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Original Article

Renoprotective Effects of Combination Treatment with Sodium-glucose Cotransporter Inhibitors and GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus According to Preceding Medication

RECAP study group

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Abstract

Aims: Combination therapy with sodium-glucose cotransporter inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP1Ras) is now of interest in clinical practice for type 2 diabetes mellitus (T2DM) management. The present study evaluated the effects of the preceding drug type on the renal outcome in clinical practice.

Methods: We retrospectively extracted T2DM patients who had received both SGLT2i and GLP1Ra treatment for at least 1 year at 18 medical facilities in Japan. A total of 331 patients in the GLP1Ra-preceding group and 312 patients in the SGLT2i-preceding group were ultimately analyzed. The multiple imputation method and the analysis using propensity score was performed for the comparison of the renal composite outcome.

Results: The incidences of the renal composite outcome in the SGLT2i- and GLP1Ra-preceding groups was 28% and 25%, respectively, with an odds ratio (OR) [95%CI] of 1.14 [0.75, 1.73] (P=0.54). Compared to the GLP1Ra-preceding group, the annual change in the eGFR as well as the change in the logarithmic value of the urine albumin-to-creatinine ratio of patients in the SGLT2i-precedig group were 0.3 mL/min/1.73 m2/year [-0.3,1.0, p=0.35], and 0.20 [-0.06, 0.47, p=0.14], respectively.

Conclusion: With combination therapy of SGLT2i and GLP1Ra, the preceding drug might not affect the renal outcome.

Keywords: sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonist, renal outcome, combination treatment, preceding drug

1 | Introduction

A cardiovascular outcome trial (CVOT) using new types of hypoglycemic agents was requested by the United States Food and Drug Administration (FDA) after a significant increase in myocardial infarction was observed in patients using rosiglitazone [1]. Several CVOTs using sodium-glucose cotransporter inhibitors (SGLT2is) demonstrated significant superiority to placebo with regard to not only cardiovascular outcomes [2-4] but also renal outcomes [2-5]. Furthermore, dapagliflozin and empagliflozin showed superiority to placebo with regard to renal outcomes in patients with chronic kidney disease (CKD) with or without diabetes mellitus (DM) [6] [7]. The FDA approved the use of dapagliflozin for treating CKD (FDA news release April 30, 2021). Based on such robust evidence concerning SGLT2is, their use is now increasing in clinical practice. Glucagon-like peptide-1 receptor agonist (GLP1Ra) is another incretin-related hypoglycemic agent, and its superiority to placebo with regard to cardiovascular outcomes was also reported by CVOTs [8-11]. However, the efficacy of SLGT2is with regard to renal outcomes is limited to CVOTs evaluating GLP1Ra [8, 12]. Based on these previous findings, the executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommended metformin and an SGLT2i as first-line treatment for patients with type 2 DM and CKD [13] and GLP1Ra as additional combination therapy for patients who failed to achieve glycemic control despite using metformin and an SGLT2i or who were unable to use these drugs or required the promotion of intentional weight loss.

SGLT2i treatment has shown superiority to GLP1Ra with regard to its renoprotective effects, especially concerning the annual estimated glomerular filtration rate (eGFR) slope, in clinical practice in Kanagawa Prefecture, Japan [14]. Furthermore, in our retrospective long-term observational study of GLP1Ra-treated patients in clinical practice, an SGLT2i was administered to 52% of patients as a concomitant drug, and a renoprotective effect was

observed only in GLP1Ra-treated patient with the concomitant use of SGLT2i (Under submission). Detailed data, such as the duration of combination therapy, were not collected in our previous study, and answers to clinical questions, such as which treatment should be performed first, have not yet been obtained. In addition, real-world studies targeting combination therapy are limited, and evidence showing a further benefit with combination treatment using an SGLT2i and GLP1Ra is insufficient at present.

The present study therefore explored the influence of GLP1Ra on the renal function in Japanese patients with type 2 DM (T2DM) and evaluated the renal effects of concomitant treatment with an SGLT2i on GLP1Ra-treated patients. In particular, both drugs are relatively expensive, so even if combination therapy does indeed have some benefit for DM management, which drug should be administered first is a clinically important and urgent concern. The aim of this study was to evaluate the renoprotective effects of combination treatment with SGLT2is and GLP-1Ra in patients with T2DM according to their preceding medication (RECAP study).

2 | Materials and Methods

2.1 | Study subjects and data collection

We conducted separate retrospective surveys of patients with T2DM using SGLT2is and GLP1Ra. A schematic of the study design is provided in Supplementary Figure S1. The survey subjects were patients who visited the clinics or hospitals of our research members, as described in Supplementary Table 1, from April 2010 to December 2021.

The inclusion criteria were patients with T2DM who were (i) treated with both an SGLT2i and GLP1Ra from April 2010 to December 2021 and for whom (ii) the period of the preceding medication was ≥6 months, (iii) the period of concomitant medication was ≥12 months, and (iv) clinical data at baseline, the time of addition, and the final observation time were available, including the age*, gender*, height, body weight [BW], systolic blood pressure [SBP], diastolic blood pressure [DBP], eGFR, glycated hemoglobin A_{1c} (HbA_{1c}) level, results of urinary tests (urine albumin-to-creatinine ratio [ACR] [mg/g Cr] or qualitative proteinuria), aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and concomitant medications* (hypoglycemic drugs, antihypertensive drugs, statins) (where "*" indicates essential data). The eGFR was calculated using the following formula: eGFR (mL/min/1.73 m^2) = 194 × $age^{-0.287}$ × $serum\ creatinine^{-1.094}$ × (0.739 for women) [15]. Qualitative proteinuria values were converted to albuminuria values using the formula reported by Sumida et al. [16]. The exclusion criteria were as follows: (i) type 1 diabetes mellitus; (ii) requirement for chronic dialysis; (iii) severe liver dysfunction (e.g. liver cirrhosis or severe infection), (iv) terminal-stage malignancy, (v) pregnancy, (vi) patients who discontinued treatment, and (vii) patients who opted out during the study.

