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ORIGINAL RESEARCH

Interplay of Chronic Kidney Disease and the Effects of Tirzepatide in Patients With Heart Failure, Preserved Ejection Fraction, and Obesity

The SUMMIT Trial

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ABSTRACT

BACKGROUND Obesity leads to both heart failure with a preserved ejection fraction (HFpEF) and to chronic kidney disease (CKD); CKD may both influence the clinical course of obesity-related HFpEF; and incretin-based drugs may influence renal function.

OBJECTIVES This analysis had dual objectives: 1) to evaluate the influence of CKD on the clinical responses to tirzepatide in patients with obesity-related HFpEF; and 2) to investigate the complexity of tirzepatide-related changes in renal function. For both objectives, we focused on discrepancies between creatinine-based and cystatin C–based estimates of the estimated glomerular filtration rate (eGFR).

METHODS The SUMMIT trial randomly assigned 731 patients with HFpEF and a body mass index ≥30 kg/m^2, who were enriched for participants with CKD. Patients received either placebo or tirzepatide for a median of 104 weeks and were followed for cardiovascular death or worsening heart failure events and for changes in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) after 52 weeks. Because of the confounding produced by obesity and changes in muscle mass, eGFR was assessed at randomization and after 12, 24, and 52 weeks by both creatinine-based and cystatin C–based formulae.

RESULTS Patients with CKD (based on creatinine or cystatin C) had greater severity of heart failure, as reflected by: 1) worse functional class, KCCQ-CSS scores, and 6-minute walk distance; 2) higher levels of NT-proBNP and cardiac troponin T; and 3) a 2-fold increase in the risk of worsening heart failure events. CKD did not influence the effect of tirzepatide to reduce the relative risk of major adverse heart failure events and to improve KCCQ-CSS, quality of life, and functional capacity, but the absolute risk reduction in the primary events was numerically greater in patients with CKD. Regarding renal function assessments, baseline eGFR-cystatin C was consistently ≈9 mL/min/1.73 m^2 lower than that eGFR-creatinine, with significant individual variance. Furthermore, tirzepatide increased eGFR at 52 weeks, assessed by both creatinine-based and cystatin C–based formulae, but with considerable discordance in individual patients. Tirzepatide produced a decline in eGFR at 12 weeks with eGFR-creatinine (but not eGFR-cystatin C), and it led to an improvement in eGFR at 52 weeks in all patients (when assessed by cystatin C), but only in patients with CKD (when assessed by eGFR-creatinine).

CONCLUSIONS The triad of obesity, HFpEF, and CKD identifies patients with considerable functional impairment and an unfavorable prognosis, who nevertheless respond favorably to tirzepatide. Long-term tirzepatide improves renal function (both by cystatin C and creatinine), but the measurement of eGFR in patients with obesity receiving incretin-based drugs is likely to be skewed by the effects of fat and muscle mass (and by changes in body composition) on the synthesis of both cystatin C and creatinine. (A Study of Tirzepatide [LY3298176] in Participants With Heart Failure With Preserved Ejection Fraction [HFpEF] and Obesity: The SUMMIT Trial; NCT04847557) (JACC. 2025;85:1721-1735)

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ABBREVIATIONS AND ACRONYMS

ANCOVA = analysis of covariance

BMI = body mass index

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

EQ-5D-5L = EuroQol 5-Dimensions 5-Level

GLP = glucagon-like peptide

HFpEF = heart failure with a preserved ejection fraction

hsCRP = high-sensitivity C-reactive protein

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PGIS = Patient Global Impression of Severity Overall Health

SGLT2 = sodium-glucose cotransporter 2

UACR = urinary albumin-creatinine ratio

Obesity not only increases the risk of heart failure and a preserved ejection fraction (HFpEF),[1-3] but it also accelerates the development and progression of chronic kidney disease (CKD).[4,5] Obesity leads to glomerular hypertrophy as a result of an expansion of plasma volume and glomerular hyperfiltration[6]; an increase in perirenal fat can promote fibrosis in the underlying renal parenchyma[7,8]; and obesity-related activation of neurohormonal systems (especially heightened renal sympathetic nerve traffic and aldosterone) and the release of proinflammatory adipocytokines can impair podocyte function and promote tubulointerstitial inflammation.[9-12] In patients with HFpEF,[13] adipocyte-secreted leptin may be particularly important in the development of CKD.[11,14,15]

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Accordingly, the shrinkage of the adipocyte mass by bariatric surgery can reduce plasma volume and systolic blood pressure,[16] and mute the deleterious actions of both leptin and aldosterone,[17,18] thus ameliorating the evolution of CKD.[19,20] Drugs that signal through the glucagon-like peptide (GLP)-1 receptor reduce the mass and the deleterious adipocytokine secretions of inflamed visceral fat depots,[21-25] thus suppressing the endocrine mechanisms that promote podocyte inflammation and injury[26-28] and reducing proteinuria.[29] Additionally, independent of their effects on adipocytes, GLP-1 receptor agonists exert direct effects to increase glomerular filtration rate and inhibit proximal renal tubular sodium reabsorption, thus influencing tubuloglomerular feedback in states of glomerular hyperfiltration.[30-32] Long-term treatment with incretin-based drugs improves renal function in patients with obesity[29,33] and has been shown to slow the progression to end-stage kidney disease in a trial of patients with CKD, many of whom also had obesity.[34]

However, it is not clear how the link between obesity and CKD might be influenced by the presence of heart failure. Heart failure imposes its own stresses on the kidney, mediated by a decrease in renal perfusion pressure and an increase in renal venous pressures.[35] Heart failure can magnify the obesity-related activation of neurohormonal systems[9-12]; increased renal sympathetic nerve traffic can interfere with the cardioprotective and nephroprotective effects of B-type natriuretic peptide as well as the renal effects of GLP-1[36-38]; and heart failure-related heightened signaling through the renin-angiotensin-aldosterone system can exert deleterious effects on the kidney.[39,40] Furthermore, many patients with heart failure are receiving drugs that can influence the course of CKD, for example, angiotensin receptor neprilysin inhibitors,[41,42] but heart failure may negate the renoprotective effect of conventional inhibitors of the renin-angiotensin system, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors.[41,43-46]

Previous studies have not explored the effects of GLP-1 receptor signaling on the kidney in patients with obesity and heart failure. In the 2 prior trials that have studied incretin-based drugs in patients with HFpEF and obesity,[47,48] kidney function was not reported, either at baseline or following randomization. One observational study suggested a renal benefit of GLP-1 receptor agonists in patients with HFpEF without obesity,[49] but this analysis was difficult to interpret due to a lack of comparability of the 2 treatment groups due to prescribing bias and other unmeasured confounders.

SUMMIT (A Study of Tirzepatide [LY3298176] in Participants With Heart Failure With Preserved Ejection Fraction [HFpEF] and Obesity), a long-term study of patients with HFpEF and obesity,[50] provided a unique opportunity to study the influence of CKD on the clinical course of HFpEF as well as the potential of CKD to modify the benefits of incretin-based treatments. The trial included a detailed evaluation of the short- and long-term effects of tirzepatide on glomerular function and albuminuria,[51] informed by the recognition that commonly-used formulae for the estimation of estimated glomerular filtration rate (eGFR) (based

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on serum creatinine or cystatin C) may be influenced by fat mass and by incretin-induced changes in body composition.[52-60]

METHODS

STUDY ARCHITECTURE. As previously described,[50,51] in collaboration with the sponsor, the steering committee of the SUMMIT trial developed and amended the study protocol, oversaw the recruitment of patients and the quality of follow-up, initiated and supervised the analyses of the data in this paper, and provided an independent interpretation of the results. The trial protocol was approved by the ethics committee at each site, and all patients provided written informed consent. The sponsor was Eli Lilly and Company. The registration identifier on clinicaltrials.gov is NCT04847557.

