Influence of Combination Therapy with Dulaglutide or Liraglutide and SGLT2 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Post-hoc Analysis of the RECAP Study

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Objective: We report that the effect of combination therapy with SGLT2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1Ra) on renal composite outcomes is not affected by the preceding drug in patients with type 2 diabetes (T2D). In this study, we performed a post-hoc analysis of dulaglutide and liraglutide users and investigated the differences between GLP1Ra.
Methods: We analyzed 266 patients treated with an SGLT2i followed by dulaglutide or liraglutide and 194 treated with dulaglutide or liraglutide followed by an SGLT2i. In addition, we analyzed dulaglutide users (n = 246) and liraglutide users (n = 214). Renal composite outcome was defined as the progression of albuminuria and/or a ≥ 30% eGFR decline.
Results: The incidence of renal composite outcomes in the SGLT2i-preceding and GLP1Ra (dulaglutide or liraglutide)-preceding groups was not significantly different. It also did not differ between the dulaglutide and liraglutide users. The incidence of ≥ 30% eGFR decline was more frequent in liraglutide users, with an odds ratio of 2.63 (95% confidence interval: 1.07–6.45, p = 0.04), with a significantly larger decrease in albuminuria in liraglutide users, with an odds ratio of 0.44 (95% confidence interval: 0.04–0.85, p = 0.03).
Conclusions: Dulaglutide and liraglutide may have different effects on albuminuria and the kidney function in combination with SGLT2i.

Key words: GLP-1 receptor agonists, SGLT2 inhibitors, renal outcomes, type 2 diabetes

INTRODUCTION

The number of patients with type 2 diabetes (T2D) is increasing worldwide. Globally, diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD) [1], and therapeutic strategies for DKD have received much attention. Glucagon-like peptide-1 receptor agonists (GLP1Ra) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) play important roles in the treatment of T2D because of their cardiorenal protective properties. Depending on the number of administrations, GLP1Ra can be divided into once-daily and once-weekly forms. Dulaglutide is a once-weekly GLP1Ra consisting of GLP1(7–37) covalently linked to an Fc fragment of human IgG4 [2]. These modifications prolong the half-life of dulaglutide by approximately five days [3]. Liraglutide is a once-weekly GLP1Ra that is identical to GLP1(7–37), except that the lysine at position 34 is substituted by arginine and has a 16-carbon fatty acid chain with a glutamic acid spacer, which is chemically attached to the remaining lysine residue at position 26 of the peptide precursor [4]. These modifications prolong the plasma half-life of liraglutide to 13 h [4]. Therefore, the structures and half-lives of these two drugs differ.

A series of studies have demonstrated that both dulaglutide and liraglutide have beneficial effects on cardiorenal outcomes in T2D patients with a high risk of cardiovascular disease [5]. In REWIND, once-weekly dulaglutide reduced renal composite outcomes compared to placebo among T2D patients who are at a high risk for cardiovascular disease [6]. In LEADER, once-daily liraglutide was shown to attenuate renal composite outcomes relative to placebo [7]. However, no studies have directly compared drugs to determine whether or not different types of GLP1Ra have different effects on renal outcomes in combination therapy with SGLT2i.

We previously reported that, in combination therapy with GLP1Ra and SGLT2i, the preceding drug did not

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affect the renal composite outcome (RECAP study) [8]. However, whether or not the use of different types of GLP1Ra in combination therapy with SGLT2i affects renal outcomes remains unclear.

In our previous study, GLP1Ra treatment with dulaglutide or liraglutide accounted for the majority of case, a few patients used exendin-based GLP1Ra, and some patients changed the type of GLP1Ra during the treatment. However, when we analyzed the changes in clinical characteristics between patients who used dulaglutide or liraglutide throughout the study and those who used others with a general linear mixed model, significant interactions were observed in the changes in the body weight (BW) and body mass index (BMI), which might have led to differences in renal outcomes (data not shown).

Therefore, in the present post-hoc analysis, we extracted cases that were treated with dulaglutide or liraglutide and investigated whether or not the preceding drug showed any influence on the renal composite outcomes and metabolic profiles in combination therapy. In addition, we analyzed whether the use of different types of GLP1Ra affected renal outcomes.