A schematic depiction of the study participants and the dataset analyzed in this study is shown in Supplementary Figure S2. Eighteen medical facilities participated in this study, and the data of 688 patients were collected. Based on these criteria, 45 patients were excluded, and

the 643 remaining patients (312 with preceding treatment with an SGLT2i [SGLT2i-preceding group] and 331 with preceding treatment with GLP1Ra [GLP1Ra-preceding group]) were analyzed as the full analysis set (FAS). In the FAS, 225 patients lacked essential clinical data or data on ACR or proteinuria, and after excluding these patients, the remaining 418 patients (227 in the SGLT2i-preceding group and 191 in the GLP1Ra-preceding group) were analyzed as the complete case analysis set (CCA).

The median treatment duration was 23 (range, 6-114) months for preceding treatment with either an SGLT2i or GLP1Ra, 31 (range, 12-85) months for combination treatment, and 59 (range, 19-134) months total.

2.2 | BP measurements at the office

The methods used for BP measurements were described in our previous report [17]. BP measurements in the office were performed at each institution using their own validated cuff oscillometric devices. According to the JSH 2014 guidelines [18] (11), BP in the office was measured in a quiet environment after resting for a few minutes in the seated position on a chair with the legs not crossed. When two consecutive measurements were taken 1-2 min apart, the average of the two measurements was defined as BP in the office.

2.3 | Outcomes

Either progression of the ACR status and/or a ≥30% decrease in the eGFR was set as the primary renal composite outcome. The change in the logarithmic value of the ACR (ΔLnACR) and the annual change in the eGFR (annualΔeGFR) were also evaluated in this study.

2.4 | Statistical analyses

Data that showed a normal distribution were presented as the mean±standard deviation (SD),

while those that showed a skewed distribution were reported as the median [25th percentile, 75th percentile]. The IBM SPSS Statistics 25.0 software program (IBM Inc., Armonk, NY, USA) was used for the statistical analyses, and a p-value <0.05 was considered significant.

2.4.1| The missing value analysis

Missing data for covariates and un-adjusted confounding factors are a major concern when conducting analyses of observational and retrospective studies, as such studies often include missing data for covariates. When a complete case analysis is performed (listwise deletion), selection bias may influence the result, and the statistical power may deteriorate. To account for missing data values, we planned to use multiple imputation (MI) as a statistical strategy [19]. MI is a procedure used to replace missing values with other plausible values by creating multiple filling-in patterns to avert bias caused by missing data. It is also recognized as an alternative approach to analyzing incomplete data [20]. In the present study, we replaced each missing value with a set of substituted plausible values by creating 100 filled-in complete datasets using the MI by chained equations method [21] [22] [23].

The breakdown of the missing data in this study is shown in Supplementary Figure S3. Covariates with a missing rate ≤25% are preferable for MI [21]. The maximum missing rates were 22.2% for the ACR at baseline, and the missing rates for other covariates were <7%.

In the imputation process, the following covariates were used to create 100 complete datasets: age, sex, height, BW, SBP, DBP, HbA_{1c}, eGFR, LnACR, types of SGLT2is and GLP1Ras used, use of the concomitant medications (hypoglycemic drugs, antihypertensive drugs and statins, and duration of treatment with either or both an SGLT2i or GLP1Ra). The clinical data not only at baseline but also at the addition and after combination that correlated with that outcome were used for MI [24].

2.4.2| The propensity score analysis using inverse probability weighting (IPW)

Compared to a randomized control trial (RCT), an observational retrospective study requires adjusting for confounding factors that can influence the results. An analysis using a propensity score (PS) is useful for minimizing the influence of the confounding factors collected in the study.

In each dataset built by MI, the PS for the GLP1Ra-preceding group was calculated by a logistic analysis using the following covariates; age, gender, height, BW, BMI, SBP, DBP, HbA_{1c}, eGFR, LnACR at baseline, history of DM, use of concomitant medications at baseline (hypoglycemic drugs, antihypertensive drugs, and statins), and durations of treatment with the preceding drug as well as combination treatment.

The IPW method using PS was applied to analyze the primary outcome. With the IPW method, three weighting methods—average treatment effect (ATE) weighting, average treatment effect on the treated (ATT) weighting, and stabilized ATE weighting (the formulae for calculating each weight are shown in Supplementary Figure S4)—and two methods of adjusting the weight to avoid extreme weighting—truncation (weighting values beyond the 99th percentile are truncated) and trimming (patients with 0.05>PS or PS>0.95 are excluded from further analyses)—are considered. Of these six models available for use with the IPW method, we selected the model with the lowest standardized differences of the covariates, which meant that the model was well balanced. The other five models were evaluated for a sensitivity analysis for the renal outcome.

In each dataset built by MI, the comparison between two groups was performed using the generalized linear model. The estimated effects in each of the imputed datasets were averaged together to give the overall estimated effect calculated using Rubin's rules [19], with these estimated effects taking into account the variability in results between imputed datasets and reflecting the uncertainty associated with the missing data [25]

2.4.3| The sensitivity analysis

PS matching and stratification were also performed as a sensitivity analysis for the renal outcome. Furthermore, the analysis using the CCA was also performed as the sensitivity analysis via the same method as with the FAS described above.