STUDY PATIENTS AND TRIAL DESIGN. The SUMMIT trial enrolled men or women, ≥40 years of age, with chronic heart failure, a left ventricular ejection fraction ≥50%, and a body mass index (BMI) of ≥30 kg/m^2. All patients demonstrated substantial functional limitation and symptom burden, as reflected by both a 6-minute walk distance of ≥100 and ≤425 m and a Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) ≤80. All patients also had evidence of increased left ventricular filling pressures or left atrial enlargement, but (in contrast to previous trials) they were not required to have increased circulating levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), so as to enroll patients who were representative of those with obesity. Additionally, eligible patients had either: 1) heart failure decompensation within the past 12 months; or 2) eGFR <70 mL/min/1.73 m^2, thereby enriching for the severity of heart failure and for the prevalence of CKD in the study population.

Eligible patients were randomized double-blind (1:1) to receive placebo or tirzepatide 2.5 mg/wk subcutaneously, in addition to their usual therapy. Randomization was stratified by: 1) heart failure decompensation within the past 12 months; 2) history of type 2 diabetes; and 3) BMI ≥35 or <35 kg/m^2. The dose of the double-blind study medication was increased by 2.5 mg every 4 weeks (as tolerated) until 15 mg/week or matching placebo could be achieved at 20 weeks following randomization. Patients were maintained on the highest tolerated dose of double-blind treatment until the end of the trial. All background treatments could be altered at the discretion of the patient's clinician.

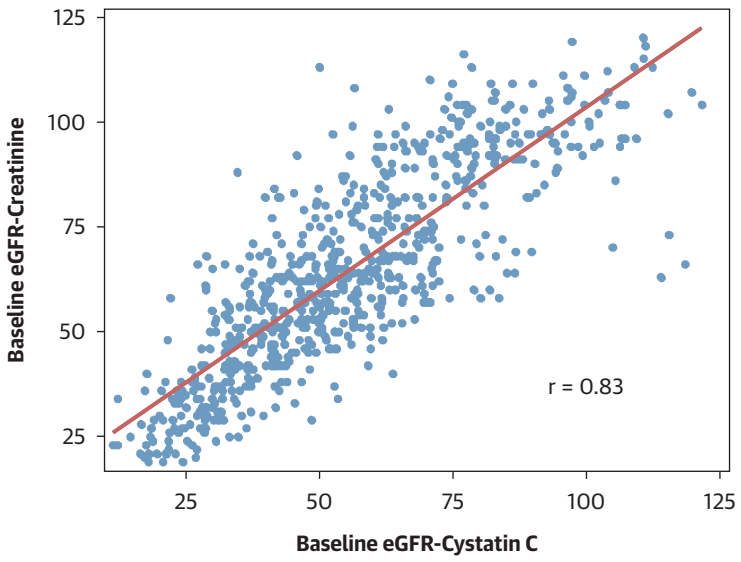
Following randomization, patients were evaluated periodically for body weight, heart failure symptom burden, and health status and vital signs. The 6-minute walk distance, KCCQ-CSS, high-sensitivity C-reactive protein (hsCRP), EuroQol 5-Dimensions 5-Level (EQ-5D-5L) Health Index score, Patient Global Impression of Severity Overall Health (PGIS), and NYHA functional class were assessed at baseline and after 52 weeks.[52] Changes in eGFR were assessed at 12, 24, and 52 weeks, and urinary albumin-creatinine ratio (UACR) was measured at 24 and 52 weeks. All randomized patients were followed for the occurrence of major adverse heart failure outcomes for the entire duration of the trial, whether or not they were taking study medications. Double-blind treatment continued until the last randomized patient was followed for 1 year.

PRESPECIFIED PRIMARY AND SECONDARY ENDPOINTS. The final primary endpoints for the trial were: 1) time-to-first adjudicated cardiovascular death or worsening heart failure event ($\alpha = 0.04$); and 2) changes in KCCQ at 52 weeks ($\alpha = 0.01$).[50] An adjudicated worsening heart failure event was defined as worsening symptoms of heart failure requiring hospitalization or intravenous or oral diuretic intensification; diuretic intensification without worsening symptoms was not defined as a worsening heart failure event. Deaths adjudicated to be of undetermined cause were included in the group of cardiovascular deaths. Key α-protected secondary outcomes were: 1) the change in 6-minute walk distance; 2) the percent change in body weight; and 3) the percent change in hsCRP, all assessed at 52 weeks. EQ-5D-5L Health Index score, PGIS, NYHA functional class, and physiological assessments (inclusive of eGFR and UACR) were additional prespecified evaluations.[61]

DATA AND STATISTICAL ANALYSES. The current analysis focuses on patients with and without CKD, defined by eGFR ≥60 or <60 mL/min/1.73 m^2. We previously reported eGFR values based on serum creatinine and the CKD-EPI equation (eGFR-creatinine).[50,51] However, because changes in eGFR-creatinine may be skewed in patients receiving GLP-1 receptor agonists due to the effect of these drugs to reduce muscle mass (and thereby serum creatinine), in the current report, we focused (in a post hoc analysis) on eGFR based on cystatin C (eGFR-cystatin C),[51] although we also report all results based on eGFR-creatinine.

According to the intention-to-treat principle, the analysis for efficacy endpoints was based on all randomized patients, and all data were included until the end of the planned treatment period, whether or not patients continued study medication. Primary outcomes were analyzed using a time-to-first event

FIGURE 1 Correlation of eGFR-Cystatin C and eGFR-Creatinine at Baseline in Individual Patients



At baseline, the assessment of estimated glomerular filtration rate (eGFR) by serum creatinine and by cystatin C were generally correlated with each other, but with substantial variance in individual patients.

approach, using a Cox regression model, with 3 covariates (history of type 2 diabetes, HFpEF probability score[33] ≥80% vs <80%, and NT-proBNP <200 or ≥200 pg/mL). Treatment effects were displayed as HRs with 95% CIs.

Changes in KCCQ, the 6-minute walk distance, and the percent changes in body weight and hsCRP were analyzed by analysis of covariance (ANCOVA), using a model including treatment and stratification variables as fixed effects, and baseline values as a covariate; hsCRP was log transformed for the analysis. Missing data at 52 weeks were imputed through multiple imputations, as prespecified.[50] For other clinical assessments and physiological variables, an ANCOVA or mixed-effects model repeated measures was used without imputation. The mixed-effects model repeated measures model included treatment, time and treatment-by-time interaction, stratification factors as fixed effects, and baseline value as a covariate. Categorical changes in NYHA functional class and PGIS Overall Health (improved, no change, or worsened) from baseline were analyzed using a proportional odds model.

For the current paper, we performed 2 sets of CKD-specific analyses, based on interaction terms in the models described in the previous paragraph. First, in both treatment groups combined, we assessed the influence of CKD on baseline clinical characteristics on the clinical course of patients. Second, we compared the effect of tirzepatide on primary, secondary, exploratory, and physiological endpoints (with a focus on between-group differences in changes in eGFR and UACR) in patients with or without CKD at baseline. For time-to-first event analyses, a full Cox regression model was used with additional terms of the subgroup and subgroup-by-treatment interactions. For ANCOVA analyses with multiple imputation, the interaction *P* value was calculated using z-statistics based on estimated treatment differences from each subgroup. For the interpretation of scatterplots displaying eGFR or changes in eGFR, we calculated Pearson correlation coefficients as well as performing cubic spline regression analysis with 2 knots.