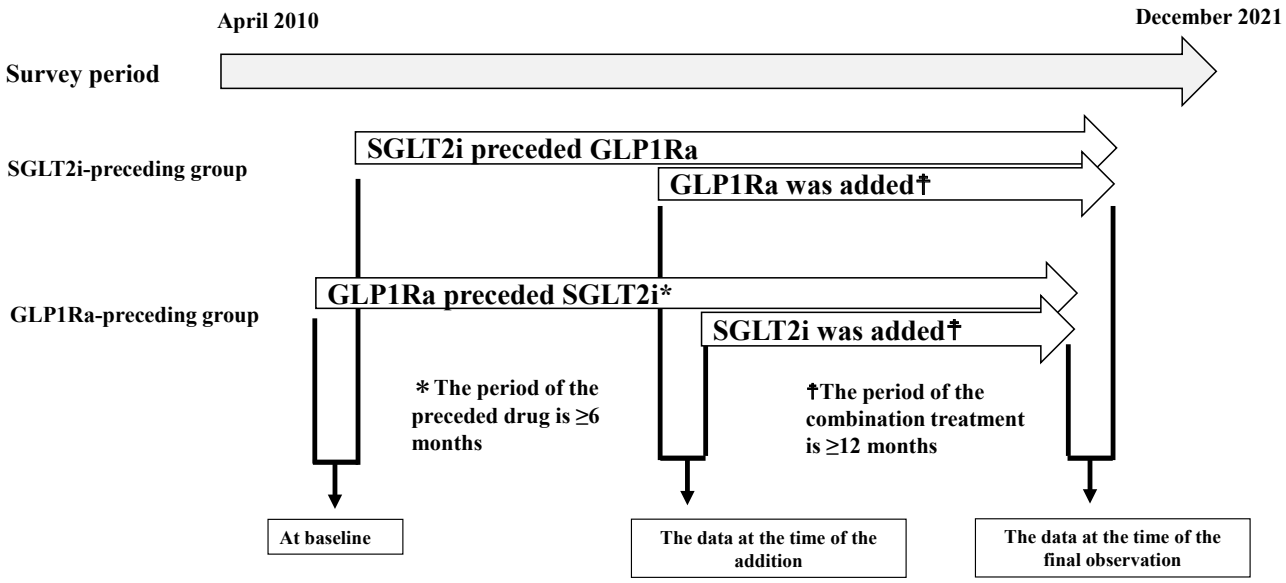
MATERIALS AND METHODS

Study design

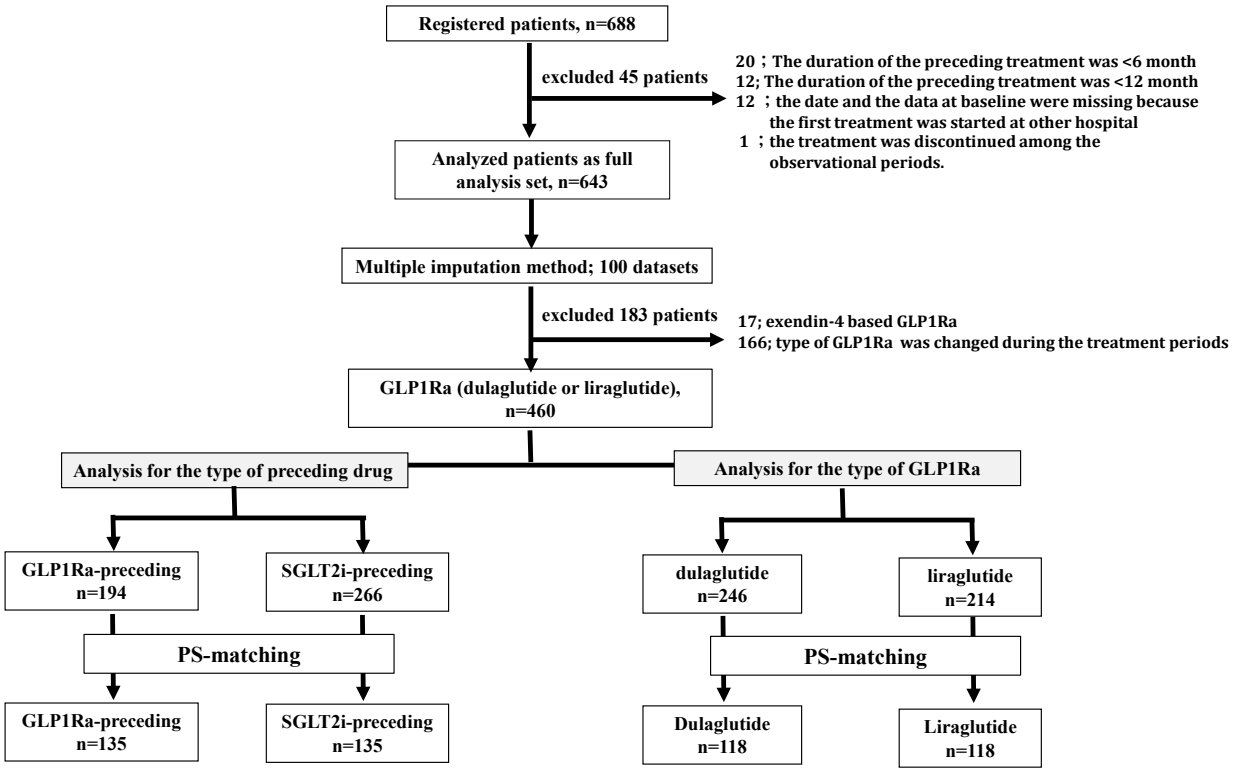
The design of the RECAP study has been reported previously [8]. Briefly, T2D patients who received both SGLT2i and GLP1Ra from April 2010 to December 2021 and met the following criteria were eligible for inclusion in this study: received their preceding medication for ≥ 6 months, received concomitant medication for ≥ 12 months, clinical data available from baseline, time of drug addition, and final observation (Supplementary fig. S1). The following data were collected: sex, age, height, BW, systolic blood pressure (SBP), diastolic blood pressure (DBP), estimated glomerular filtration rate (eGFR), glycated hemoglobin A_{1c} (HbA_{1c}), urinalysis results (urine albumin-to-creatinine ratio (ACR) [mg/g Cr] or qualitative proteinuria), alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, platelet counts, and concomitant medications (hypoglycemic drugs, antihypertensive drugs, and statins). eGFR was determined as follows: eGFR (mL/min/1.73 m^2) = 194 $\times$ $age^{-0.287}$ $\times$ serum $creatinine^{-1.094}$ $\times$ (0.739 for women) [9]. Qualitative proteinuria values were converted to albuminuria values using the following formula: predicted ACR = exp (5.2659 + 0.2934 $\times$ log (min (PCR [protein-to-creatinine ratio]/50, 1)) + 1.5643 $\times$ log (max (min(PCR/500, 1), 0.1)) + 1.1109 $\times$ log (max (PCR/500, 1)) -0.0773 $\times$ (if female) + 0.0797 $\times$ (if diabetic) + 0.1265 $\times$ (if hypertensive))) [10]. Patients with any of the following conditions were excluded from the study: type 1 diabetes, chronic dialysis, severe liver dysfunction (e.g., liver cirrhosis or severe infection), terminal-stage malignancy, pregnancy, or treatment discontinuation. Patients who opted out during the study period were also excluded.

Based on the inclusion criteria, we extracted data from 643 patients treated with SGLT2i and GLP1Ra. In this post-hoc analysis, data of 17 patients who used exendin-based GLP1Ra and 166 patients who changed the types of GLP1Ra during the treatment were excluded; data from 460 patients (246 with dulaglutide and 214 with liraglutide) were thus analyzed in this post-hoc study. Of these 460 patients, 266 had previously been treated with SGLT2is and were later treated with dulaglutide or liraglutide (SGLT2i-preceding group), and 194 patients had previously been treated with dulaglutide or liraglutide and were later treated with an SGLT2i (GLP1Ra-preceding group) (Supplementary fig. S2).

The present study was approved by the Institutional Review Board for Clinical Research of Tokai University, Japan on December 6, 2021.



Supplementary Fig. S1 Schematic of the design of the RECAP study
Patients with T2D treated with both SGLT2i and GLP1Ra between April 2010 and December 2021. Patients who had been on monotherapy for at least 6 months and combination therapy for at least 12 months were enrolled in the study.
Abbreviations: GLP1Ra, glucagon-like peptide 1 receptor agonist; PS, propensity score; SGLT2i, sodium-glucose co-transporter inhibitor.