- PS matching;

Because the PS for each patient was calculated with each dataset built by MI, the average PS was used as the representative value. PS matching was performed using these representative PS values with the following algorithm: 1:1 nearest neighbor match with a caliper value of 0.047, calculated as 0.2-fold of the SD of PS [26] with no replacement. The comparison between two groups for the clinical characteristics was performed using an unpaired *t*-test for the parametric variables, the Mann-Whitney rank-sum test for non-parametric variables, and the chi-square test for the categorical data in the unmatched cohort model. The paired *t*-test for parametric variables, Wilcoxon's signed-rank test for non-parametric variables, and McNemar's test for categorical data were used in the PS-matched cohort model. The odds ratios [ORs] for the renal outcome were calculated using a Cox regression analysis.

- PS stratification

To ensure the robustness of the results, an analysis by PS stratification was also performed. All patients were stratified into PS quintiles, and the Mantel-Haenszel method was performed to calculate the OR and 95% confidence interval (CI).

2.4.4| Multivariable logistic regression analysis for the renal composite outcome

A multivariable logistic regression analysis to evaluate independent predictors of the renal composite outcome associated with potential predictors was performed on the CCA. This analysis included the following clinical parameters as covariates: gender, the history of T2DM,

the types of GLP1Ras and SGLT2is, age, BW, MAP, HbA_{1c}, eGFR, and LnACR at baseline as well as concomitant medications (anti-hypertensive drugs, hypoglycemic drugs, and statins), ΔBW, ΔHbA_{1c}, ΔMAP, and the durations of treatment with the preceding SGLT2i or GLP1Ra and combination treatment thereof.

This study was approved by the Institutional Review Board for Clinical Research, Tokai University, Japan (approval on December 6, 2021).

3 | Results

3.1| PS-IPW model in the FAS with MI

The clinical characteristics at baseline in the FAS (n=643) are shown in the left column in Table 1. At the time of the final observation, the types of SGLT2is and GLP1Ras that were administered in this study were ipragliflozin (n=67, 10%), dapagliflozin (n=158, 25%), tofogliflozin (n=69, 11%), luseogliflozin (n=32, 5%), canagliflozin (n=67, 10%), and empaglifozin (n=147, 23%) for SGLT2i, and liraglutide (n=214, 33%), dulaglutide (n=246, 38%), lixisenatide (n=9, 1%), and exenatide (8, 1%) for GLP1Ra. The number of patients who changed drug types was 103 (16%) for SGLT2is and 166 (26%) for GLP1Ras.

The standardized differences among the clinical baseline characteristics and the concomitant drugs depending on the type of weighting model employed are shown in Supplementary Figure S5. The median values and ranges of the standardized differences obtained when applying ATE weighting with truncation of values >99th percentiles, ATT weighting with truncation of values >99th percentiles, stabilized ATE weighting with truncation of values >99th percentiles, ATE weighting with PS-based trimming (trimming by $0.05 \leq PS \leq 0.95$), ATT weighting with PS-based trimming, and stabilized ATE weighting with PS-based trimming were 0.025 (<0.001–0.16), 0.030 (<0.001–0.12), 0.030 (<0.001–0.13), 0.020 (<0.001–0.08), 0.035 (<0.001–0.13), and 0.020 (<0.001–0.08), respectively. Based on this analysis of the standardized differences using six models, the model using stabilized ATE weighting with PS-based trimming was used for the primary analysis of the renal outcome in this study.

The middle column in Table 1 shows the clinical characteristics at baseline in PS-IPW using the stabilized ATE weighting model. Table 2 shows the main results of this study, and the middle column of Table 2 shows the results of the PS-IPW method analysis with stabilized ATE weighting with PS-based trimming based on the generalized linear model. During the

observation period, the incidences of the renal composite outcome in the SGLT2i- and GLP1Ra-preceding groups were 28% and 25%, respectively, with the OR [95% CI] being 1.14 [0.75, 1.73] (P=0.54). The ORs for a ≥30% decrease in the eGFR and the progression of the albuminuria stage were 0.83 [0.46, 1.49] (P=0.53) and 1.26 [0.78, 2.05] (p=0.35), respectively. Regarding the change in the clinical findings after the combination treatment, the decrease in the BW in the GLP1Ra-preceding group was significantly larger than that in the SGLT2i-preceding group by 1.9 kg [95% CI, 0.5, 3.2] (p=0.006); however, the change in the SBP, DBP, MAP, and HbA_{1c} did not show a significant difference between the groups.

3.2| Sensitivity analyses

- PS matching model in the FAS with MI

The clinical characteristics and the concomitant drugs at baseline in the PS matching model that included 203 patients in each group are shown in the left column of Table 1. The range of the standardized differences of the covariates was 0.0-0.12, so the PS-matched model was thought to be well-balanced between the groups. The renal outcomes in the PS matching model are shown in the left column of Table 2. The renal composite outcome, including the progression of the albuminuria status and a ≥30% decrease in the eGFR, showed no significant difference between the two groups. Regarding the PS-IPW model, a larger decrease in the BW was observed in the GLP1Ra-prededing group than in the SGLT2i-prededing group (p=0.01).

- PS stratification model in the FAS with MI

In each of the 100 sets built by MI, all patients in the FAS were stratified into quintiles based on the PS. ORs were analyzed using the Mantel-Haenzel method for the incidence of the outcome in each of the 100 sets, and the statistical estimators of the analysis of each set were integrated according to the Rubin rule. There was no significant difference between the two groups, and the ORs for the renal composite outcome, the progression of the albumin status,

and a ≥30% decrease in the eGFR were 1.06 [0.72, 1.58] (p=0.76), 1.23 [0.79, 1.93] (p=0.35), and 0.74 [0.41, 1.32] (p=0.31), respectively.