RESULTS

At baseline, the eGFR-cystatin C was correlated with the eGFR-creatinine in individual patients ($r = 0.83$), but in many individuals, but the 2 estimates varied by as much as 50% in either direction, indicative of significant unexplained variance (Figure 1). The mean

eGFR-cystatin C (n = 719) was lower than the mean eGFR-creatinine (n = 731): 55.3 ± 22.4 mL/min/1.73 m^2 vs 64.4 ± 22.4 mL/min/1.73 m^2; $P < 0.0001$. The eGFR-cystatin C was consistently lower than the eGFR-creatinine by ≈9 mL/min/1.73 m^2 across the entire spectrum of baseline values for eGFR (**Figure 2**). Accordingly, CKD—defined as an eGFR <60 mL/min/1.73 m^2—was a feature of 61% of the patients using eGFR-cystatin C as compared with only 46% of the patients using eGFR-creatinine.

INFLUENCE OF CKD ON THE BASELINE CHARACTERISTICS AND CLINICAL COURSE OF PATIENTS WITH HFpEF AND OBESITY. Of the patients with eGFR-cystatin C measurements at baseline, as compared with the 278 patients without CKD, the 441 patients with CKD were older and had greater severity of heart failure. Specifically, as compared with patients without CKD, patients with CKD were more likely to have NYHA functional class III symptoms (34.7% vs 16.2%), atrial fibrillation (33.1% vs 12.9%), and a history of a recent heart failure decompensation (70.7% vs 24.5%); had higher serum levels of NT-proBNP (median 281 ng/mL vs 68 ng/mL) and cardiac troponin T (20 ng/L vs 9 ng/L); all $P < 0.001$; and had worse KCCQ-CSS scores (51.8 ± 18.7 points vs 56.0 ± 17.7 points; $P = 0.003$) and 6-minute walk distances (278 ± 83 m vs 340 ± 64 m; $P < 0.001$) (**Table 1**). Patients with CKD were more likely to be receiving diuretic agents and a SGLT2 inhibitor, but the 2 groups did not differ with respect to baseline values for systolic blood pressure, hemoglobin A_{1c}, ejection fraction, body weight, or hsCRP. Similar patterns were apparent when CKD was defined by eGFR-creatinine (Supplemental Table 1).

Following randomization, patients with CKD were approximately twice as likely to experience worsening heart failure events, when compared with patients without CKD. For the primary events endpoint, the CKD-vs-no-CKD interaction P values were 0.043 and 0.069 for eGFR-creatinine-based and eGFR-cystatin C-based thresholds, respectively. For nonfatal worsening heart failure events, the CKD-vs-no-CKD interaction P values were 0.038 for the creatinine-based eGFR and 0.044 for cystatin C-based eGFR thresholds for the identification of CKD. In the placebo group, the primary events endpoint occurred in 18.8% of patients with CKD vs 9.8% of patients without CKD, 11.2 vs 5.3 events per 100 patient-years of follow-up, respectively. Nonfatal exacerbation of heart failure occurred in 17.8% of patients with CKD vs 9.8% of patients without CKD, 10.2 vs 5.3 events per 100 patient-years of follow-up, respectively. By contrast, the magnitude of the placebo response at 52 weeks was not influenced by the presence of CKD for either KCCQ-CSS or for 6-minute walk distance (**Table 2**). Similar patterns were observed when CKD was defined by eGFR-creatinine (Supplemental Table 2).

INFLUENCE OF CKD ON THE EFFECTS OF TIRZEPATIDE ON PRIMARY AND KEY SECONDARY ENDPOINTS. Overall, as previously reported,[50] the composite of cardiovascular death or worsening heart failure event occurred in 36 patients (9.9%) in the tirzepatide group and 56 patients (15.3%) in the placebo group (HR: 0.62; 95% CI: 0.41-0.95; $P = 0.026$). When events treated with oral diuretic intensification were omitted from the analysis, the effect of tirzepatide remained unchanged (HR: 0.57; 95% CI: 0.34-0.95; $P = 0.03$).

For the primary events endpoint, the effect of tirzepatide in patients with or without CKD defined by eGFR-cystatin C was similar: HR: 0.67 (95% CI: 0.41-1.05) in patients with CKD and 0.58 (95% CI: 0.24-1.32) in patients without CKD; interaction $P = 0.77$ (**Table 2**). For patients with CKD, the event rates were 11.2 and 7.6 per 100 patient-years of follow-up for placebo and tirzepatide, respectively; for patients without CKD, the event rates were 5.3 and 4.7 per 100 patient-years of follow-up for placebo and tirzepatide, respectively. Therefore, tirzepatide produced a numerically larger absolute risk reduction in patients with CKD, as compared with without CKD, that is, the prevention of 3.6 vs 1.6 primary endpoint events, respectively, for 100 patients treated for 1 year. CKD did not influence the response to tirzepatide on the primary events endpoint, when events treated with oral diuretic intensification were omitted from the analysis (interaction $P = 0.88$) or for worsening heart failure events requiring hospitalization, urgent care intravenous drug or oral diuretic intensification (interaction $P = 0.23$) (**Table 2**). Similar patterns of responses were observed when CKD was defined by eGFR-creatinine (Supplemental Table 2).

As reported previously,[50] overall, the between-treatment group difference in the KCCQ-CSS score at 52 weeks was +6.9 points (95% CI: 3.3-10.6 points; $P < 0.001$). The improvement in KCCQ-CSS score was meaningful in patients with and without CKD defined by eGFR-cystatin C: between-group difference +7.0 points (95% CI: 2.8-11.2 points) in patients with CKD and between-group difference +6.2 points (95% CI: 0.9-11.5 points) in patients without CKD, with no difference between CKD and no CKD, interaction

TABLE 1 Baseline Characteristics of Patients With and Without Chronic Kidney Disease