Supplementary Fig. S2 Schematic of the study participants
A total of 688 patients were registered, and 45 were excluded. The data of 643 patients (SGLT2i-preceding group, n = 312; GLP1Ra (dulaglutide or liraglutide)-preceding group, n = 331) were analyzed as the full analysis set (FAS). The multiple imputation method was applied to FAS data. In this post-hoc analysis, data of 17 patients who used exendin-based GLP1Ra and 166 patients who changed the type of GLP1Ra during the treatment were excluded. Of the 623 remaining patients, 460 who used liraglutide or dulaglutide were extracted. The differences in the type of preceding drug and the different types of GLP1Ras, liraglutide, and dulaglutide were analyzed using the propensity score (PS) inverse probability weighting method and PS matching method.
Abbreviations: GLP1Ra, glucagon-like peptide 1 receptor agonist; PS, propensity score; SGLT2i, sodium-glucose co-transporter inhibitor.

Outcomes

The renal composite outcome was defined as the progression of albuminuria and/or a ≥ 30% eGFR decline. We also evaluated the changes in eGFR and logarithmic value of ACR (LnACR).

Statistical analyses

IBM SPSS Statistics (version 28.0; IBM Inc., Armonk, NY, USA) was used for statistical analyses. Statistical significance was set at $P < 0.05$.

Missing value analysis

To account for missing data, we used the multiple imputation (MI) method. We replaced each missing value with a set of substituted plausible values by creating 100 complete filled-in datasets using MI with the chained-equations method.

Propensity score analysis using inverse probability weighting

Propensity score (PS) analysis was used to minimize the influence of confounding factors. In the comparison between the GLP1Ra (dulaglutide or liraglutide)-preceding group and SGLT2i-preceding group, in each dataset built using MI, the PS for the SGLT2i-preceding group was calculated by logistic analysis, using the following covariates: age, sex, height, BW, BMI, SBP, DBP, HbA_{1c}, eGFR, LnACR at baseline, history of T2D, use of concomitant medications at baseline, duration of treatment with the preceding drug, and combination therapy. The inverse probability weighting (IPW) method using PS was used to analyze the outcomes. We selected the model using the stabilized average treatment effect (ATE) weighting with trimming (patients with PS < 0.05 or PS > 0.95, were excluded from further analyses) because this model showed the lowest standardized differences in covariates. Comparisons of renal outcomes or clinical characteristics after combination therapy were performed using a generalized linear model (GLM).

In the comparison between the liraglutide and dulaglutide groups, the PS for the liraglutide group was calculated using the same covariates described above, adding the type of preceding drug, and the PS-IPW model was analyzed with the same algorithm.

Sensitivity analysis

PS matching for the sensitivity analysis was performed with the following algorithm: 1:1 nearest-neighbor match and no replacement with a caliper value of 0.047 for the analysis of the type of preceding drug, and 0.043 for the analysis of the type of GLP1Ra, which were calculated as 0.2 × the value of the standard difference in PS.

RESULTS

Analyses of differences in the type of preceding drug

The baseline data are presented in Table 1. In the unadjusted model in the left column, the GLP1Ra (dulaglutide or liraglutide)-preceding and SGLT2i-preceding groups showed significant differences in HbA_{1c} level (73.6 ± 17.3 mmol/mol [8.9 ± 1.6%] vs. 70.0 ± 17.6 mmol/mol [8.6 ± 1.6%]), period of combination therapy (months) (36.5 ± 16.9 vs. 26.8 ± 12.1, $p < 0.001$), total study period (months) (63.6 ± 25.1 vs. 51.3 ± 15.2, $p < 0.001$), and use of metformin (48% vs. 61%, $p = 0.006$) at baseline. In the PS-IPW model, the range of standardized differences in covariates was 0.001−0.09. Therefore, the groups were considered well balanced. The middle column of Table 2 presents the results of the PS-IPW analysis based on GLM. During the observation period, the incidence of renal composite outcomes was 28% in the SGLT2i-preceding group and 25% in the GLP1Ra (dulaglutide or liraglutide)-preceding group, with an odds ratio (OR) of 1.13 (95% confidence interval [CI]: 0.68−1.88, $p = 0.63$). The decrease in BW was 1.4 kg larger in the GLP1Ra (dulaglutide or liraglutide)-preceding group, which amounted to a statistically significant difference (95%

Table 1 Clinical baseline characteristics on the analysis for the type of preceding drug