- The analysis using PS in the CCA

An analysis using the same statistical method for PS-IPW, PS matching, and PS stratification was performed as a sensitivity analysis in the CCA. The clinical characteristics at baseline in the PS-IPW model and PS matching model are shown in supplementary table S1. The distributions of the PS before and after matching are shown in supplementary Figure S6. The renal outcomes and change in the clinical characteristics after combination treatment are shown in supplementary table S2. There were no significant differences in the renal outcomes between the two groups, but a larger decrease in the BW was observed in the GLP1Ra-prededing group than in the SGLT2i-prededing group (1.9 [0.2, 3.7] (p=0.03 in the PS-IPW model and p=0.03 in the PS matching model). The mean incidence of the renal outcomes based on the quintiles of all patients in the CCA are shown in supplementary Figure S7.

Table 3 shows the summary of the renal outcomes based on the primary analysis by the PS-IPW method and the sensitivity analysis performed in this study. The results derived from each model were presumed to be similar to the results of the primary analysis, and the validity of the primary analysis was considered sufficient.

3.3| Results of a multivariable logistic regression analysis for the renal composite outcome

A logistic regression analysis showed that the mean arterial BP at baseline, the LnACR at baseline, and the change in the mean arterial BP were independent factors influencing the renal composite outcome, with ORs [95% CIs] of 1.05 [1.02, 1.07] (p<0.001), 1.18 [1.03, 1.34] (p=0.02), and 1.02 [1.00, 1.05] (p=0.03), respectively.

4 | Discussion

In this study, the renal outcomes were compared among 643 patients who received combination treatment of an SGLT2i and GLP1Ra for approximately 3 years. There was no significant difference in the outcomes with regard to the preceding drug, despite the study being considered to include a sufficient treatment period and number of patients to evaluate the renal outcomes.

In recent CVOTs using GLP1Ras, the proportion with concomitant treatment with an SGLT2i has been increasing, reaching 7% in the Harmony outcome trials [10], 10.4% in the Pioneer 6 trials [27], and 15% in the AMPLITUDE O trials [11], and there is as much interest in the impact of combination treatment on the cardiovascular and renal outcomes as which drug specifically improves the outcomes. RCTs comparing the outcomes between combination- and placebo-treated groups would be ideal, but these would be too costly and require too much time to perform, so we performed this retrospective observational study to assess the renal outcomes. It is not common for these two drugs to be started at the same time, instead being more common for one drug to be given first and the other added later. Therefore, we evaluated the significance of combination treatment by conducting a study to determine whether renal outcomes in clinical practice differed depending on which drug was administered first.

The mechanism underlying the improvement in the cardiovascular and renal outcomes by SGLT2i or GLP1Ra treatment remains unclear. SGLT2is and GLP1Ras commonly decrease the plasma glucose level, BW, and BP, which leads to the improvement of insulin resistance and the beta cell function [28]. However, different mechanisms are considered to underlie the exertion of organ-protecting effects. With GLP1Ras, natriuresis through the inhibition of sodium-hydrogen exchanger 3 isoform (NHE3) [29], a direct effect on the renal vascular endothelium [30], and a decrease in inflammation and oxidative stress [31] [32] related to its renoprotective effects are reported to be involved. In contrast, in addition to reducing oxidative

stress [33] and suppressing fibrosis [34], the hemodynamic effect of a decrease in the intraglomerular pressure by dilating the efferent renal artery via suppression of tubule-glomerular feedback (TGF) reportedly plays a major role in the renoprotective effects induced by SGLT2is [35].

CVOTs using GLP1Ras have clarified that their renoprotective effect mainly involved reducing albuminuria by approximately 20% compared to a placebo [36] [37]. A meta-analysis showed that GLP1Ra treatment significantly improved the renal composite outcome by 17% (hazard ratio [HR] 0.89 [95% CI, 0.78-0.89, $p<0.001$]) but did not improve the worsening of the renal function (HR 0.87 [95% CI, 0.73-1.03]), indicating that GLP1Ras mainly ameliorated albuminuria [38]. In contrast, the renoprotective effects of dapagliflozin were also observed in patients with microalbuminuria [39], and a network meta-analysis showed that SGLT2i treatment significantly improved the renal outcomes in patients with albuminuria (relative risk (RR) 0.64 [95% CI, 0.57-0.73]) as well as without it (RR 0.49 [95% CI, 0.39-0.62]) [40].

Regarding the renoprotective effect induced by SGLT2i treatment, the reduction in the intraglomerular pressure through vasodilation of the afferent renal arterioles via tubuloglomerular feedback is considered the key mechanism [35]. However, Bomml et al. revealed that dilation of the efferent renal arteriole led to a reduction in the intraglomerular pressure in patients with T2DM [41]. Thus, the mechanisms underlying the renoprotective effects exerted by SGLT2is or GLP1Ras are not fully understood. In addition to the common anti-metabolism effects, different renoprotective effects are presumed, so further renoprotective effects in combination treatment can be expected. We believe that a further analysis of the data we collected in this study will enable us to clarify the significance of combination treatment and its effects on different pathologies.