	Patients With Chronic Kidney Disease		Patients Without Chronic Kidney Disease		
	Tirzepatide (n = 212)	Placebo (n = 229)	Tirzepatide (n = 145)	Placebo (n = 133)	*P* Value[a]
Age, y	70.0 ± 8.6	68.9 ± 9.5	58.7 ± 9.6	58.0 ± 9.6	<0.001
Female	129 (60.8)	119 (52.0)	69 (47.6)	71 (53.4)	0.125
Race					<0.001
American Indian, Alaska Native or Pacific Islanders	8 (3.8)	4 (1.7)	18 (12.4)	20 (15.0)	
Asian	30 (14.2)	45 (19.7)	28 (19.3)	28 (21.1)	
Black or African American	15 (7.1)	9 (3.9)	7 (4.8)	5 (3.8)	
White	158 (74.5)	171 (74.7)	91 (62.8)	80 (60.2)	
Other or mixed race	1 (0.5)	0 (0)	1 (0.7)	0 (0)	
Region					<0.001
United States	64 (30.2)	59 (25.8)	17 (11.7)	7 (5.3)	
Latin America	102 (48.1)	109 (47.6)	86 (59.3)	85 (63.9)	
Asia	30 (14.2)	45 (19.7)	28 (19.3)	28 (21.1)	
Other	16 (7.5)	16 (7.0)	14 (9.7)	13 (9.8)	
NYHA functional class					<0.001
II	138 (65.1)	149 (65.1)	118 (81.4)	115 (86.5)	
III-IV	74 (34.9)	80 (34.9)	27 (18.6)	18 (13.5)	
Measures of adiposity					
Body mass index, kg/m^2	38.2 ± 6.4	38.0 ± 6.7	38.6 ± 6.5	38.4 ± 7.5	0.36
Waist-to-height ratio	0.74 ± 0.09	0.73 ± 0.09	0.73 ± 0.09	0.73 ± 0.08	0.20
Left ventricular ejection fraction, %	61.4 ± 6.8	60.6 ± 6.4	60.6 ± 6.1	60.8 ± 5.9	0.74
Coronary artery disease	67 (32.1)	73 (32.2)	43 (30.1)	33 (25.0)	0.21
Hemoglobin A_{1c}, %	6.5 ± 1.0	6.3 ± 1.0	6.2 ± 0.9	6.3 ± 1.1	0.07
NT-proBNP, pg/mL	325 (128-679)	276 (118-781)	68 (25-162)	69 (25-207)	<0.001
Estimated glomerular filtration rate, based on cystatin C, mL/min/1.73 m^2	39.6 ± 11.7	41.6 ± 11.2	78.6 ± 14.4	78.3 ± 14.5	<0.001
Urinary albumin-creatinine ratio, mg/g	205 ± 501	169 ± 558	51 ± 185	31 ± 61	<0.001
KCCQ-CSS score, points	53.1 ± 18.0	50.6 ± 19.4	55.1 ± 17.8	57.1 ± 17.6	0.003
6-minute walk distance, m	278 ± 80	279 ± 85	344 ± 63	337 ± 65	<0.001
High-sensitivity C-reactive protein, mg/L	6.4 ± 9.9	5.9 ± 9.2	4.8 ± 5.2	5.6 ± 7.0	0.14
Cardiac troponin T, ng/L	20 ± 17	19 ± 14	9 ± 10	9 ± 10	<0.001
Systolic blood pressure, mm Hg	127 ± 13	129 ± 14	129 ± 13	128 ± 13	0.88
Hospitalization/urgent visit for heart failure within the past 12 months	61 (28.8)	68 (29.7)	107 (73.8)	103 (77.4)	<0.001
Atrial fibrillation at baseline	75 (35.4)	71 (31.0)	18 (12.4)	18 (13.5)	<0.001
Cardiovascular medications					
Diuretic agents	161 (75.9)	179 (78.2)	102 (70.3)	88 (66.2)	0.011
RAS and neprilysin inhibitor	168 (79.2)	182 (79.5)	119 (82.1)	111 (83.5)	0.29
Beta-blocker	178 (77.7)	149 (70.3)	92 (63.4)	84 (63.2)	0.026
Mineralocorticoid receptor antagonist	79 (37.3)	84 (36.7)	48 (33.1)	41 (30.8)	0.20
SGLT2 inhibitor	49 (23.1)	42 (18.3)	17 (11.7)	15 (11.3)	0.002

Values are mean ± SD, n (%), or median (Q1-Q3). The threshold for chronic kidney disease is based on 60 mL/min/1.73 m^2 as assessed by cystatin C. [a]Patients with vs without chronic kidney disease.

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RAS = renin-angiotensin system; SGLT2 = sodium-glucose cotransporter 2.

$P = 0.86$ (Table 2). A similar pattern of responses to tirzepatide in patients with and without CKD was seen when CKD was defined by eGFR-creatinine (Supplemental Table 2).

As compared with placebo, tirzepatide produced an improvement in 6-minute walk distance, EQ-5D-5L Health Index, PGIS, and NYHA functional class, with similar effects in patients with and without CKD (Table 2). At 52 weeks, both patients with and without CKD showed decreases in hsCRP and in body weight, with a similar magnitude of effect in patients with and without CKD. Similar findings were seen when CKD was defined by eGFR-creatinine (Supplemental Table 2).

COMPARISON OF eGFR-CYSTATIN C VS eGFR-CREATININE IN EVALUATING THE EFFECTS OF TIRZEPATIDE ON KIDNEY FUNCTION DURING SHORT- AND LONG-TERM TREATMENT. At both 12 and 52 weeks, changes in eGFR-cystatin C and changes in eGFR-creatinine in individual patients

TABLE 2 Effects in the Tirzepatide and Placebo Groups in Patients With and Without Chronic Kidney Disease

	Patients With Chronic Kidney Disease			Patients Without Chronic Kidney Disease			
	Tirzepatide	Placebo	HR, Proportional OR, or Difference (95% CI)	Tirzepatide	Placebo	HR, Proportional OR, or Difference (95% CI)	Interaction *P* Value[a]
Primary heart failure outcomes							
Cardiovascular death or worsening heart failure requiring hospitalization, urgent intravenous drugs or intensification of oral diuretics	27 (12.7)	43 (18.8)	0.67 (0.41-1.08)	9 (6.2)	13 (9.8)	0.56 (0.24-1.32)	0.77
Cardiovascular death or worsening heart failure requiring hospitalization or urgent intravenous drugs	17 (8.0)	31 (13.5)	0.57 (0.31-1.03)	6 (4.1)	8 (6.0)	0.64 (0.22-1.86)	0.88
Adjudicated worsening heart failure event requiring hospitalization, urgent intravenous drug or oral diuretic intensification	24 (11.3)	39 (17.0)	0.65 (0.39-1.08)	5 (3.4)	13 (9.8)	0.31 (0.11-0.88)	0.23
Change in symptoms, health status and functional assessments from baseline to 52 wk							
Change in KCCQ-CSS, points	+18.9 ± 1.6	+11.9 ± 1.5	+7.0 (2.8-11.2)	+20.7 ± 1.8	+14.5 ± 2.0	+6.2 (0.9-11.5)	0.86
Change in 6-min walk Distance, m	+19 ± 5	+10 ± 5	+10 (−4 to 24)	+37 ± 6	+11 ± 6	+26 (11-42)	0.12
Change in EQ-5D-5L health index, points	+0.11 ± 0.01	+0.05 ± 0.01	+0.065 (0.03-0.10)	+0.14 ± 0.02	+0.09 ± 0.02	+0.05 (0.01-0.10)	0.83
Change in NYHA functional class, % improved/worse	36.0/2.2	24.1/4.0	2.08 (1.29-3.36)	29.6/(0.7)	15.5/1.6	2.64 (1.36-5.10)	0.73
Change in Patient Global Impression of Severity, % improved/worse	61.7/8.0	45.3/10.0	1.93 (1.25-2.97)	61.7/3.3	50.4/13.9	2.11 (1.22-3.63)	0.94
Change in physiological variables from baseline to 52 wk							
Change in body weight, %	−13.3 ± 0.6	−2.2 ± 0.6	−11.1 (−12.8 to −9.5)	−14.5 ± 0.6	−2.4 ± 0.7	−12.1 (−13.9 to −10.3)	0.43
Change in high-sensitivity C-reactive protein, %	−35.5 ± 6.2	−3.9 ± 7.0	−32.8 (−46.9 to −15.1)	−43.6 ± 5.0	−10.6 ± 7.1	−36.9 (−49.9 to −20.4)	0.71
Change in cystatin C-based estimated glomerular filtration rate, mL/min/1.73 m^2	+2.1 ± 0.9	−1.1 ± 1.0	+3.3 (0.7-5.8)	+2.5 ± 1.3	−0.8 ± 1.5	+3.3 (−0.6 to 7.2)	0.98
Change in urinary albumin-creatinine ratio, mg/g	−13.8 ± 8.0	−3.0 ± 11.1	−11.1 (−33.3 to 18.3)	−16.2 ± 6.7	+7.1 ± 10.6	−21.8 (−39.0 to 0.4)	0.51
Change in systolic blood pressure, mm Hg	−4.2 ± 1.1	+ 1.9 ± 1.1	−6.1 (−9.1 to −3.1)	−5.6 ± 1.1	−2.6 ± 1.1	−3.0 (−5.9 to −0.1)	0.16
Change in heart rate, beats/min	+3.6 ± 0.8	+1.2 ± 0.7	+2.4 (0.3-4.5)	+2.5 ± 0.8	−0.6 ± 0.9	+3.1 (0.9-5.3)	0.61