	Unadjusted			PS-IPW model (by stabilized ATE with trimming)			PS-matching model		
	GLP1Ra (dulaglutide or liraglutide)-preceding group, n=194	SGLT2i-preceding group, n=266	p-value*	GLP1Ra (dulaglutide or liraglutide) -preceding group, n=194†	SGLT2i-preceding group, n=260†	Standardized difference	GLP1Ra (dulaglutide or liraglutide) -preceding group, n=135	SGLT2i-preceding group, n=135	Standardized difference
Age (year-old)	56.4±13.7	57.0±12.5	0.63	57.0±14.0	57.1±12.4	0.008	57.7±14.2	57.3±12.8	0.03
Sex (female [%])	86 (44%)	107 (40%)	0.38	86 (44%)	114 (44%)	0.01	59 (44%)	58 (43%)	0.01
A history of T2D >10 years (%)	163 (84%)	200 (75%)	0.07*	152 (78%)	205 (79%)	0.01	111 (82%)	101 (75%)	0.18
BW (kg)	78.9±17.6	79.0±18.5	0.96	77.9±17.5	78.2±18.0	0.02	78.6±18.0	79.0±18.1	0.02
BMI	29.5±5.1	29.2±5.5	0.55	29.1±5.0	29.2±5.4	0.02	29.3±4.9	29.3±5.4	0.0
SBP (mmHg)	132.5±9.5	135.3±19.0	0.11	132.6±18.8	134.2±18.6	0.09	134.0±19.6	134.1±17.9	0.005
DBP (mmHg)	76.8±12.6	78.4±13.7	0.19	76.6±12.2	77.5±13.1	0.07	77.2±12.6	77.8 ±13.2	0.05
MAP (mmHg)	95.3±13.4	97.4±13.6	0.11	95.3±12.7	96.4±13.1	0.09	96.1±13.3	96.6±13.0	0.04
HbA_{1c} (mmol/mol [%])	73.6±17.3 (8.9±1.6)	70.0±17.6 (8.6±1.6)	0.03	72.6±17.1 (8.8±1.6)	72.3±19.6 (8.8±1.8)	0.02	73.1±16.9 (8.8±1.5)	72.2±19.3 (8.8±1.8)	0.05
eGFR (mL/min/1.73 m^2)	76.0±26.4	77.7±26.1	0.49	77.8±25.8	77.7±26.4	0.004	74.9±25.4	77.6±28.2	0.10
ACR (mg/gCr)	39.9 [11.2, 178.7]	31.1 [10.9, 121.2]	0.45	33.8 [11.8, 172.6]	37.2 [12.7, 169.0]		34.7 [11.1, 194.7]	33.7 [12.1, 132.1]	
LnACR	3.91±1.96	3.78±2.00	0.49	3.81±1.88	3.85±1.92	0.02	3.86±2.00	3.79±1.90	0.04
Duration of the preceding treatment (month)	27.1±20.9	24.6±13.4	0.12	24.5±18.6	24.5±13.4	0.001	24.7±18.4	24.6±14.0	0.006
Duration of the combination treatment (month)	36.5±16.9	26.8±12.1	<0.001	30.9±15.7	29.9±13.4	0.07	30.4±14.1	31.6±12.9	0.09
Total duration of the study (month)	63.6±25.1	51.3±15.2	<0.001	55.4±23.2	54.4±15.6	0.05	55.1±21.0	56.2±14.9	0.06
Concomitant medications									
Sulphonylurea	47 (24%)	77 (29%)	0.26	55 (28%)	72 (28%)	0.01	33 (24%)	40 (30%)	0.12
Metformin	93 (48%)	162 (61%)	0.006	108 (56%)	148 (57%)	0.03	72 (53%)	75 (56%)	0.04
Insulin	95 (49%)	112 (42%)	0.14	82 (42%)	116 (45%)	0.05	64 (47%)	61 (45%)	0.04
Pioglitazone	18 (9%)	40 (15%)	0.07	24 (12%)	34 (13%)	0.02	16 (12%)	18 (13%)	0.04
αGI	26 (13%)	43 (16%)	0.41	27 (14%)	40 (15%)	0.04	20 (15%)	18 (14%)	0.04
Glinide	11 (6%)	12 (5%)	0.57	9 (5%)	12 (5%)	0.001	9 (7%)	6 (4%)	0.10
RAS inhibitor	95 (49%)	135 (51%)	0.71	95 (49%)	133 (51%)	0.04	63 (47%)	67 (50%)	0.06
CCB	85 (44%)	97 (37%)	0.11	77 (40%)	106 (41%)	0.02	55 (41%)	57 (42%)	0.03
βblocker	26 (13%)	45 (17%)	0.30	28 (14%)	39 (15%)	0.02	19 (14%)	16 (12%)	0.07
MRB	7 (4%)	9 (3%)	0.90	6 (3%)	9 (3%)	0.02	6 (4%)	4 (3%)	0.08
Thiazide	16 (8%)	15 (6%)	0.27	11 (6%)	16 (6%)	0.02	12 (9%)	11 (8%)	0.03
Loop	11 (6%)	11 (4%)	0.45	8 (4%)	11 (4%)	0.005	7 (5%)	6 (4%)	0.03
Statin	95 (49%)	140 (53%)	0.44	95 (49%)	134 (52%)	0.05	68 (50%)	72 (53%)	0.06

Values are mean ± SD, n/total n (%), or median [lower quantile, upper quantile].

*P-values by unpaired t-test or chi-square test.

†Calculated number of subjects after weighting

Abbreviations: αGI, alpha-glucosidase inhibitor; ATE, average treatment effect; BMI, body mass index; BW, body weight; DBP, diastolic blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration; GLP1Ra, glucagon-like peptide 1 receptor agonists; HbA_{1c}, glycated hemoglobin A_{1c}; IPW, inverse provability weighting; LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; MRB, mineral corticoid receptor blocker; PS, propensity score; RAS, renin-angiotensin system; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter inhibitor; T2D, type 2 diabetes.

CI: 0.2–2.5, p = 0.03).

The results of the PS-matched model used for sensitivity analysis are shown in the right columns of Tables 1 and 2. The baseline data for the PS-matched model, which included 135 patients in each group, are presented in the right column of Table 1. As shown in the right column of Table 2, no significant differences were observed in renal composite outcomes between the two groups.

Analyses of the differences between dulaglutide and liraglutide

The baseline data are presented in Table 3. In the unadjusted model in the left column, the dulaglutide and liraglutide groups showed significant differences in the period of preceding therapy, combination therapy, total study period, type of preceding drug, and use of sulfonylurea, metformin, and insulin (p = 0.002, < 0.001, < 0.001, < 0.001, 0.003, 0.01, and < 0.001, respectively). In the PS-IPW model (middle column), the range of standardized differences in the covariates was 0.01–0.09, indicating a well-balanced model. The middle column of Table 4 presents the results of the PS-IPW analysis based on GLM. During the observation period, the incidence of renal composite outcomes was 28% in the liraglutide group and 25% in the dulaglutide group, with an OR of 1.16 (95% CI: 0.61–2.23, p = 0.65). The incidence of a ≥ 30% decrease in eGFR was more frequent in the liraglutide group (14%) than in the dulaglutide group (6%), with an OR of 2.63 (95% CI: 1.07–6.45, p = 0.04), while a significantly larger decrease in LnACR (OR 0.44 (95% CI: 0.04–0.85, p = 0.03) was observed in the liraglutide group than in the dulaglutide group.