The present results indicated that whichever drug was administered first did not influence the renal effect after combination treatment. To reduce the selection bias while

maintaining the sample size of the study, we included all patients who met the inclusion criteria. Therefore, the study subjects included both patients with a high risk of cardiovascular events and those without any such risk. In the future, it will be necessary to conduct subgroup analyses, including analyses depending on risk factors, such as CKD, age, and the history of cardiovascular disease, to verify whether or not the renal effect differs due to the preceding drugs. Regarding the result of the PS-IPW analysis, the annual change in the eGFR of the SGLT2i-preceding patients was significantly smaller than that in the GLP1Ra-preceding patients ($p=0.04$). A previous study comparing SGLT2i and GLP1Ra demonstrated the superior renal composite outcomes in SGLT2i-treated patients, who showed a smaller decrease in the annual eGFR than the GLP1Ra-treated patients [42], a finding not consistent with the results of this study. However, PS matching did not show such a difference in results. PS matching and PS-IPW do not necessarily estimate the same effect size, as the patient populations being compared are different between these two approaches. Although the difference in the distribution of the PS may influence the results, i.e. the existence of confounding factors that strongly affect the PS, further research will be necessary to make a firm conclusion.

In our analysis, a robustly significantly greater BW loss was observed in the GLP1Ra-preceding patients than in the SGLT2i-preceding patients. The changes in the BW induced by hypoglycemic drugs compared to a placebo were previously reported in a network meta-analysis, and both GLP1Ras and SGLT2is were shown to decrease the BW by approximately 1-2 kg [43]. The PIONEER 2 trial, which involved a direct comparison between oral semaglutide and empagliflozin, demonstrated the superiority of the BW decrease by oral semaglutide (4.7 kg) compared to that by empagliflozin (3.8 kg) at 52 weeks ($P = 0.0114$) [44]. Calorie loss through the huge amount of glucosuria achieved by inhibiting SGLT2 leads to BW loss, but a continuous decrease in the BW was not observed in these patients, possibly because the caloric intake was increased [45]. GLP1Ras, by contrast, decrease the BW mainly by

suppressing the appetite. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes on treatment of hyperglycemia in type 2 diabetes [46] and KDIGO 2022 clinical practice guideline for diabetes management in CKD [47] recommended that, in patients with established atherosclerotic cardiovascular disease or CKD already taking SGLT2i, a combination of a GLP1Ra and SGLT2i be considered if further intensification of glycemic control is required. Furthermore, GLP-1RA/SGLT2i combination should also be preferentially used for patients in whom promoting weight loss is a priority. In patients who are expected to receive combination treatment with an SGLT2i and GLP1Ra, it seems logical to recommend GLP1Ra-preceding treatment in order to prioritize BW loss, as our results showed that SGLT2i-preceding treatment did not improve the renal outcome. However, the present results alone are not sufficient, and there is a possibility that the current guidelines will be changed based on the accumulation of further evidence in the future suggesting that SGLT2 treatment does not necessarily have to be performed first.

An RCT is necessary to obtain results with a high level of evidence. Although our study was a retrospective observational study, and the evidence level was lower than that for an RCT, this study with its medium-sized sample and long observation period of approximately five years was sufficient to observe renal outcomes (the proportions with renal composite outcomes among the GLP1Ra- and SGLT2i-preceding patients were 26% and 27%, respectively; Table 2). Combination treatment with an SGLT2i and GLP1Ra is highly expected by general practitioners and is recommended in several guidelines for patients with poor glycemic control and obesity; however, we were only able to find research regarding combination treatment with small sample sizes or short observation periods, and no study has yet evaluated the renal outcomes. Future long-term and large-scale RCTs may be difficult to perform due to their high cost and large effort required. We therefore believe that our study will be of great clinical interest and is novel and relevant to our needs.

In the present study, the sensitivity analysis included PS matching and PS stratification with the FAS, and PS-IPW, PS matching, and PS stratification of the complete dataset were performed. Regardless of which analysis methods were used, the renal outcomes were similar, so the present results were considered to be robust. In contrast, the results of 95% CIs suggest that there may be some superiority for the progression of the albuminuria status in the GLP1Ra-preceding patients and for the decrease in the eGFR in the SGLT2i-preceding patients.

Study limitations

Several limitations associated with the present study warrant mention. Because this is a retrospective cohort study, the most serious concern is selection bias. Our study included only patients who were able to continue treatment, with patients who gave up or temporarily stopped treatment due to adverse effects or poor adherence excluded. The adverse effects potentially induced by GLP1Ras, such as epigastralgia or nausea, are well known, and adherence may have been poor in some cases because GLP1Ras were administered via injection during the study period. Not few patients were suspected to stop GLP1Ra treatment. Genital infection due to SGLT2i treatment is also a well-known adverse effect, but among hypoglycemic drugs, the highest and second-highest rates of adherence and persistence were consistently observed in metformin and SGLT2i users, respectively, while injection therapies, including GLP1Ras, have shown low adherence and persistence rates [48]. In contrast, Malik et al. reported that almost equal adherence to therapy and discontinuation were observed among patients who started SGLT2i or GLP1Ra treatment for the first year [49]. Adherence to treatment may vary depending on the patient characteristics, and oral semaglutide has been available in Japan since 2021, which may change the results of comparing the adherence between SGLT2is and GLP1Ras in the future. In the present study, patients with a BMI of nearly 30 were included, a higher value than the average BMI of 24.3 among T2DM patients in Japan [50]. Liraglutide

has been available for use in Japan since 2019, but the proportion of GLP1Ra usage has not been very large thus far (**https://www.mhlw.go.jp/bunya/iryouhoken/database/zenpan/dl/cyouzai_doukou_topics_h31_01-01.pdf)**. Therefore, our study may have included many patients with severe obesity and poor adherence to diet and exercise therapy who had no choice but to use a GLP1Ra for a long period of time. There are thus concerns about whether or not the patients in the present study are representative of Japanese T2DM patients in clinical practice. Another limitation of this study is the small dose of GLP1Ra administered, as dosages are lower in Japan than in other countries. Since 2019, a maximum liraglutide dose of 1.8 mg per day has been able to be administered in clinical practice in Japan, but many patients in the present study did not receive the maximum dose. For dulaglutide, only a dose of 0.75 mg can be used in Japan. Whether or not relatively low-dose GLP1Ras exert sufficient hypoglycemic effects or organ-protective effects is unclear. It may thus be a limitation to compare these results directly with evidence from CVOTs.