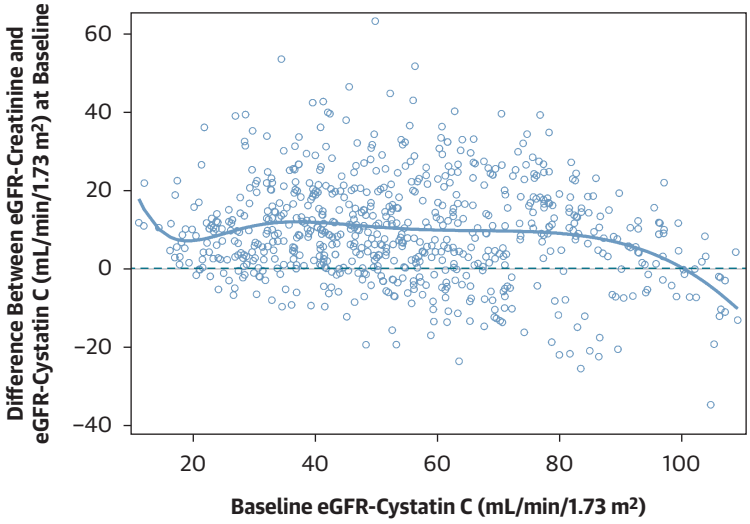
Values are n (%) unless otherwise indicated. The threshold for chronic kidney disease is based on 60 mL/min/1.73 m^2 as assessed by cystatin C. Effects on heart failure events and deaths are shown as time-to-event analyses. Data for high-sensitivity C-reactive protein were log-transformed before analysis. [a]Patients with vs without chronic kidney disease.

EQ-5D-5L = EuroQol 5-Dimensions 5-Level; KCCQ = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score.

were weakly correlated with each other. As shown in Figure 3, the correlation coefficients were somewhat stronger and the regression lines were somewhat steeper in the tirzepatide-treated patients than in the placebo-treated patients, for example, at both 12 and 52 weeks, $r = 0.45$ for tirzepatide-treated patients ($P < 0.05$) and $r = 0.36$ in placebo-treated patients ($P \geq 0.15$), indicating lesser discordance over time in the assessment of changes in glomerular function by eGFR-cystatin C and by eGFR-creatinine in patients treated with tirzepatide.

As compared with placebo, when all patients were analyzed, and based on eGFR-creatinine, treatment with tirzepatide was accompanied by a significant decrease in eGFR at 12 weeks (−3.0 mL/min/1.73 m^2 [95% CI: −4.5 to −1.5 mL/min/1.73 m^2] $P < 0.001$), which was followed by a significant improvement in eGFR at 52 weeks (between-group change, tirzepatide vs placebo +1.9 mL/min/1.73 m^2 [95% CI: 0.2-3.7 mL/min/1.73 m^2]) $P = 0.028$ (Figure 4). By contrast, based on eGFR-cystatin C, the initial decline in eGFR was smaller in magnitude and was no longer significant,

FIGURE 2 Differences in eGFR-Cystatin C and eGFR-Creatinine in Individual Patients as a Function of Baseline eGFR-Cystatin C



The figure shows the results using spline regression analysis with 2 knots. At baseline, the assessment of estimated glomerular filtration rate (eGFR) by serum creatinine was consistently ≈9 mL/min/1.73 m^2 higher than the assessment of eGFR by cystatin C across the entire range of glomerular function.

whereas the improvement at 52 weeks was more apparent (+2.9 [95% CI: 0.9-4.9]; $P = 0.004$). In general, as compared with baseline and corrected for placebo, tirzepatide-related changes in eGFR-cystatin C were consistently shifted toward more positive values than tirzepatide-related changes in eGFR-creatinine at all time points following randomization (ie, 12, 24, and 52 weeks) (Figure 4).

Additionally, the magnitude of the placebo-corrected increase in eGFR with tirzepatide at 52 weeks was constant across the broad spectrum of values for baseline eGFR when assessed by eGFR-cystatin C and displayed as a continuous variable (Figure 5A). By contrast, when based on eGFR-creatinine, an increase in eGFR at 52 weeks was seen primarily in patients with an eGFR 40 to 60 mL/min/1.73 m^2 (Figure 5B). When analyzed by CKD subgroups at 52 weeks, the effect size for the change in eGFR-cystatin C attributable to tirzepatide was similar in patients with or without CKD (+3.3 [95% CI: 0.7-5.8] and +3.3 [95% CI: −0.6 to 7.2]), respectively; interaction $P = 0.98$, whereas the effect size for the change in eGFR-creatinine attributable to tirzepatide was greater in patients with vs without CKD (+3.7 [95% CI: 0.9-6.5] and +0.4 [95% CI: −2.2 to 2.9]), respectively (interaction $P = 0.09$) (Table 2, Supplemental Table 2).

Overall, when all patients were combined, as compared with placebo, tirzepatide decreased the UACR at 24 weeks (−25%; 95% CI: −35.5% to −12.7%; $P < 0.001$) and at 52 weeks (−15.1%; 95% CI: −28.0% to 0.1%; $P = 0.051$). At 52 weeks, macroalbuminuria (defined as urinary albumin excretion >300 mg/g of serum creatinine) was present in 55 patients (15.0%) in the placebo group, but in only 32 patients (8.8%) in the tirzepatide group. The magnitude of the decrease in the UACR at 52 weeks was similar in patients with or without CKD, whether CKD was defined by cystatin C or by creatinine-CKD-EPI (Table 2, Supplemental Table 2).

INFLUENCE OF CKD ON THE SAFETY OF TIRZEPATIDE. The presence or absence of CKD did not influence the frequency of gastrointestinal symptoms in the 2 treatment groups. Gastrointestinal symptoms were reported in 116 (54.2%) tirzepatide-treated patients vs 63 (27.5%) placebo-treated patients with CKD ($P < 0.001$) and in 78 (58.8%) tirzepatide-treated patients vs 33 (24.8%) placebo-treated patients with no CKD ($P < 0.001$), both defined by cystatin C. Similar results were noted when CKD was defined by eGFR-creatinine.

