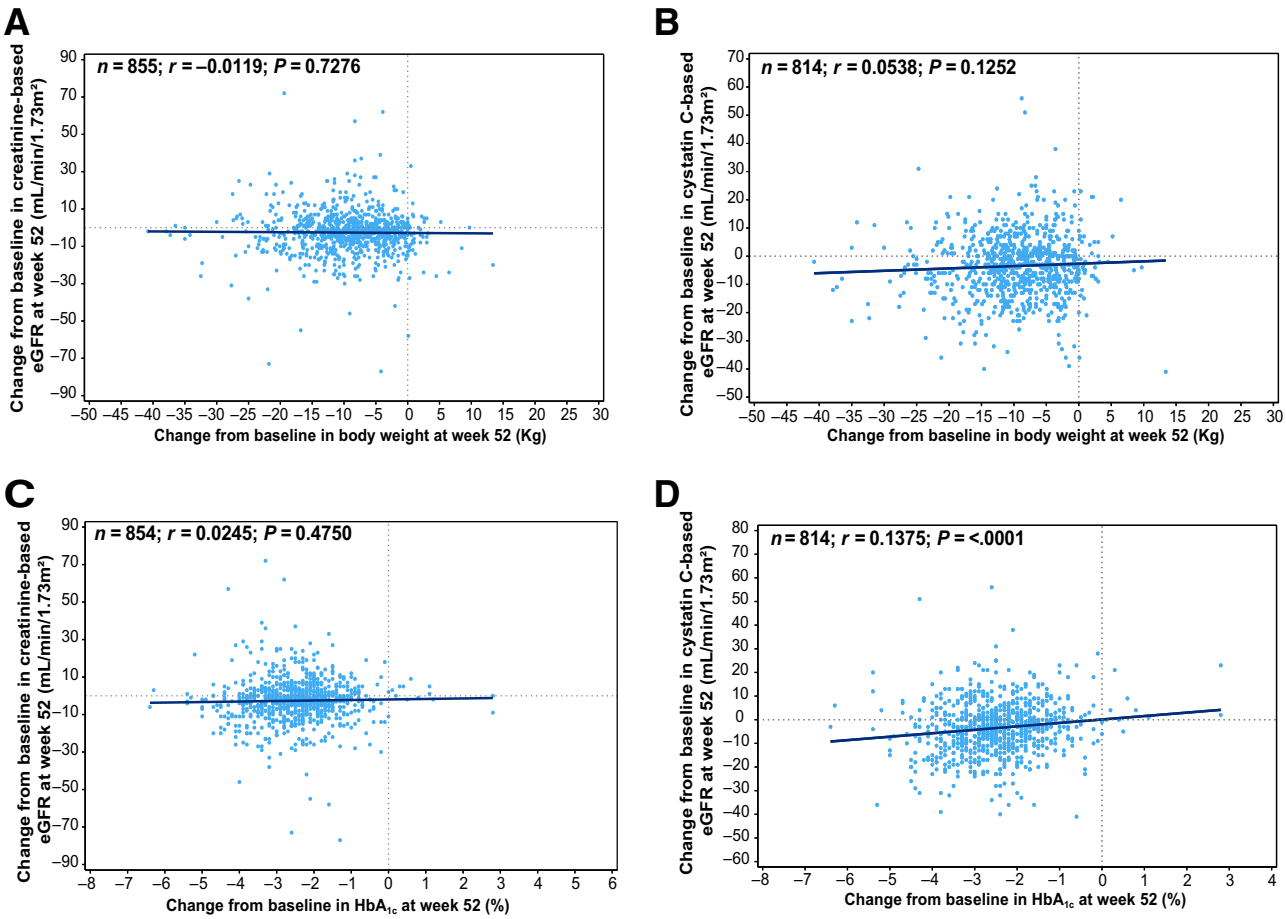

Figure 3—Correlations between eGFR and body weight and HbA_{1c}. Correlation between change from baseline in eGFR-creatinine and change from baseline in body weight (*A*), change from baseline in eGFR-cystatin C and change from baseline in body weight (*B*), change from baseline in eGFR-creatinine and change from baseline in HbA_{1c} (*C*), and change from baseline in eGFR-cystatin C and change from baseline in HbA_{1c}, at week 52 (*D*). eGFR-creatinine and eGFR-cystatin C were estimated using the 2009 and 2012 CKD-EPI equations, respectively.

between these measures may be associated with increased risk of cardiovascular outcomes and frailty (11,12).

Our findings are consistent with those observed with selective GLP-1 receptor agonists. In the AWARD-7 trial, dulaglutide reduced the eGFR decline in patients with type 2 diabetes and chronic kidney disease versus insulin (13) and similarly showed no relationship between changes in body weight and eGFR, whether calculated with serum creatinine or cystatin C (14). Conversely, intensive weight loss interventions such as bariatric surgery affect muscle mass and eGFR estimates (15,16). A study of Roux-en-Y gastric bypass surgery in people with obesity, with or without type 2 diabetes, reported that weight loss was associated with reduction in a measure of skeletal muscle mass along with decreased plasma creatinine and increased eGFR-creatinine levels (4). However, eGFR-cystatin C and directly measured GFR by iohexol were unchanged, indicating that bariatric surgery–related muscle loss can lead to an overestimation of kidney function when assessed by eGFR-creatinine. The concordance of eGFR-creatinine, eGFR-cystatin C, and eGFR-creatinine/cystatin C measures in SURPASS-4 indicate that the findings were unlikely to be influenced by muscle mass changes despite weight loss.

In 2021, a new eGFR estimation equation was introduced that does not include a race coefficient, the inclusion of which has no biological basis and may contribute to structural racism (8). Consistent effects in eGFR changes were observed in the original 2009 and 2021 creatinine-based equations. Interestingly, a modest but statistically significant correlation between HbA_{1c} and eGFR-cystatin C changes was observed with both tirzepatide and insulin. This may be a chance finding but could also represent a reduction in glomerular hyperfiltration. This is a well-recognized mechanism of glycemic control to slow kidney injury that would need to be assessed in mechanistic studies with directly measured GFR. Mediation analyses of effects of GLP-1 receptor agonists on slowing eGFR decline suggest the salutary outcomes are mediated, in small part, by better glycemic control (17). Additionally, a causal link between obesity and chronic kidney disease is supported by Mendelian randomization studies (18–20).

In conclusion, the effect of tirzepatide to slow eGFR decline was confirmed whether eGFR was estimated by creatinine, cystatin C, or both. This eGFR benefit held across subgroups defined by demography, glycemic control, sodium–glucose cotransporter-2 inhibitor use, body weight, albuminuria, and eGFR. SURPASS-CVOT (ClinicalTrials.gov identifier NCT04255433) will provide new data on effects of tirzepatide on secondary outcomes, including urine albumin-to-creatinine ratio and new or

worsening kidney disease in type 2 diabetes.

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