5 | CONCLUSION

This study suggested the possibility that, when administering combination therapy of an SGLT2i and GLP1Ra, the drug administered first may not affect the renal composite outcome.

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DATA AVAILAVILITY

Data are available from the Tokai University Data Access/ Institutional Review Board for Clinical Research, Tokai University, for investigators, bound by confidentiality 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@is.icc.u-tokai.ac.jp.

CONFLICTS OF INTEREST

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

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Table legends

Table 1. Clinical characteristics at baseline (FAS with MI, n=643)

Table 2. Renal outcomes and clinical characteristics after combination treatment (FAS with MI, n=643)

Table 3. Results of a sensitivity analysis for the renal outcomes: Odds ratios of SGLT2i-preceding patients compared to GLP1Ra-preceding patients

Supplementary legends

Supplementary Figures

Supplementary Figure S1. Schematic of the study design

Supplementary Figure S2. Schematic depiction of the study participants

Supplementary Figure S3. Breakdown of the missing data

Supplementary Figure S4. Calculation of the weight using the propensity score

Supplementary Figure S5. Standardized differences of each IPW model

Supplementary Figure S6. Distribution of the propensity score before and after matching (CCA)

Supplementary Figure S7. Mean incidence of the renal outcomes based on the quintiles of all patients in the CCA

Supplementary Tables

Supplementary Table S1. Clinical characteristics at baseline (CCA, n=418)

Supplementary Table S2. Renal outcomes and clinical characteristics after combination treatment (CCA set, n=418)

Table 1. Clinical characteristics at baseline (FAS with MI, n=643)

	Unadjusted			PS-IPW; stabilized ATE with trimming			PS-matching		
	GLP1Ra-preceding group, N=331	SGLT2i-preceding group, N=312	P-value	GLP1Ra-preceding group, N=327†	SGLT2i-preceding group, N=293†	Standardized difference	GLP1Ra-preceding group, N=203	SGLT2i-preceding group, N=203	Standardized difference
Age (year-old)	55.7±13.5	56.5±12.7	0.10	56.3±13.9	56.8±12.5	0.04	57.1±13.6	57.0±13.2	0.007
Sex (female [%])	152 (46%)	130 (42%)	0.27*	148 (45%)	131 (45%)	0.01	89 (44%)	87 (43%)	0.02
A history of DM >10 years (%)	281 (85%)	237 (76%)	0.006*	260 (80%)	233 (80%)	<0.001	165 (81%)	159 (78%)	0.07
BW (kg)	79.5±20.1	79.4±18.1	0.95	79.2±19.1	78.7±18.0	0.03	78.7±18.5	78.8±17.0	0.006
BMI	29.8±6.3	29.5±5.6	0.51	29.6±5.8	29.5±5.6	0.02	29.4±5.5	29.2±5.3	0.04
SBP (mmHg)	132.0±18.4	135.4±18.9	0.02	132.9±18.4	133.7±18.4	0.04	133.1±19.1	134.7±19.4	0.08
DBP (mmHg)	76.6±12.3	78.7±13.6	0.04	77.2±12.3	77.4±13.1	0.02	76.7±12.4	78.2±13.5	0.12
MAP (mmHg)	95.0±12.7	97.6±13.6	0.02	95.7±12.6	96.2±13.1	0.04	95.5±13.0	97.0±13.9	0.11
HbA_{1c} (mmol/mol [%])	73.6±18.6 (8.9±1.7)	71.0±17.3 (8.6±1.6)	0.07	72.8±18.1 (8.8±1.7)	73.2±18.9 (8.8±1.7)	0.02	72.8±17.8 (8.7±11.6)	71.9±18.2 (8.7±1.7)	0.05
eGFR (mL/min/1.73 m^2)	78.8±28.7	78.2±26.0	0.79	79.1±27.9	78.7±26.5	0.02	76.6±26.7	77.7±26.9	0.04
ACR (mg/gCr)	36.6[10.4, 11.9]	34.1 [11.9, 131.3]		37.8 [11.3, 152.9]	35.7 [11.9, 131.3]		39.2 [11.3, 141.2]	35.7 [11.6, 142.0]	
LnACR	3.75±1.91	3.76±1.97	0..91	3.77±1.86	3.77±1.88	<0.001	3.72±1.90	3.77±1.95	0.003
Duration of the preceding treatment (month)	31.8±23.1	23.9±14.0	<0.001	26.2±20.0	24.8±14.4	0.08	25.1±18.3	24.7±14.5	0.03
Duration of the combination treatment (month)	38.8±18.6	28.5±13.5	<0.001	33.3±17.1	32.1±15.2	0.08	31.6±15.0	31.9±14.0	0.02
Total duration of the study (month)	70.6±27.0	52.4±15.7	<0.001	59.5±24.4	56.9±16.1	0.13	56.7±19.4	56.6±14.7	0.006
Concomitant medications									
Sulphonylurea	108 (33%)	91 (29%)	0.34*	100 (31%)	85 (29%)	0.03	58 (29%)	64 (32%)	0.06
Metformin	169 (51%)	190 (61%)	0.01*	187 (57%)	170 (58%)	0.02	115 (57%)	114 (56%)	0.01
Insulin	141 (43%)	140 (45%)	0.56*	140 (43%)	131 (45%)	0.04	95 (47%)	90 (44%)	0.05
Pioglitazone	35 (11%)	51 (16%)	0.03*	43 (13%)	41 (14%)	0.02	29 (14%)	29 (14%)	0
αGI	40 (12%)	48 (15%)	0.22*	42 (13%)	41 (14%)	0.03	30 (15%)	29 (14%)	0.01
Glinide	14 (4.2%)	14 (4.5%)	0.87*	15 (5%)	14 (5%)	0.01	11 (5%)	11 (5%)	0
RAS inhibitor	166 (50%)	160 (51%)	0.77*	165 (50%)	155 (53%)	0.05	108 (53%)	96 (47%)	0.12
CCB	128 (39%)	110 (35%)	0.37*	126 (39%)	115 (39%)	0.01	83 (41%)	83 (41%)	0
B blocker	53 (16%)	49 (16%)	0.92*	49 (15%)	44 (15%)	0.001	33 (16%)	33 (16%)	0
MRB	14 (4%)	12 (%)	0.81*	14 (4%)	13 (4%)	0.01	10 (5%)	9 (4%)	0.02
Thiazide	29 (9%)	16 (5%)	0.07*	22 (7%)	19 (6%)	0.01	13 (6%)	14 (7%)	0.02
Loop	24 (7%)	14 (5%)	0.14*	18 (6%)	14 (5%)	0.03	10 (5%)	11 (5%)	0.02
Statin	160 (48%)	160 (51%)	0.46*	157 (48%)	147 (50%)	0.04	109 (54%)	98 (45%)	0.11