DISCUSSION

CKD is a hallmark of HFpEF,[62,63] and it is the seminal clinical feature that distinguishes patients with obesity and hypervolemia-related heart failure from obesity-related HFpEF.[64] Both hypertension and

diabetes increase the risk of HFpEF and CKD,[65] and obesity sensitizes the kidney to the injurious effects of systolic blood pressure.[66] Systemic and endothelial inflammation not only leads to HFpEF,[67] but also accelerates the rate of decline in kidney function.[9,68,69] Persistent renal injury causes abnormalities of left ventricular mass and diastolic filling that are identical to those seen in HFpEF,[70,71] and the diminished renal perfusion and increased renal venous pressures in HFpEF can adversely influence glomerular structure and function.[72] Drugs used for the treatment of heart failure (eg, diuretic agents, conventional inhibitors of the renin-angiotensin system and mineralocorticoid receptor antagonists) can exacerbate azotemia.[44,73,74] Importantly, most patients with HFpEF have obesity (defined by BMI), and nearly all have excess visceral adiposity (defined by waist-to-height ratio).[3,75] The resulting glomerular hyperfiltration, perirenal adipose tissue-driven inflammation and adipocytokine-mediated podocyte dysfunction are important contributors to CKD.[6-15] Diuretics may be particularly likely to worsen renal function in patients with HFpEF and obesity.[73] Yet, despite the substantial mechanistic interplay and their frequent coexistence, the clinical triad of HFpEF, obesity and CKD has received little attention. The newly minted term—*cardiovascular-kidney-metabolic syndrome*—typically focuses on atherosclerotic disease and diabetes, infrequently on obesity, and almost never on HFpEF.[76]

Despite its importance, the assessment of renal function is confounded in patients with obesity and HFpEF.[52-57] Most studies of kidney function in patients with HFpEF have relied on the indexed estimation of eGFR based on serum creatinine. However, creatinine-based estimates of eGFR were never validated in patients with obesity,[55,56] in whom the weight component of body surface area may not be driven by skeletal muscle mass.[77] Furthermore, weight loss in patients with obesity is accompanied by decreases in skeletal muscle mass; thus, changes in eGFR based on serum creatinine might lead to unwarranted observations about changes in glomerular function.[53,56] As a result of these concerns, in the current paper, we focused on eGFR-cystatin C in the belief that this approach might avoid the difficulties of creatinine-based formulae. Herein, we show that estimates of eGFR based on cystatin C are ≈9 mL/min/1.73 m^2 lower than those based on serum creatinine, a between-estimate difference that is similar to that reported by others in patients with obesity, but without HFpEF.[52-59] Using eGFR-cystatin C to determine the 60 mL/min/1.73 m^2 threshold, >60% of our patients had CKD. We attributed this high prevalence to our eligibility criteria, which encouraged the participation of patients with impaired glomerular function.

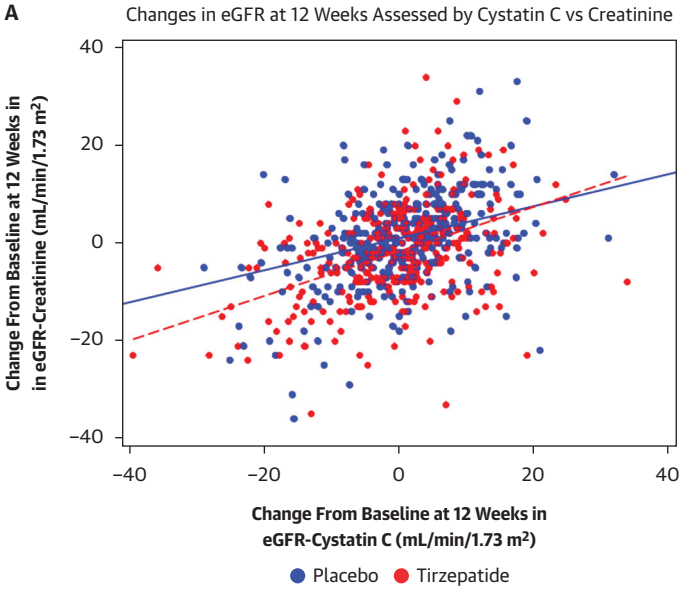
Previous studies have suggested that certain features of HFpEF are exaggerated in patients who also have CKD. Among those with HFpEF and obesity in the SUMMIT trial, patients with CKD had worse symptoms, health status, and exercise tolerance; higher circulating levels of NT-proBNP and troponin; but similar values for systolic blood pressure, hemoglobin A_{1c}, body weight, and hsCRP. A similar CKD-related clinical profile has been reported by others in HFpEF cohorts not defined by obesity.[78-80] When treated with placebo, patients in the SUMMIT trial with CKD had a substantially higher risk of cardiovascular death and worsening heart failure events. A CKD-heightened incidence of events is consistent with earlier reports in HFpEF, which relied on creatinine-based eGFR or eGFR-cystatin C.[63,79-84] It is noteworthy that CKD did not influence the magnitude of the placebo effects on KCCQ-CSS and 6-minute walk distance. These findings indicate that CKD in patients with HFpEF and obesity identifies a large subgroup with more advanced heart failure and at exceptional risk of an unfavorable outcome, a risk that does not appear to be related to elevated systolic blood pressures, glycemic control, or enhanced systemic inflammation.

In the SUMMIT trial, the presence or absence of CKD did not influence the favorable effects of tirzepatide on worsening heart failure events, on health status assessed by KCCQ-CSS, on exercise tolerance assessed by 6-minute walk distance, and on functional capacity or quality of life. Interestingly, a prior trial also did not demonstrate an influence of baseline CKD on the effect of dapagliflozin in HFpEF.[80] However, it was not clear that this pattern of response would apply to incretin-based treatments, since the influence of baseline kidney function on the responses to semaglutide in patients with HFpEF enrolled in the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) and STEP-HFpEF-DM (Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes) trials was not reported.[47,48] Furthermore, semaglutide did not reduce the risk of worsening heart failure events in patients enrolled in the FLOW trial (HR: 0.88; 95% CI: 0.53-1.48), 80% of whom had an eGFR <60 mL/

min/1.73 m^2.[85] Therefore, the findings of the SUMMIT trial are novel and important. Interestingly, given the high risk of patients with CKD and the similarity in relative risk reduction for the primary events endpoint in patients with and without CKD, the absolute risk reduction in primary events when patients with HFpEF, obesity, and CKD were treated with tirzepatide was numerically larger than that seen in patients without CKD, that is, for 100 patients treated for 1 year, the dual GLP-1/glucose-dependent insulinotropic peptide (GIP) receptor agonist prevented 3.6 vs 1.6 events in patients with and without CKD, respectively.

Drugs used for the treatment of HFpEF can have favorable or deleterious effects on kidney function.[41] In patients with HFpEF, neprilysin inhibition with sacubitril/valsartan has been shown, not only to slow the rate of decline in glomerular filtration rate, but also to reduce the risk of end-stage kidney disease.[42] SGLT2 inhibition in patients with HFpEF has been reported to favorably influence eGFR slopes,[79,80] but without an effect on the risk of major kidney events,[46] and mineralocorticoid receptor antagonism may exert deleterious effects on glomerular function.[44,86] In patients with diabetes, GLP-1 receptor agonists have been reported to diminish eGFR during short-term treatment, but to improve glomerular function during long-term treatment,[34,87,88] a biphasic effect that is similar to that observed with mineralocorticoid receptor antagonists and SGLT2 inhibitors.[79,86] However, in patients receiving GLP-1

FIGURE 3 Comparison of Changes in Glomerular Filtration Rate (eGFR-Cystatin C vs eGFR-Creatinine) at 12 Weeks and 52 Weeks