The results of the PS-matched model used for the sensitivity analysis are shown in Tables 3 and 4. Baseline data for the PS-matched model, which included 118 patients in each group, are presented in the right-hand column of Table 1. The levels of standardized difference in some covariates (period of preceding therapy, combination therapy, and the use of metformin, calcium channel blocker, and mineral corticoid receptor blocker) were over 0.14, which might indicate that the confounding by these covariates could

Table 2 Renal outcomes and clinical characteristics after combination treatment on the analysis for the type of preceding drug

	Unadjusted			PS-IPW model (by stabilized ATE with trimming)			PS-matching model		
	GLP1Ra (dulaglutide or liraglutide) - preceding group, n=194	SGLT2i-preceding group, n=266	p-value*	GLP1Ra (dulaglutide or liraglutide)-preceding group, n=194†	SGLT2i-preceding group, n=260†	GLM#	GLP1Ra (dulaglutide or liraglutide) - preceding group, n=135	SGLT2i-preceding group, n=135	p-value**
Renal outcomes and function									
a) Incidence of renal composite outcome	54 (28%)	65 (24%)	0.47	49 (25%)	72 (28%)	1.13 [0.68, 1.88], p=0.63	36 (27%)	42(31%)	0.41
Progression of ACR status	33 (17%)	48 (18%)	0.68	33 (17%)	53 (20%)	1.25 [0.70, 2.27], p=0.45	22(16%)	32(24%)	0.15
Progression to microalbuminuria	20 (10%)	31 (12%)	0.68	22 (11%)	31 (12%)	1.03 [0.50, 2.13], p=0.93	17(13%)	13(10%)	0.56
Progression to macroalbuminuria	12 (6%)	18 (7%)	0.75	11 (6%)	22 (8%)	1.63 [0.67, 3.95], p=0.28	7 (5%)	12 (9%)	0.30
≥30% decrease in the eGFR	26 (13%)	21 (8%)	0.06	22 (11%)	23 (9%)	0.78 [0.39, 1.59], p=0.50	17(13%)	13(10%)	0.56
b) Changes in eGFR									
Change rate in the eGFR (%)	-10.8±20.5	-6.6±21.3	0.03	-10.4±19.3	-7.5±22.3	2.9 [-1.3, 7.2], p=0.18	-9.5±20.4	-6.5±23.6	0.28
Annual changes in the eGFR (mL/min/1.73 m^2/year)	-1.9±3.7	-1.7±4.2	0.54	-2.2±4.1	-1.7±4.0	0.5 [-0.4, 1.4], p=0.25	-2.0±4.0	-1.4±4.1	0.22
c) Changes in LnACR	-0.05±1.56	0.07±1.61	0.41	-0.10±1.51	0.16±1.60	0.26 [-0.05, 0.57], p=0.10	-0.11±1.39	0.21±1.59	0.10
Clinical characteristics after combination treatment									
eGFR (mL/min/1.73 m^2)	67.1±25.5	71.2±25.2	0.08	69.3±25.1	70.6±25.9	1.3 [-4.0, 6.6], p=62	67.2±25.3	71.4±28.5	0.20
LnACR	3.86±1.84	3.85±1.93	0.98	3.71±1.79	4.01±2.00	0.31 [-0.07, 0.70], p=0.11	3.75±.78	3.99±1.92	0.27
BW (kg)	74.0±16.5	75.5±18.0	0.35	73.1±16.6	74.7±17.7	1.6 [-1.8, 5.0], p=0.36	73.9±17.5	75.1±16.9	0.56
SBP (mmHg)	128.4±16.2	128.9±15.7	0.75	127.3±17.1	129.5±16.1	2.2 [-1.4, 5.8], p=0.24	128.4±16.8	129.9±17.3	0.45
DBP (mmHg)	73.4±11.7	74.9±3.1	0.21	72.7±12.4	74.6±13.0	1.8 [-0.9, 4.5], p=0.18	73.4±11.9	74.5±14.1	0.52
MAP (mmHg)	91.7±11.7	92.9±12.2	0.31	90.9±12.5	92.9±12.0	2.0 [-0.7, 4.6], p=0.15	91.8±2.1	93.0±13.2	0.44
HbA_{1c} (mmol/mol [%])	62.6±14.8 (7.9±1.4)	62.6±16.6 (7.9±1.5)	0.99	61.5±14.0 (7.8±1.3)	63.4±7.1 (7.8±1.6)	1.9 [-1.3, 5.1] (0.2 [-0.1, 0.5]), p=0.25	60.9±14.2 (7.7±1.3)	64.1±18.6 (8.0±1.7)	0.08
Change in the clinical findings									
Change in BW (kg)	-4.9±5.9	-3.5±6.7	0.02	-4.8±5.4	-3.4±6.8	1.4 [0.2, 2.5], p=0.03	-4.7±5.3	-3.9±7.1	0.24
Change in SBP (mmHg)	-4.1±20.7	-6.5±1.2	0.23	-5.3±20.5	-4.7±21.9	0.5 [-3.9, 5.0], p=0.81	-5.6±21.8	-4.2±21.2	0.58
Change in DBP (mmHg)	-3.3±13.1	-3.5±13.8	0.91	-3.9±13.2	-3.0±13.8	0.9 [-1.9, 3.7], p=0.52	-3.7±13.1	-3.3±13.8	0.76
Change in MAP (mmHg)	-3.6±14.3	-4.5±14.5	0.51	-4.3±14.3	-3.5±14.7	0.8 [-2.3, 3.9], p=0.61	-4.3±14.6	-3.6±14.8	0.65
Change in HbA_{1c} (mmol/mol [%])	-11.0±20.9 (-1.0±1.9)	-7.5±21.2 (0.7±1.9)	0.08	-11.1±20.7 (-1.0±1.9)	-9.0±21.6 (-0.8±2.0)	2.2 [-2.2, 6.5] (0.2 [-0.2, 0.6]), p=0.33	-12.2±21.2 (-1.1±1.9)	-8.1±23.3 (-0.7±2.1)	0.11

Values are mean ± SD, n/total n (%), or the difference [95% CI], and P-value.

*P-values by chi-square test or unpaired t-test

†Calculated number of subjects after weighting

#Data present as OR for SGLT2i-preceding group compared to GLP-1Ra preceding group, the difference [95% CI] and P-value analyzed by GLM.

**P-values by McNemar test, or paired t-test

Abbreviations: ATE, average treatment effect; BW, body weight; DBP, diastolic blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration; GLM, generalized linear model; GLP1Ra, glucagon-like peptide 1 receptor agonists; HbA_{1c}, glycated hemoglobin A_{1c}; IPW, inverse provability weighting; LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; OR, odds ratio; PS, propensity score; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter inhibitor.