Values are mean±SD or n/total n (%). P values by unpaired t-test or *chi-square test

†Calculated number of subjects after weighting

Abbreviation; αGI, alpha glucosidase inhibitor; ATE, average treatment effect; BMI, body mass index; BW, body weight; DBP, diastolic blood pressure; CCB, calcium channel blocker; DM, diabetes mellitus; eGFR, estimated glomerular filtration; FAS, full analysis set; GLP1Ra, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin A1c; IPW, inverse provability weighting; LNACR, logarithmic value of urine albumin-to- creatinine ratio; MAP, mean arterial pressure; MI, multiple imputation; MRB, mineral corticoid receptor blocker; PS, propensity score; RAS, renin-angiotensin system inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter inhibitor

Table 2. Renal outcomes and clinical characteristics after combination treatment (FAS with MI, n=643)

	Unadjusted			PS-IPW; Stabilized ATE with trimming			PS-matching		
	GLP1Ra-preceding group, N=331	SGLT2i-preceding group, N=312	P-value	GLP1Ra-preceding group, N=327*	SGLT2i-preceding group, N=293*	GLM†	GLP1Ra-preceding group, N=203	SGLT2i-preceding group, N=203	P-value#
Renal outcomes and function									
a) Incidence of renal composite outcome	88 (27%)	81 (26%)	0.79**	82 (25%)	81 (28%)	1.14 [0.75, 1.74], p=0.54	54 (27%)	58 (29%)	p=0.61
Progression of ACR status	57 (17%)	60 (19%)	0.54**	55 (17%)	60 (20%)	1.26 [0.78, 2.05], p=0.35	36 (18%)	43 (21%)	p=0.37
≥30% decrease in the eGFR	42 (13%)	26 (8%)	0.10**	36 (11%)	27 (9%)	0.83 [0.46, 1.49], p=0.53	24 (12%)	17 (8%)	p=0.32
b) Changes in eGFR									
Change rate in the eGFR (%)	-10.1%±20.9	-7.5±21.5	0.12††	-9.8±19.7	-8.1±21.9	1.8 [-1.8, 5.3], p=0.33	-9.4±19.3	-7.6±22.7	0.37
Annual changes in the eGFR (mL/min/1.73 m^2/year)	-1.7±3.4	-1.7±4.1	0.90††	-2.0±3.8	-1.6±3.8	0.3 [-0.3, 1.0], p=0.35	-1.8±3.6	-1.5±3.6	0.37
c) Changes in LnACR	0.07±1.51	0.10±1.63	0.81††	-0.01±1.48	0.2±1.64	0.20 [-0.06, 0.47], p=0.14	0.06±1.53	0.17±1.60	0.47
Clinical characteristics after combination treatment									
eGFR (mL/min/1.73 m^2)	70.1±27.5	71.4±26.1	0.54††	70.8±27.0	71.4±26.6		69.0±26.4	70.8±26.5	0.51
LnACR	3.82±1.80	3.86±1.93	0.75††	3.76±1.77	3.97±2.02		3.78±1.78	3.94±2.00	0.39
BW (kg)	74.0±18.4	75.9±17.7	0.19††	73.9±18.2	75.2±17.7		73.6±18.3	75.5±17.2	0.27
SBP (mmHg)	128.7±16.0	128.9±16.4	0.83††	128.4±16.7	129.4±17.3		129.3±16.1	128.9±17.4	0.84
DBP (mmHg)	74.5±11.8	74.9±13.1	0.65††	74.2±12.5	74.3±12.9		74.6±12.3	74.6±12.5	0.97
MAP (mmHg)	92.5±11.7	92.9±12.4	0.68††	92.3±12.5	92.7±12.4		92.8±12.0	92.7±12.3	0.91
HbA_{1c} (mmol/mol [%])	63.9±15.7 (8.0±1.4)	63.4±16.7 (8.0±1.5)	0.70††	62.9±15.3 (7.9±1.4)	63.5±16.4 (8.0±1.5)		62.9±15.2 (7.9±1.4)	62.4±15.0 (7.9±1.4)	0.75
Change in the clinical findings									
Change in BW (kg)	-5.5±8.2	-3.5±6.6	<0.001††	-5.3±8.4	-3.5±6.7	1.9 [0.5, 3.2], p=0.006	-5.1±7.6	-3.3±6.4	0.01
Change in SBP (mmHg)	-3.3±20.0	-6.5±21.0	0.05††	-4.5±20.6	-4.3±21.6	0.20 [-3.6, 4.0], p=0.92	-3.9±20.6	-5.8±21.8	0.36
Change in DBP (mmHg)	-2.1±13.1	-3.7±13.4	0.12††	-3.0±13.5	-3.1±13.4	-0.1 [-2.5, 2.2], p=0.91	-2.1±13.1	-3.6±13.5	0.25
Change in MAP (mmHg)	-2.5±14.0	-4.6±14.2	0.05††	-3.5±14.4	-3.5±14.3	-0.03 [-2.6, 2.5], p=0.98	-2.7±14.2	-4.3±14.7	0.25
Change in HbA1c (mmol/mol [%])	-9.7±19.9 (-0.9±1.8)	-7.6±20.9 (-0.7±1.8)	0.20††	-9.9±20.0 (-0.9±1.8)	-9.6±21.1 (-0.9±1.9)	0.3 [-3.3, 3.9] (0.03 [-0.3, 0.4]), p=0.86	-9.9±20.0 (-0.9±1.8)	-9.5±20.5 (-0.9±1.9)	0.83