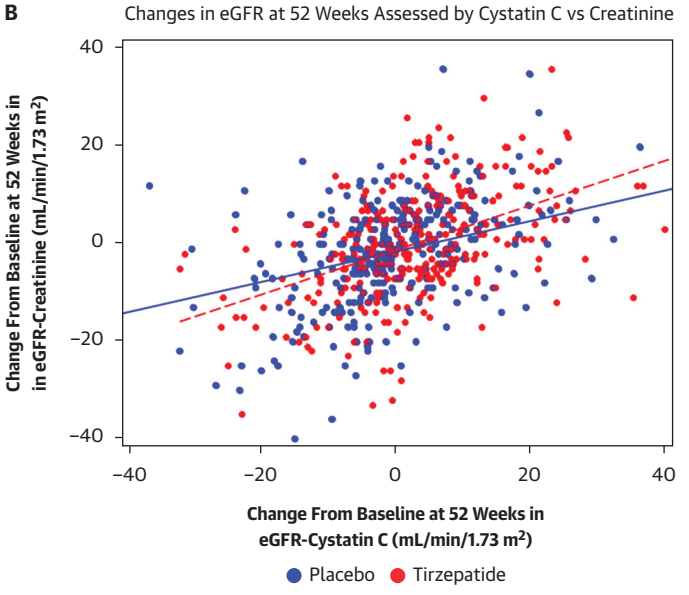


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FIGURE 3 Continued

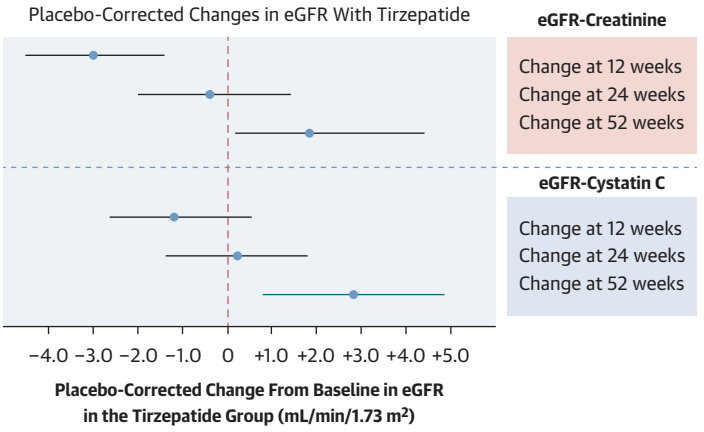
(A) Comparison of changes in glomerular filtration rate (estimated glomerular filtration rate [eGFR]-cystatin C vs eGFR-creatinine) at 12 weeks in the placebo and tirzepatide groups is shown. From baseline to 12 weeks following randomization, changes in eGFR-cystatin C and changes in eGFR-creatinine in individual patients were weakly correlated with each other. The correlation coefficients were somewhat stronger and the regression lines were somewhat steeper in the tirzepatide-treated patients (shown in red circles and lines) than in the placebo-treated patients (shown in blue circles and lines), $r = 0.45$ for tirzepatide-treated patients ($P < 0.05$) and $r = 0.36$ in placebo-treated patients ($P \geq 0.15$), thus indicating lesser discordance over time in the assessment of changes in glomerular function by eGFR-cystatin C and by eGFR-creatinine in patients treated with tirzepatide. (B) Comparison of changes in glomerular filtration rate (eGFR-cystatin C vs eGFR-creatinine) at 52 weeks in the placebo and tirzepatide groups is shown. From baseline to 52 weeks following randomization, changes in eGFR-cystatin C and changes in eGFR-creatinine in individual patients were weakly correlated with each other. The correlation coefficients were somewhat stronger and the regression lines were somewhat steeper in the tirzepatide-treated patients (shown in red circles and lines) than in the placebo-treated patients (shown in blue circles and lines), $r = 0.45$ for tirzepatide-treated patients ($P < 0.05$) and $r = 0.36$ in placebo-treated patients ($P \geq 0.15$), thus indicating lesser discordance over time in the assessment of changes in glomerular function by eGFR-cystatin C and by eGFR-creatinine in patients treated with tirzepatide.

receptor agonists, serial measurements of creatinine-based eGFR may be confounded by an effect of these drugs to reduce muscle mass,[89] and the resulting decline in serum creatinine may imply an improvement in kidney function that has not taken place.[53,56] Semaglutide has been reported to improve eGFR-cystatin C and decrease the risk of kidney disease progression in patients with CKD.[34] However, the renal effects of these drugs in obesity with HFpEF are not known, because kidney function was not assessed following randomization in the STEP-HFpEF and STEP-HFpEF-DM trials in patients with HFpEF and obesity.

In the SUMMIT trial, tirzepatide improved glomerular function and reduced proteinuria at 52 weeks; however, the pattern of the benefit on eGFR varied with the formula used to assess eGFR. Using eGFR-creatinine, there was a significant early dip in eGFR at 12 weeks, and renal function appeared to be improved at 52 weeks only in patients with an eGFR 40 to 60 mL/min/1.73 m^2. A nearly identical pattern of response was seen in patients with diabetes with tirzepatide in the SURPASS-4 trial (A Study of Tirzepatide [LY3298176] Once a Week Versus Insulin Glargine Once a Day in Participants With Type 2 Diabetes and Increased Cardiovascular Risk),[89] which also relied on eGFR-creatinine. By contrast, when eGFR was assessed by cystatin C, we did not observe an early eGFR dip, and the magnitude of the improvement in eGFR was constant across the entire range of values for baseline eGFR. Similarly, the effect of tirzepatide to reduce albuminuria at 52 weeks was also not influenced by the baseline eGFR. Taken together, these observations suggest that the early decline in eGFR reported with incretin-based drugs might be related to the use of creatinine-based eGFR formulae.[57,89]

However, the assessment of eGFR-cystatin C has its own difficulties. As seen in **Figure 2**, eGFR-cystatin C was consistently higher than eGFR-creatinine in our patients with HFpEF and obesity at baseline. This finding is consistent with numerous previous reports,[52-59] and it has been attributed to an action of adipocytes to synthesize cystatin C,[58] and thus, cystatin C-based formulae may systematically underestimate eGFR in patients with obesity.[58,59] Furthermore, tirzepatide-induced decreases in adipocyte mass (and thus, cystatin C production) might cause artifactual increases in eGFR-cystatin C, potentially explaining why tirzepatide-related changes in eGFR-cystatin were consistently shifted toward more positive values (when compared with tirzepatide-related changes in eGFR-creatinine) at all time points following randomization (**Figure 4**). Additionally, tirzepatide-related weight loss was accompanied by lessening in the discordance between changes in glomerular function assessed by eGFR-cystatin C and by eGFR-creatinine over time (**Figure 3**), a finding consistent with a drug-related decrease in the synthesis of cystatin C by adipose tissue. Taken together, the effects of incretin-based drugs on both fat mass and muscle mass (ie, sources of cystatin C and creatinine, respectively) suggest that neither approach represents an unbiased assessment of glomerular function. Interestingly, changes in eGFR using the 2 methods were not well correlated with each other even in patients receiving placebo.

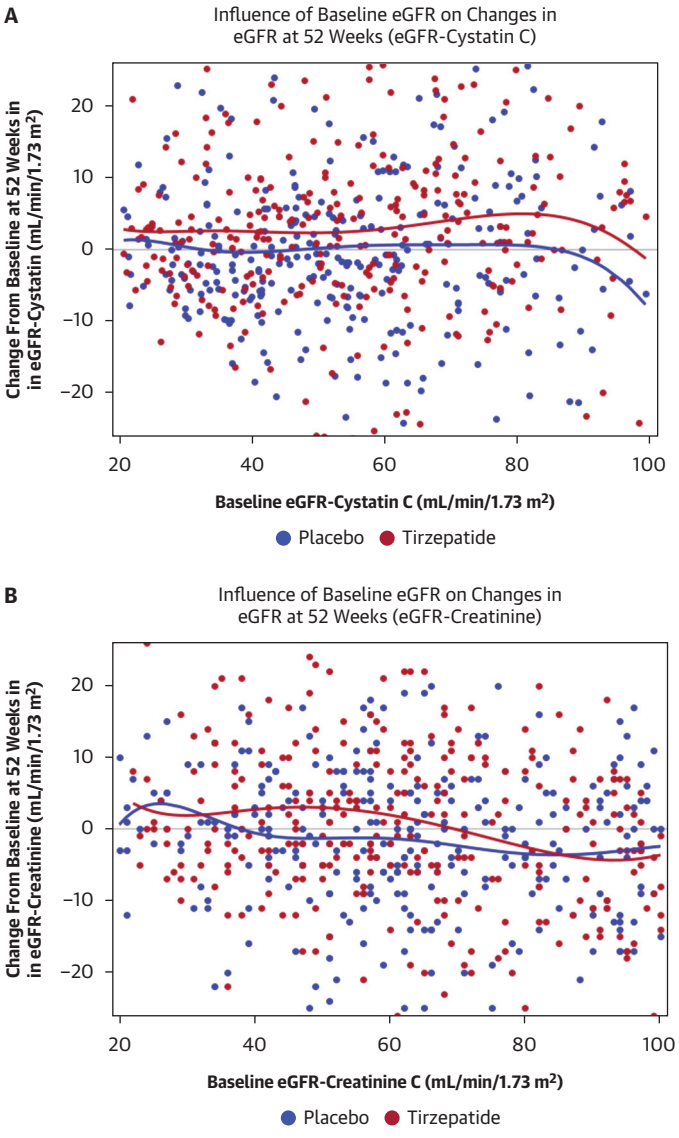
FIGURE 4 Effect of Tirzepatide (Placebo-Corrected) on Glomerular Filtration Rate at 12, 24, and 52 Weeks, Assessed by eGFR-Cystatin C and eGFR-Creatinine



As compared with placebo, when all patients were analyzed, and based on estimated glomerular filtration rate (eGFR)-creatinine, treatment with tirzepatide was accompanied by a significant decrease in eGFR at 12 weeks ($P < 0.001$), which was followed by a significant improvement in eGFR at 52 weeks ($P = 0.028$). By contrast, based on eGFR-cystatin C, the initial decline in eGFR was smaller in magnitude and was no longer significant, whereas the improvement at 52 weeks was larger and more apparent ($P = 0.004$). In general, as compared with baseline and corrected for placebo, tirzepatide-related changes in eGFR-cystatin C were consistently shifted toward more positive values, as compared with tirzepatide-related changes in eGFR-creatinine at all time points following randomization (ie, 12, 24, and 52 weeks), possibly related to an effect of tirzepatide to reduce adipocyte mass, and thus, the synthesis of cystatin C. According to the intention-to-treat principle, all randomized patients with a baseline value for eGFR-creatine (n = 731) or for eGFR-cystatin C (n = 719) were included in these analyses, and prespecified imputation methods were used for the small number of patients who had missing data points at 12, 24, and 52 weeks following randomization.

STUDY STRENGTHS AND LIMITATIONS. The findings of the current trial should be considered in light of its strengths and limitations. We did not measure eGFR

FIGURE 5 Influence of Baseline eGFR on the Change in eGFR (Both Assessed by eGFR-Cystatin C and eGFR-Creatinine)



(A) Influence of baseline estimated glomerular filtration rate (eGFR) on the change in eGFR (both assessed by eGFR-cystatin C) at 52 weeks in placebo and tirzepatide groups is shown. The figure shows the results using spline regression analysis with 2 knots, separately for the placebo and tirzepatide groups. When based on cystatin C, the magnitude of the placebo-corrected increase in eGFR with tirzepatide at 52 weeks was constant across the broad spectrum of values for baseline eGFR. (B) Influence of baseline eGFR on the change in eGFR (both assessed by eGFR-creatinine) at 52 weeks in placebo and tirzepatide groups is shown. The figure shows the results using spline regression analysis with 2 knots, separately for the placebo and tirzepatide groups. When based on eGFR-creatinine, the placebo-corrected increase in eGFR with tirzepatide at 52 weeks was seen primarily in patients with an eGFR 40 to 60 mL/min/1.73 m^2.

using a constant infusion of inulin, iothalamate, or iohexol, and thus, we did not assess renal function in a manner that was unconfounded by obesity or by changes in muscle or fat mass. However, we assessed the influence of baseline eGFR (using 2 different estimates) and GLP-1 receptor signaling in a double-blind randomized long-term trial of tirzepatide, thus avoiding the biases of previous reports based on observational studies.[49] Although the SUMMIT trial enrolled only 731 patients, this number was sufficient to discern a meaningful influence of eGFR on the clinical course of patients with HFpEF, and there was no influence of CKD on any efficacy endpoint. However, the trial was substantially underpowered to ascertain any potential effect of tirzepatide to reduce the risk of progression of CKD to end-stage kidney disease.

CONCLUSIONS

The triad of HFpEF, obesity, and CKD represents an intriguing subphenotype with greater severity of and disability related to heart failure, and a substantially increased risk of cardiovascular death and worsening heart failure events. Baseline eGFR did not influence the magnitude of the relative risk reduction produced by tirzepatide on major adverse heart failure outcomes or its effect to enhance health status. Tirzepatide improved renal function during long-term treatment, but the assessment of eGFR by creatinine-based and cystatin C-based formulae in patients receiving incretin-based drugs may be confounded by obesity and the effect of treatment on fat and muscle mass.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Packer has served as a consultant for 89bio, AbbVie, Actavis, Altimmune, Alnylam, Amarin, Amgen, Ardelyx, ARMGO, AstraZeneca, Attralus, Biopeutics, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Lilly, Imara, Medtronic, Moderna, Novartis, Pharmacocosmos, Reata, Regeneron, Roche, and Salamandra. Dr Zile has received research support from the U.S. Department of Veterans Affairs (Project Nos. BX005943, BX005848); and has served as a consultant for Abbott, Adona Medical, Aria CV, Avery Therapeutics, Boehringer Ingelheim, Boston Scientific, Cardiovascular Research Foundation Clinical Trials Center, CVRx, DIASTOL Therapeutics, EBR, Edwards Lifesciences, Lilly, GenKardia, Innoventric, KestraMedical, Medtronic, Merck, Morphic Therapeutics, Novartis, Pulnova, Salubris Biotherapeutics, Sonata, SRNALYTICS, V-WAVE, and Vectorious. Dr Kramer has served as a consultant for Eli Lilly and Co; and has received research grant support from Eli Lilly and Co, Bristol Myers Squibb, and Cytokinetics. Drs Murakami and Ou are employees of Eli Lilly and Co. Dr Borlaug has received research grant support from the National Institutes of Health and the U.S. Department of Defense,

AstraZeneca, Axon, Corvia, Novo Nordisk, and Tenax Therapeutics; has served as a consultant for Actelion, Amgen, Aria, Axon Therapies, BD, Boehringer Ingelheim, Cytokinetics, Edwards Lifesciences, Lilly, Imbria, Janssen, Merck, Novo Nordisk, NGM, NXT, and VADovations; and is a named inventor (U.S. Patent No. 10,307,179) for the tools and approach for a minimally invasive pericardial modification procedure to treat heart failure.

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APPENDIX For supplemental tables, please see the online version of this paper.