Table 3 Clinical baseline characteristics on the analysis of comparison between liraglutide and dulaglutide

	Unadjusted			PS-IPW model (by stabilized ATE with trimming)			PS-matched model		
	Dulaglutide, n=246	Liraglutide, n=214	p-value*	Dulaglutide, n=240†	Liraglutide, n=207†	Standardized difference	Dulaglutide, n=118	Liraglutide, n=118	Standardized difference
Age (years)	59.0±13.2	56.7±12.6	0.06	57.7±13.7	57.9±12.3	0.02	58.4±12.8	57.6±12.6	0.06
Sex (female [%])	112 (46%)	81 (38%)	0.10*	96 (40%)	92 (44%)	0.09	48 (41%)	47 (40%)	0.02
A history of DM >10 years (%)	192 (78%)	171 (80%)	0.39*	188 (78%)	164 (80%)	0.02	91 (77%)	88 (75%)	0.06
BW (kg)	76.9±18.5	79.8±17.6	0.08	78.0±18.5	78.9±17.8	0.05	78.7±18.3	78.1±17.0	0.03
BMI	28.9±5.7	29.2±5.0	0.52	28.9±5.3	29.3±5.2	0.08	29.2±5.8	28.8±4.7	0.07
SBP (mmHg)	132.3±20.0	130.8±17.5	0.37	131.7±18.1	132.3±17.3	0.03	132.0±20.1	131.9±17.0	0.01
DBP (mmHg)	76.2±13.4	76.8±2.5	0.67	77.1±12.8	77.7±12.9	0.05	77.2±13.5	76.5±12.1	0.06
MAP (mmHg)	94.9±13.5	94.8±12.8	0.88	95.3±12.7	95.9±13.1	0.05	95.4±14.0	95.0±12.3	0.03
HbA_{1c} (mmol/mol [%])	70.2±14.9 (8.6±1.4)	71.8±18.8 (8.6±1.7)	0.30	71.4±16.2 (8.7±1.5)	72.5±21.1 (8.8±1.9)	0.06	73.1±16.8 (8.8±1.5)	72.7±18.0 (8.8±1.6)	0.02
eGFR (mL/min/1.73 m^2)	73.2±26.4	75.1±25.9	0.44	75.0±28.2	75.2±30.9	0.01	75.2±26.2	76.4±26.7	0.05
ACR (mg/gCr)	39.3 [13.6, 151.6]	30.5 [9.9, 184.5]		32.2 [13.2, 140.1]	41.0 [13.6, 245.5]		34.8 [13.8, 104.0]	30.1 [11.8, 167.8]	
LnACR	3.79±2.03	3.85±1.97	0.75	3.77±1.87	3.94±2.19	0.09	3.74±1.93	3.81±2.04	0.04
AST (IU/L)	28.3±18.1	27.9±15.9	0.80	28.8±17.7	28.6±18.2	0.01	29.4±18.5	28.6±16.9	0.05
ALT (IU/L)	33.8±25.2	36.0±28.2	0.38	36.2±28.7	35.1±26.6	0.04	36.3±28.6	36.0±26.1	0.01
FIB-4 index	1.36±0.85	1.30±0.78	0.41	1.35±0.89	1.41±1.00	0.06	1.41±0.90	1.34±0.85	0.09
Duration of the preceding treatment (months)	23.4±14.2	28.2±19.4	0.002	25.1±21.4	26.7±17.1	0.08	21.4±15.4	24.3±16.2	0.18
Duration of the combination treatment (months)	28.3±12.8	33.9±17.0	<0.001	29.9±13.7	29.0±16.2	0.06	30.8±13.4	27.9±13.9	0.21
Total duration of the study (months)	51.7±16.2	62.1±24.1	<0.001	55.0±21.8	55.8±21.6	0.04	52.2±17.4	52.1±18.1	0.01
Preceding drug (SGLT2i)	180 (73%)	86 (40%)	<0.001	137 (57%)	122 (59%)	0.04	72 (61%)	74 (63%)	0.04
Concomitant medications									
Sulphonylurea	74 (30%)	39 (18%)	0.003*	58 (24%)	43 (21%)	0.08	21 (18%)	22 (19%)	0.02
Metformin	154 (63%)	109 (51%)	0.01*	128 (53%)	117 (57%)	0.06	71 (60%)	59 (50%)	0.21
Insulin	74 (30%)	131 (61%)	<0.001*	109 (46%)	96 (46%)	0.02	65 (55%)	66 (56%)	0.02
Pioglitazone	32 (13%)	22 (10%)	0.37*	26 (11%)	27 (13%)	0.07	13 (11%)	12 (10%)	0.03
αGI	37 (15%)	32 (15%)	0.98*	34 (14%)	32 (16%)	0.04	17 (14%)	20 (17%)	0.07
Glinide	12 (5%)	14 (7%)	0.44*	15 (6%)	12 (6%)	0.02	7 (6%)	8 (7%)	0.04
RAS inhibitor	131 (53%)	100 (47%)	0.16*	123 (52%)	109 (53%)	0.03	61 (52%)	56 (48%)	0.09
CCB	109 (44%)	81 (38%)	0.16*	95 (40%)	91 (44%)	0.09	51 (43%)	43 (36%)	0.14
β blocker	38 (15%)	35 (18%)	0.79*	44 (19%)	37 (18%)	0.01	21 (18%)	20 (17%)	0.02
MRB	9 (4%)	15 (7%)	0.11*	15 (6%)	12 (6%)	0.02	6 (5%)	10 (9%)	0.14
Thiazide	16 (7%)	15 (7%)	0.83*	21 (9%)	15 (7%)	0.06	8 (7%)	9 (8%)	0.03
Loop	9 (4%)	16 (7%)	0.07*	18 (8%)	18 (9%)	0.04	8 (7%)	10 (9%)	0.06
Statin	136 (55%)	113 (53%)	0.59*	141 (59%)	115 (56%)	0.06	64 (54%)	69 (59%)	0.09

Values are mean ± SD, n/total n (%), or median [lower quantile, upper quantile].

*P-values by unpaired t-test or chi-square test.

†Calculated number of subjects after weighting

Abbreviations: αGI, alpha-glucosidase inhibitor; ATE, average treatment effect; BMI, body mass index; BW, body weight; DBP, diastolic blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration; GLP1, glucagon-like peptide 1; HbA_{1c}, glycated hemoglobin A_{1c}; IPW, inverse provability weighting; LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; MRB, mineral corticoid receptor blocker; PS, propensity score; RAS, renin-angiotensin system; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter inhibitor; T2D, type 2 diabetes.

not be diminished. As shown in the right column of Table 4, no significant differences were observed in the renal composite outcomes between the two groups; however, a larger decrease in LnACR was observed in the liraglutide group than in the dulaglutide group (p = 0.03), which was consistent with the results of the PS-IPW model.

DISCUSSION

In this post-hoc analysis, we investigated whether dulaglutide or liraglutide affects renal outcomes as a preceding drug in combination with SGLT2i. In both PS-IPW and PS matching, renal outcomes did not differ significantly between the GLP1Ra (dulaglutide or liraglutide)-preceding group and SGLT2i-preceding group. Importantly, we demonstrated for the first time that the incidence of a ≥ 30% eGFR decline was more frequent in the liraglutide group than in the dulaglutide group, with an OR of 2.63 (95% CI: 1.07–6.45, p = 0.04), while a significantly larger decrease in LnACR (OR: 0.44, 95% CI: 0.04–0.85, p = 0.03) was observed in the liraglutide group than in the dulaglutide group. Both SGLT2i and GLP1Ra have been shown to exert renoprotective effects through different mechanisms.

Table 4 Renal outcomes and clinical characteristics after combination treatment on the analysis of comparison between liraglutide and dulaglutide

	Unadjusted			PS-IPW model (by stabilized ATE with trimming)			PS-matched model		
	Dulaglutide, n=246	Liraglutide, n=214	p-value*	Dulaglutide, n=240†	Liraglutide, n=207†	GLM#	Dulaglutide, n=118	Liraglutide, n=118	p-value**
Renal outcomes and function									
a) Incidence of renal composite outcome	60 (28%)	59 (24%)	0.43	61 (25%)	58 (28%)	1.16 [0.61, 2.23], p=0.65	26 (22%)	31 (26%)	0.51
Progression of ACR status	46 (19%)	35 (16%)	0.49	49 (20%)	35 (17%)	0.78 [0.37, 1.65], p=0.52	21 (18%)	20 (17%)	0.73
Progression to microalbuminuria	30 (12%)	21 (10%)	0.51	31 (13%)	21 (10%)	0.73 [0.31, 1.77], p=0.49	12 (17%)	15 (13%)	0.57
Progression to macroalbuminuria	17 (7%)	13 (6%)	0.70	18 (8%)	14 (7%)	0.45 [0.30, 2.85], p=0.89	9 (8%)	6 (5%)	0.47
≥30% decrease in the eGFR	17 (7%)	30 (14%)	0.01	14 (6%)	29 (14%)	2.63 [1.07, 6.45], p=0.04	7 (6%)	13 (11%)	0.11
b) Changes in the eGFR									
Change rate in the eGFR (%)	-7.2±20.1	-9.7±22.2	0.20	-8.3±19.7	-10.1±24.3	-1.7 [-7.9, 4.4], p=0.59	-8.7±18.7	-8.8±22.0	0.96
Annual changes in the eGFR (mL/min/1.73 m^2/year)	-1.7±3.8	-1.8±4.1	0.84	-1.8±3.6	-2.2±4.8	-0.4 [-1.5, 0.78], p=0.54	-2.0±3.9	-2.1±4.7	0.81
c) Changes in the LnACR	0.17±1.65	-0.16±1.57	0.03	0.21±1.78	-0.24±1.77	-0.44 [-0.85, -0.04], p=0.03	0.18±1.60	-0.28±1.55	0.03
Clinical characteristics after combination treatment									
eGFR (mL/min/1.73 m^2)	68.8±25.1	70.1± 25.7	0.60	70.2±25.8	70.1±28.9	-0.1[-7.5, 7.4] , p=0.99	70.5±24.8	71.2±24.9	0.84
LnACR	3.74±1.88	3.96±1.92	0.22	3.92±1.97	3.85±.98	-0.07[-0.54, 4.21], p=0.78	3.83±1.85	3.72±1.85	0.68
BW (kg)	75.7±18.1	74.1±16.5	0.32	17.0±18.4	75.6±17.6	0.6{-3.8, 5.0}, p=0.79	75.3±18.0	74.9±16.4	0.86
SBP (mmHg)	127.6±15.9	129.6±15.9	0.19	130.5±16.7	128.8±70.6	-1.7[-6.1, 2.7], p=0.45	130.0±16.2	127.6±16.6	0.27
DBP (mmHg)	74.4±13.1	74.1±12.0	0.78	74.2±13.6	74.4±14.3	0.2[-3.6, 3.9], p=0.93	74.4±2.3	74.3±12.6	0.96
MAP (mmHg)	92.2±12.1	92.6±11.8	0.70	93.0±12.9	92.5±14.1	-0.5[-4.1, 3.2],p=0.81	92.9±12.0	92.1±2.5	0.59
HbA_{1c} (mmol/mol [%])	63.8±14.8 (8.0±1.4)	61.4±16.9 (7.8±1.6)	0.11	61.8±14.2 (7.8±1.3)	62.9±18.2 (7.9±1.7)	1.1[-2.6, 4.7], p=0.57 (0.1[-0.2,0.4])	62.4±15.3 (7.9±1.4)	62.9±17.4 (7.9±1.6)	0.84
Changes in the clinical findings									
Change in BW (kg)	-3.6±6.4	-4.7±6.4	0.05	-3.6±6.6	-4.3±6.2	-0.6 [-2.0, 0.8], p=0.38	-3.8±6.6	-4.2±6.1	0.67
Change in SBP (mmHg)	-5.4±22.2	-5.5±19.8	0.99	-3.3±21.9	-6.5±22.8	-3.2 [-8.7, 2.4], p=0.26	-3.9±23.3	-8.0±19.2	0.14
Change in DBP (mmHg)	-3.0±13.6	-4.0±13.5	0.43	-3.5±13.9	-5.5±16.0	-2.0 [-6.0, 2.0], p=0.32	-3.0±13.1	-4.6±13.7	0.32
Change in MAP (mmHg)	-3.8±14.5	-4.5±14.3	0.61	-3.4±14.6	-5.8±17.1	-2.4 [-6.5, 1.8], p=0.26	-3.3±14.7	-5.7±14.2	0.17
Change in HbA_{1c} (mmol/mol [%])	-9.5±18.8 (-0.9±1.7)	-8.3±23.6 (-0.8±2.2)	0.55	-10.2±17.9 (-0.9±1.6)	-10.3±26.5 (-0.9±2.4)	-0.1 [-6.0, 5.8] (-0.01 [-0.5, 0.5]), p=0.98	-11.6±19.5 (-1.1±1.8)	-10.6±24.3 (-1.0±2.2)	0.72

Values are mean ± SD, n/total n (%), or the difference [95% CI], and P-value.

*P-values by chi-square test or unpaired t-test

†Calculated number of subjects after weighting

#Data present as OR for liraglutide group compared to dulaglutide group, the difference [95% CI] and P-value analyzed by GLM.

**P-values by McNemar test, or paired t-test

Abbreviations: ATE, average treatment effect; BW, body weight; DBP, diastolic blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration; GLM, generalized linear model; GLP1Ra, glucagon-like peptide 1 receptor agonists; HbA1c, glycated hemoglobin A1c; IPW, inverse provability weighting; LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; OR, odds ratio; PS, propensity score; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter inhibitor.

SGLT2i have been shown to improve hyperfiltration and oxygen supply in the kidney, and increase ketone bodies, all of which contribute to renoprotection [11–13]. In contrast, GLP1Ra promotes natriuresis and decreases inflammation and oxidative stress [14]. Therefore, combination therapy with SGLT2i and GLP1Ra, which aims to provide renal protection from multiple perspectives, is an ideal approach. Neuen *et al.* reported a study to estimate the effects of combination therapy with GLP1Ra, SGLT2i, and finerenone on cardiovascular, kidney, and mortality outcomes [15]. They demonstrated that the combination of GLP1Ra, SGLT2i, and finerenone was associated with a reduced risk (HR: 0.65, 95% CI: 0.55–0.76) of major adverse cardiovascular events (MACE: nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) and CKD progression (defined as doubling of serum creatinine, kidney failure, or death resulting from kidney failure: HR: 0.42, 95% CI: 0.31–0.56) relative to conventional therapy [15]. They also demonstrated that the combination of GLP1Ra and SGLT2i could reduce the risk of MACE and CKD progression relative to monotherapy with GLP1Ra or SGLT2i [15]. An observational study reported that combination therapy with GLP1Ra and SGLT2i reduced the incidence of cardiovascular events relative to GLP1Ra or SGLT2i use alone (HR: 0.154, 95% CI: 0.038–0.622, p = 0.009 vs. GLP1Ra and HR: 0.170, 95% CI: 0.046–0.633, p = 0.008 vs. SGLT2i) [16]. Therefore, a combination therapy with GLP1Ra and SGLT2i is expected to be beneficial. In our analysis, a significant BW reduction was observed in the GLP1Ra (dulaglutide or liraglutide)-preceding group compared to the SGLT2i-preceding group. The drug that should be started first may be determined based on the priorities of each individual case.

The strength of this study is the direct comparison of the effects of dulaglutide and liraglutide in combination with SGLT2i on renal outcomes. We did not observe any marked differences in the renal composite outcomes between dulaglutide and liraglutide. However, liraglutide showed more potent albuminuria-lowering effects than dulaglutide but also a more frequent incidence of a ≥ 30% eGFR decline. The reason for these observations remains unclear. In LEADER, liraglutide was shown to reduce albuminuria but not slow the

eGFR slope compared to placebo among T2D patients with an eGFR ≥ 60 mL/min/1.73 m^2 [17]. In contrast, dulaglutide was shown to reduce kidney function-related outcomes (≥ 40% sustained eGFR decline, ESKD, or renal-related death) [18]. Interestingly, liraglutide has been shown to slow the eGFR slope compared to placebo in T2D patients with eGFR < 60 mL/min/1.73 m^2 [17]. These observations suggest that the effects of dulaglutide and liraglutide on albuminuria and eGFR decline may differ. In our study, the baseline eGFR (mL/min/1.73 m^2) of participants was 76.0 ± 26.4 (dulaglutide or liraglutide-preceding group) and 77.7 ± 26.1 (SGLT2i-preceding group) (Table 1). We suspect that the background of the participants may have affected the results.

Our study has several limitations. First, semaglutide was not included because it was not clinically available during the target period of the RECAP study. Semaglutide was shown to slow the eGFR decline relative to placebo in a post hoc analysis of SUSTAIN-6 and PIONEER-6 [19]. More recently, FLOW demonstrated that semaglutide use is associated with reduced composite renal outcomes in patients with T2D and CKD [20]. In FLOW, 3,533 T2D individuals with CKD were enrolled in the study. The primary composite outcome consisted of kidney failure (dialysis, transplantation, or eGFR < 15 mL/min/1.73 m^2), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes. After a median follow-up period of 3.4 years, the semaglutide group showed a 24% reduction in the risk of a primary composite outcome relative to the placebo group (HR 0.76, 95% CI: 0.66−0.88, p = 0.0003) [20]. In the FLOW trial, participants were stratified according to the use or non-use of SGLT2i and randomized to receive semaglutide or placebo to investigate the efficacy of combining SGLT2i [21]. In this analysis, the benefit of semaglutide on primary composite outcomes was observed with or without the use of SGLT2i [21]. This does not indicate that semaglutide and SGLT2i combination therapy has no additive effects because participants using SGLT2i at baseline and those in whom SGLT2i was initiated during the study showed reduced risk reduction (HR 0.70, 95% CI: 0.59−0.82) in the primary outcomes [21]. If semaglutides were included in the analysis in our study, the results may have been different. Second, the dose of dulaglutide in this study was 0.75 mg, which was lower than that used in REWIND (1.5 mg). The possibility that differences in dosage may have influenced the results cannot be ruled out. Third, participants treated with exendin based-GLP1Ra were not analyzed because of the small number of participants.

In conclusion, in an analysis limited to dulaglutide or liraglutide users, renal outcomes did not differ markedly between the preceding drugs in combination therapy with SGLT2i. Dulaglutide and liraglutide showed different effects on albuminuria and eGFR decline. Further studies including semaglutide are required to fully understand the effect of combination therapy with SGLT2i and GLP1Ra on renal outcomes.

DATA AVAILABILITY

Data are available from the Tokai University Data Access/Institutional Review Board for Clinical Research for investigators, bound by confidential agreements. Contact details: Masao Toyoda MD, PhD, Division of Nephrology, Endocrinology, and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan (e-mail: m-toyoda@tokai.ac.jp).

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DISCLOSURE

The authors declare no conflicts of interest in association with the present study.

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