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

* Calculated number of subjects after weighting

†Data present as the difference [95%CI] and P-value analyzed by GLM.

♯McNemar test, ** chi-square test, ††unpaired t-test

Abbreviation; ATE, average treatment effect; BW, body weight; DBP, diastolic blood pressure; CI,
635 confidence interval, eGFR, estimated glomerular filtration; FAS, full analysis set; GLM, generalized linear model, GLP1Ra, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin A1c; IPW, inverse provability weighting; LNACR, logarithmic value of urine albumin-to- creatinine ratio; MAP, mean arterial pressure; MI, multiple imputation; PS, propensity score; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter inhibitor

Table 3. Results of a sensitivity analysis for the renal outcomes: Odds ratios of SGLT2i-preceding patients compared to GLP1Ra-preceding patients

			Renal composite outcome	Progress of albuminuria status	≧30% decrease in eGFR
FSA with MI	Unadjusted		0.96 [0.83, 1.16]	1.07 [0.87, 1.31]	0.81 [0.66, 1.00]
	PS-Matching		1.05 [0.76, 1.44], p=0.77	1.12 [0.79, 1.60], p=0.53	0.81 [0.49, 1.34], p=0.42
	PS-IPW	stabilized ATE with trimming*	1.14 [0.75, 1.74], p=0.54	1.26 [0.78, 2.05], p=0.35	0.83 [0.46, 1.49], p=0.53
		ATE with trimming	1.14 [0.75, 1.74], p=0.54	1.26 [0.78, 2.05], p=0.35	0.83 [0.46, 1.49], p=0.53
		ATT with trimming	1.16 [0.73, 1.83], p=0.54	1.22 [0.72, 2.07], p=0.47	0.90 [0.50, 1.65], p=0.74
		stabilized ATE with truncation	1.14 [0.75, 1.73], p=0.54	1.27 [0.78, 2.05], p=0.33	0.82 [0.46, 1.46], p=0.50
		ATE with truncation	1.14 [0.75, 1.73], p=0.54	1.27 [0.79, 2.06], p=0.33	0.82 [0.49, 1.46], p=0.50
		ATT with truncation	1.15 [0.73, 1.81], p=0.55	1.21 [0.71, 2.06], p=0.48	0.90 [0.49, 1.63], p=0.72
	PS-stratification		1.06 [0.72, 1.58], p=0.76	1.23 [0.79, 1.93], p=0.35	0.74 [0.41, 1.32], p=0.31
CCA	Unadjusted		0.92 [0.76, 1.12]	1.09 [0.84, 1.39]	0.75 [0.61, 0.91]
	PS-Matching		0.93 [0.54, 1.60], p=0.93	1.13 [0.57, 2.21], p=0.73	0.61 [0.29, 1.29], p=0.61
	PS-IPW	stabilized ATE with trimming	1.02 [0.61, 1.68], p=0.95	1.26 [0.70, 2.27], p=0.44	0.70 [0.35, 1.40], p=0.32
		ATE with trimming	1.02 [0.61, 1.68], p=0.95	1.26 [0.70, 2.27], p=0.44	0.70 [0.35, 1.40], p=0.32
		ATT with trimming	1.17 [0.67, 2.06], p=0.58	1.31 [0.68, 2.52], p=0.42	0.84 [0.41, 1.71], p=0.63
		stabilized ATE with truncation	0.99 [0.61, 1.61], p=0.97	1.27 [0.71, 2.26], p=0.42	0.68 [0.34, 1.33], p=0.26
		ATE with truncation	0.99 [0.61, 1.63], p=0.99	1.28 [0.72, 2.27], p=0.41	0.68 [0.34, 1.33], p=0.27
		ATT with truncation	1.05 [0.62, 1.79], p=0.86	1.19 [0.63, 2.24], p=0.59	0.76 [0.38, 1.53], p=0.44
	PS-stratification		0.93 [0.56, 1.53], p=0.76	1.15 [0.65, 2.07], p=0.63	0.69 [0.35, 1.37], p=0.29

Values are the differences [95%CI] and P-value.

*The primary analysis. Truncation of the 99th percentile is utilized in model A, and trimming by $0.05 \leq PS \leq 0.95$ is utilized in model B.

Abbreviations: ACR, urine albumin-to-creatinine ratio; ATE, average treatment effect; ATE, average treatment effect on the treated; eGFR, estimated glomerular filtration; GLP1Ra, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor