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Comparative Effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Classes of Glucose-Lowering Medications on Renal Outcome in Type 2 Diabetes

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Abstract

Objective: To assess whether sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy is associated with a favorable renal prognosis for patients with type 2 diabetes mellitus (T2DM) outside the clinical trials setting.

Participants and Methods: This retrospective study analyzed routinely collected health care records of ~160 medical institutions in Japan from April 1, 2014, to December 31, 2017/2018 (varying at the institutional level). Adults with T2DM but without end-stage renal disease who initiated either SGLT2i or other classes of glucose-lowering medications (o-GLM) were matched using propensity score. The primary outcome was the time course of estimated glomerular filtration rate (eGFR) displayed in spline curve. The composite of renal worsening (>40% decline in eGFR) and the development of eGFR<30 mL/1.73 m² per minute was evaluated as a secondary outcome. Two sensitivity analyses were conducted to determine the robustness of results.

Results: We compared a matched cohort of 1433 SGLT2i users and 2739 o-GLM users (mean age: 61 years). The eGFR declined over time in both groups during the observation period (median: 17 months; maximum: 54 months), with a slower eGFR slope observed in SGLT2i users. This slower decline was consistently observed across different SGLT2i agents and different baseline eGFR groups. The cumulative incidence of composite renal endpoints was lower in the SGLT2i group with a hazard ratio of 0.70 (95% CI, 0.50-0.98; P=.039). Those findings were consistent in sensitivity analyses limited to the period adherent to the initial drug regimen and with a different approach for propensity score calculation.

Conclusion: In a matched cohort of T2DM patients, SGLT2i use was associated with preserved renal function relative to o-GLM use over 2 to 4 years.

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The renoprotective effect of sodium-glucose cotransporter-2 inhibitor (SGLT2i) medications — the latest glucose-lowering medication (GLM) that promotes glucosuria — is an emerging topic in diabetology and nephrology, as well as in clinical practice.¹⁻³ Several randomized controlled trials (RCTs) have consistently

shown that SGLT2i delayed the decline of renal function over 1 to 3 years in patients with type 2 diabetes mellitus (T2DM).⁴⁻⁷ Additionally, a meta-analysis found that SGLT2i use may halve the risk for advanced kidney disease in patients with T2DM.⁸ However, this knowledge is mainly derived from placebo-controlled trials; hence, it is



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unclear whether SGLT2i classes have a renoprotective effect superior to GLMs of other classes (o-GLM). Further, it is yet to be examined whether favorable outcomes in RCTs are reproducible in broader populations than a specialized research environment.⁹

In the present study, we compared the progression of renal disease between patients with T2DM initiating SGLT2i and those initiating o-GLM using large-scale data from electronic medical records in Japan.

PARTICIPANTS AND METHODS

The Institutional Review Board at Kyoto University approved this study. Individual consent was waived because we used anonymized data.

Data Source

This population-based, new-user, active-comparator, longitudinal cohort study used the real-world data (RWD) database; this database is maintained by Health, Clinic, and Education Information Evaluation Institute (HCEI; Kyoto, Japan) — a not-for-profit research service foundation, with support from Real World Data Co., Ltd (Kyoto, Japan). This database contains the records of ~20 million patients from ~160 medical institutions across Japan. The stored information includes demographic data, diagnoses, prescriptions, procedures, and laboratory results from both outpatient and inpatient services. The data were automatically extracted from electronic medical records at each medical institution. Patient records are maintained by allocating unique identifiers for each individual, which are valid within the same institution.

Base T2DM Cohort

The base T2DM cohort included adult patients with T2DM and both (1) at least one or more prescription of GLM after April 2014 when SGLT2i was introduced in Japan; and (2) at least one or more laboratory result for both hemoglobin A1c (HbA1c) and serum creatinine (s-Cr) at an outpatient visit. The definition for an adult patient in

this cohort was 20 years of age or older as of 2014.

The use of GLM was identified by the Anatomical Therapeutic Chemical code of “A10.” Diagnosis of T2DM relied on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes of E11 (“diabetes mellitus, type 2”) and E14 (“diabetes, unspecified”). We included code E14 because our preliminary search showed that it was found in more than 50% of individuals in our dataset. To minimize the risk of disease misclassification for individuals with the diagnostic code E14, we excluded patients who also had any of the following codes at any visit: E10 (“diabetes mellitus, type 1”), E12 (“diabetes mellitus, malnutrition-related”), and E13 (“other specified diabetes mellitus”). We did not use code O241 (“pre-existing T2DM in pregnancy”) to identify patients with T2DM.

HCEI screened and extracted data on patients with at least one diagnosis of diabetes (diagnostic code: E10–E14) from the oldest electronically stored records at each institution to the end of 2017/2018 (depending on the institution). Subsequent extractions were performed by the authors to assemble the base T2DM cohort (E11 and E14).

Study Cohort

From the base T2DM cohort, we constituted a study cohort of SGLT2i initiators and o-GLM initiators. Patients who initiated SGLT2i or o-GLM after April 2014 were retrieved, with or without medication use before April 2014; a patient could enter the cohort only once, and SGLT2i initiators and o-GLM initiators were mutually exclusive. The index date of each patient was defined as the earliest date when SGLT2i or o-GLM was started after April 2014, including switch or add-on. To enter the study cohort, more than 365 days of data history in an RWD institution before the index date was required to see the baseline variables such as comorbidity or medication use. Additionally, laboratory evaluations of (1) s-Cr and HbA1c before the index date within 90 days; and (2) measurement of

s-Cr after 90 days or longer from the index date were both required for study cohort entry. We only included individuals with a baseline estimated glomerular filtration rate (eGFR) greater than or equal to 30 mL/1.73 m² per minute to maintain consistency with participants in previous RCTs of SGLT2i. Records of individuals were traced at the end of the last visit at each institution, regardless of whether the index treatment was continued (intention-to-treat basis). The observation period for renal outcomes was defined as the index date to the last date of available s-Cr measurement at each institution. The time window of this study is summarized in [Supplemental Figure 1](#) (available online at <http://www.mayoclinicproceedings.org>).

Definition of Outcomes

We calculated the eGFR using the following well-validated formula that was specifically developed for the Japanese population.¹⁰

$$eGFR \text{ (mL/min per } 1.73 \text{ m}^2\text{)} = 194 \times s\text{-Cr}^{-1.094} \text{ (mg/dL)} \times \text{age}^{-0.287} \text{ (years)} \\ (\times 0.739 \text{ for females})$$

The baseline eGFR of each individual was estimated using s-Cr results measured at the closest visit within 90 days of the index date.

Study Outcomes

As a primary outcome, we graphically presented spline curves showing eGFR progression over time in SGLT2i users and o-GLM users without statistical testing for significance (because of the statistical software that we used). As first subgroup analysis, these graphical presentations were provided separately in three categories stratified by baseline renal function: baseline eGFR greater than or equal to 90, 60 to 89, and 30 to 59 mL/1.73 m² per minute. The evolution of eGFR was also presented in the second subgroup analysis stratified by six SGLT2i formulations.

As a secondary outcome, the incidence of sustained renal worsening and the development of eGFR less than 30 mL/1.73 m² per

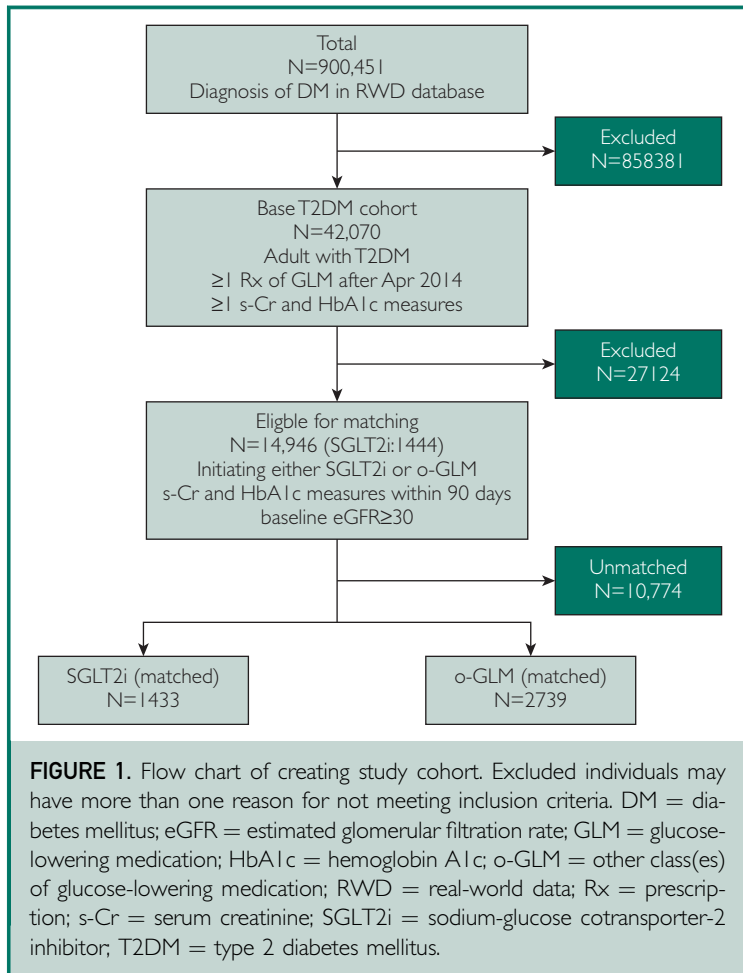
minute were combined into a composite renal endpoint and compared between groups. Renal worsening was defined as a greater than 40% decline of eGFR from the baseline value.^{11,12} For both endpoints, at least two measurements 30 days or more apart were required to ensure sustained deterioration.

Statistical Analysis

Descriptive statistics were used to summarize patient profiles and were reported as means with standard deviations, medians with interquartile ranges (IQRs), or numbers with percentages.

We performed propensity score (PS)-based analyses to ensure the baseline balances at initiating SGLT2i or o-GLM.¹³ Variables for PS calculations were age (at index date), sex, calendar year of the index date, baseline eGFR, HbA1c (closest to the index date), hypertension (diagnosed before the index date), diabetic retinopathy (diagnosed before the index date), and cumulative days exposed to any GLM within 365 days of preceding the index date (categorized into <120 days, 120–240 days, and ≥240 days). These variables were selected a priori because they are known or potential risk factors of diabetic nephropathy or the proxy for risk factors. PS was calculated using the logistic regression model, and the nearest-neighbor caliper width of 0.1 multiplied by the standard deviation of the PS distribution was used for matching. For each SGLT2i initiator, up to two o-GLM initiators were matched without replacement. Balancing after matching was assessed by standardized differences. A greater than 10% standardized difference indicates a residual imbalance between two groups.

The progression of eGFR after the initiation of SGLT2i could be nonlinear — “initial dip and subsequently stable”³; hence, eGFR in both groups was expressed in spline curves. Measurements of eGFRs were likely correlated within individuals; thus, to develop spline curves, we selected a generalized additive mixed-effects model that can incorporate nonlinear relationships with correlated data.¹⁴ For interpretability, a



piecewise mixed-effects model was tested as a post hoc analysis.¹⁵ First, we detected a change point of eGFR from obtained data. Second, we calculated the eGFR slopes before and after the change point approximating that the eGFR trajectory was linear; in this model, correlations within-persons were also considered. The unadjusted Cox proportional hazards model was used to estimate the hazard ratio (HR), 95% CI, and *P* value for the cumulative incidence of the composite renal endpoint between two groups; a robust variance estimator was used for calculation to account for the clustering within matched pairs.¹⁶ A Kaplan-Meier plot was created to observe a time to the first occurrence of composite endpoint; patients were followed at the occurrence of renal worsening, deteriorated eGFR (<30

mL/1.73 m² per minute), or the last s-Cr measurement, whichever came first. A two-sided *P* value less than .05 indicated statistical significance. All analyses were performed with R, version 3.5.2, together with distributed packages (Supplemental Table 1; available online at <http://www.mayoclinicproceedings.org>).

Sensitivity Analysis

Two sensitivity analyses were conducted to assess the robustness of our analyses. First, we created a new spline curve limited to the period under the initial therapeutic regimen. For this analysis, data were limited from the index date to the last s-Cr measurement date before discontinuation (defined as an absence or a gap of ≥120 days until the next prescription of the index GLM), or switching to or adding another class of GLM, whichever occurred first; for those individuals without such events, all available data were used in the analysis. Second, a nonparsimonious, one-to-two PS matching was conducted to assess how the selection of PS variables affected cohort selection and primary renal outcome. Forty-six variables for this analysis were determined by modifying the covariates in the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study,¹⁷ including numerous risk factors for micro- and macrovascular complications, relevant drugs, and procedures (Supplemental Table 2; available online at <http://www.mayoclinicproceedings.org>).

Quantitative Bias Analysis

We calculated E-value (as relative risk) to evaluate the minimal strength of unmeasured confounding to negate the observed HR in our survival analysis.¹⁸ The higher the E-value is, the stronger the unmeasured confounding should be to explain away the observed association.

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TABLE 1. Baseline Characteristics Before and After Propensity Score Matching

Variable	SGLT2i ^a Before Match (N=1444)	o-GLM Before Match (N=13502)	%SMD ^b Before Match	SGLT2i After Match (N=1433)	o-GLM After Match (N=2739)	%SMD After Match
Age (years)	60.6	68.2	-59.2	60.8	61.0	-1.9
Male (%)	63.1	62.4	-1.3	63.1	61.9	-2.5
HbA1c (%)	8.0	7.6	21.0	7.9	8.0	-2.1
eGFR (mL/1.73 m ² per min)	76.2	71.8	16.8	76.1	76.1	0.06
Index year (%)						
2014	9.5	28.6	-65.2	9.7	8.6	3.3
2015	21.8	29.0	-17.8	21.9	22.9	-2.5
2016	31.9	24.3	16.2	31.9	31.5	0.9
2017	36.8	18.2	38.7	36.3	37.0	-0.8
Hypertension (%)	69.7	65.7	8.6	69.6	69.3	6.8
Retinopathy (%)	24.7	20.5	9.6	24.7	24.8	-1.6
GLM exposure ^c (%)						
<120 days	36.7	64.6	-57.8	37.0	38.0	-2.1
120-239 days	4.9	2.7	10.3	4.8	4.3	2.4
≥240 days	58.4	32.8	52.0	58.2	57.7	1.0

^aeGFR = estimated glomerular filtration rate; GLM = glucose-lowering medication; HbA1c = hemoglobin A1c; o-GLM = other glucose-lowering medication; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SMD = standardized mean difference.
^bAbsolute SMD < 10% regarded as negligible imbalance.
^cDays exposed to other class of GLM within 365 days before either SGLT2i or o-GLM.

RESULTS

Characteristics of Study Population

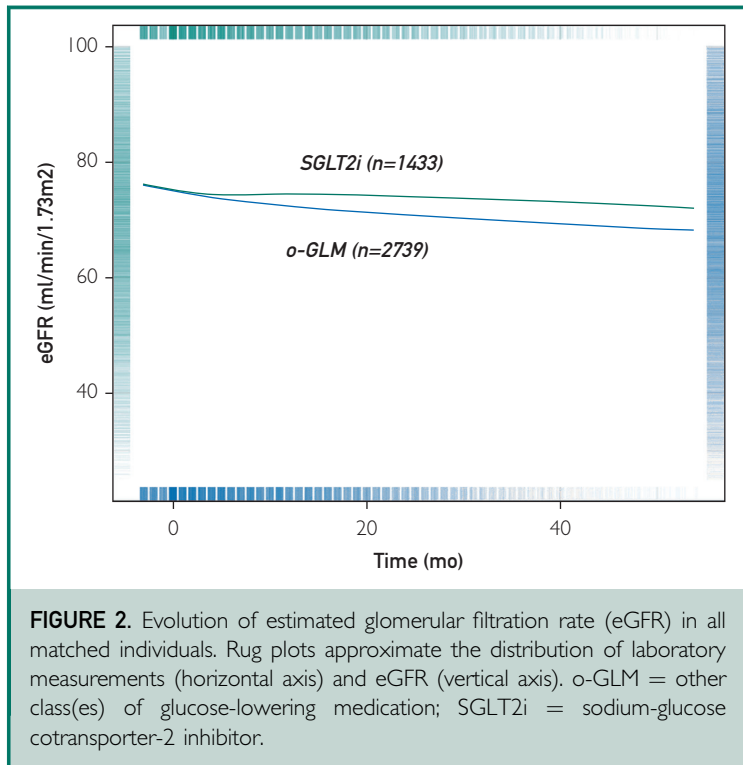
From HCEI, we obtained data from 900,451 individuals with all types of diabetes, regardless of medication use or age. We then formed a base T2DM cohort of 42,070 individuals (Figure 1). The median age in 2014 was 69 (IQR: 61-77) years old, and 62.4% of individuals were male (n=26,272). Among the 42,070 individuals, 14,946 persons initiating either SGLT2i or o-GLMs met the inclusion criteria: 1444 in the SGLT2i group and 13,502 in the o-GLM group. The two groups differed in age, glyce-mic control, baseline renal function, and history of medication use (Table 1). The time course of eGFR in this population is shown in Supplemental Figure 2 (available online at <http://www.mayoclinicproceedings.org>).

PS matching created a cohort comprising 1433 SGLT2i users and 2739 o-GLM users of a well-matched and balanced population

(Table 1, Supplemental Figures 3 and 4 [available online at <http://www.mayoclinicproceedings.org>]); male patients accounted for ~62%, and the mean age was 61 years. In this matched cohort, index GLMs in SGLT2i users were ipragliflozin (n=441; 30.8%), empagliflozin (n=313; 21.8%), dapagliflozin (n=228; 16.1%), tofo-gliflozin (n=210; 14.7%), luseogliflozin (n=131; 9.1%), and canagliflozin (n=108; 7.5%). In the o-GLM group, dipeptidyl peptidase-4 inhibitor (33.2%) was the most commonly used class of index GLM, followed by metformin (24.7%) and insulin (20.4%); in this group, 404 individuals (14.7%) initiated some combination of o-GLM, with dipeptidyl peptidase-4 inhibitor and metformin being the most common (n=218).

Study Outcomes

During a median observation period of 17 months per person (IQR: 9-27 months,



maximum: 54 months), the evolution of eGFR is shown in Figure 2 (the partially expanded graph with 95% confidence bands and observed “initial dip” in SGLT2 users is presented as Supplemental Figure 5; available online at <http://www.mayoclinicproceedings.org>). Overall, the eGFR slope was more gradual in SGLT2i group. In the post hoc analysis, there was a change point at ~6 months in slope of SGLT2i group and at ~10 months in o-GLM group, respectively. The annual decline of eGFR after the change point was also slower in SGLT2i group (0.86 [95% CI, 0.71- 1.01] mL/ 1.73 m² per minute in the SGLT2i group vs 2.06 [95% CI, 1.93- 2.18] mL/1.73 m² per minute in the o-GLM group).

In the subgroup analyses, the beneficial effects of SGLT2i were consistent across SGLT2i class (Supplemental Figure 6; available online at <http://www.mayoclinicproceedings.org>) and different baseline renal functions, with the largest effect observed in patients with baseline greater than or equal to 90 mL/ 1.73 m² per minute (Supplemental Figure 7; available online at <http://www.mayoclinicproceedings.org>). The dynamics of HbA1c during the same period are presented in

Supplemental Figure 8 (available online at <http://www.mayoclinicproceedings.org>), in which better glycemic control is shown in o-GLM users.

During the observation period, the composite of renal events occurred in 46 of 1433 SGLT2i users (3.2%) and 121 of 2793 o-GLM users (4.4%). The cumulative incidence was lower in SGLT2i users, with an HR of 0.70 (95% CI, 0.50-0.98; *P*=.038) (Figure 3). Each incidence rate of renal worsening or the development of eGFR less than 30 mL/1.73 m² per minute was numerically lower in SGLT2i users, but the difference was not significant for renal worsening (31 vs 80 events, HR, 0.71; 95% CI, 0.47-1.07; *P*=.11 for renal worsening; and 30 vs 84 events, HR, 0.66, 95% CI, 0.43-1.00; *P*=.047 for the development of eGFR<30 mL/1.73 m² per minute).

The E-values for incident composite renal endpoints were 2.21 (with lower limit of confidence of 1.16).

Sensitivity Analysis

In the first sensitivity analysis limited to the period under the same drug regimen, any of discontinuation of index drug and/or switch/add-on of other classes of GLM were observed in 1957 individuals (640 of 1433 SGLT2i users [44.7%] and 1317 of 2739 o-GLM users [48.1%]). The median observation period for these 1957 patients was 6 months and 12 months for overall cohort, respectively. In the second sensitivity analysis with nonparsimonious PS matching, 1402 SGLT2i users and 2594 o-GLM users formed a cohort with good covariate balancing (Supplemental Figures 9 and 10; available online at <http://www.mayoclinicproceedings.org>). In both sensitivity analyses, the decline of eGFR was slower in the SGLT2i group (Supplemental Figures 11 and 12; available online at <http://www.mayoclinicproceedings.org>), similar to the finding in the primary analysis.

DISCUSSION

This comparative effectiveness research assessed whether SGLT2i had a renoprotective effect in a general population of

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T2DM. Compared with o-GLM use in a PS-matched cohort, SGLT2i use was overall associated with preserved renal function, independent of glycemic control. The renal benefits of SGLT2i were noted across SGLT2i class and different baseline renal function, with the largest effects among patients with better baseline eGFR.

SGLT2is have a unique glucose-lowering action, and are considered a promising agent that confers renoprotection in T2DM. Besides cardiovascular benefits, the renal benefits of SGLT2i were reported from several cardiovascular outcome trials^{19,20} and one recent renal-outcome trial involving patients with T2DM and chronic kidney disease (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation [CREDENCE] trial). The present study was designed to investigate whether these benefits were verified in observational data of clinical practice where different factors from RCTs may influence the renal effect of GLM.²¹

Unexpectedly, glycemic control was better in o-GLM users than in SGLT2i users in our study (Supplemental Figure 8; available online at <http://www.mayoclinicproceedings.org>). As also observed in the CREDENCE trial,⁷ the renoprotective effect of SGLT2i is likely to act through glucose-independent mechanisms.²² The possible nonglycemic mechanisms are thought to be pleiotropic including a reduction in glomerular hyperfiltration and pressure, lowering blood pressure and the body weight reduction induced by SGLT2i²³; other possible mechanisms are currently under study. In our study, the reason for the improved glycemic control in o-GLM users is unclear, but it may reflect unmeasured factors such as difference in adherence rate.

One important yet unanswered issue is which patients benefit most from SGLT2i therapy. Theoretically, the amount of excreted urinary glucose as well as plasma glucose-lowering level depends on kidney function; thus, the expected effectiveness of SGLT2i can be decreased with impaired renal function.²⁴ In our study, consistent with this pharmacologic view, the largest difference of eGFR slope between SGLT2i and o-GLM user groups was found among

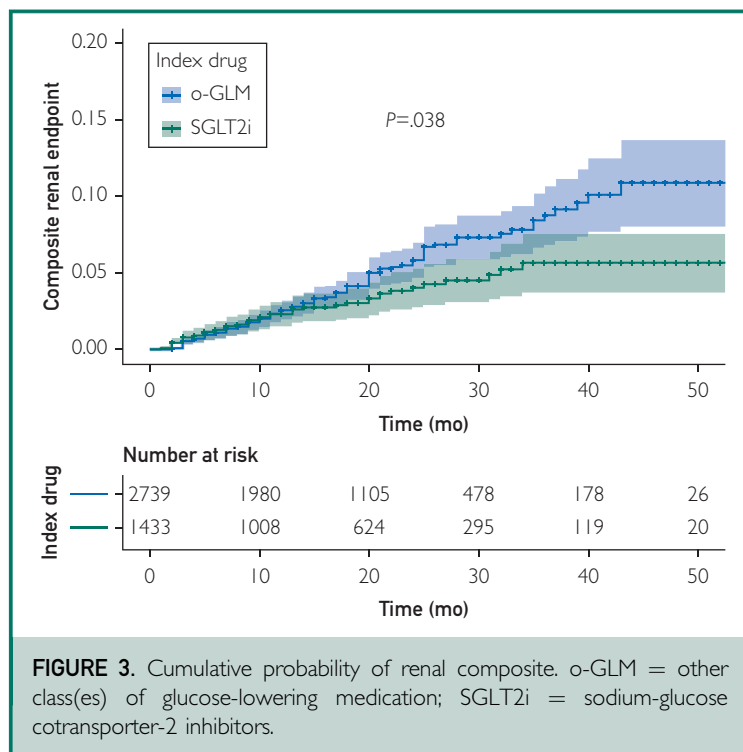


FIGURE 3. Cumulative probability of renal composite. o-GLM = other class(es) of glucose-lowering medication; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

persons with an eGFR greater than or equal to 90 mL/1.73 m² per minute (Supplemental Figure 7; available online at <http://www.mayoclinicproceedings.org>). This finding is similar to the results of the meta-analyses from cardiovascular outcome trials (SGLT2i was favorable in patients with better renal function), but may differ from the findings from the CREDENCE trial that specifically enrolled patients at risk of renal disease progression (SGLT2i was favorable in patients with worse renal function). The reason for such discrepancy is uncertain, but it is plausible that the renal benefit of SGLT2i can be influenced by the patient risk profile, given the divergence of SGLT2i mechanism. Further research as to whom SGLT2i therapy delivers its best value may be warranted.

A major strength of our study was that we used objective measures of the renal endpoint. Observational studies using health care databases often determine the renal endpoint using a claims code for chronic renal disease or end-stage renal disease, for which the coding accuracy is uncertain or dependent on the physician's opinion or the reimbursement policy.²¹ This renal

endpoint is also patient-centered, as compared with intermediated outcomes such as glycated hemoglobin. In addition, this study evaluated the renoprotective effect of various SGLT2i, involving agents from ipragliflozin (30%) to canagliflozin (7.5%). A renoprotective effect was observed both in an analysis combining all SGLT2i (Figure 2) and in analyses separated by each SGLT2i agent (Supplemental Figure 6).

Our study also had certain limitations. First, our matched cohort of SGLT2i users and o-GLM users may not be comparable if critical confounders were missed or misspecified in the PS model. For this reason, we performed a different model development in the sensitivity analysis (“non-parsimonious PS matching”), and observed a similar trend in the evolution of eGFR in both groups. Furthermore, to assess how unmeasured factors could influence our estimated HR for the renal composite endpoint, we calculated E-value as 2.21. These sensitivity analyses could limit the room for unmeasured confounders. Second, our observation period was relatively short to conclude the long-term renal effect of SGLT2i. Although a recent study found that the initial eGFR decline was associated with long-term adverse renal disease,²⁵ studies with longer follow-up duration are warranted to assess the net benefit of SGLT2i for renal outcome. Third, the misclassification of T2DM may have occurred in individuals with a diagnosis code of E14. However, GLM use was required to be enrolled into the study cohort, and we believe that this inclusion criterion limited the chance of misclassification.^{26,27} Fourth, this study did not examine the incidence of the initiation of chronic dialysis and renal death, given the Japanese situation and the nature of the database. In Japan, the introduction and maintenance of chronic dialysis are often performed in private, specialist dialysis clinics; in such cases, follow-up was often terminated in RWD institutions. Renal death was also not easily certified in our database for similar reasons. However, the development of eGFR less than 30 mL/1.73 m² per minute occurred in a total of 114 cases, and the number of patients requiring chronic dialysis was expected to be fewer. Finally, there were relatively few

drug-naïve individuals in our matched cohort. It is therefore unclear whether SGLT2i is recommended as the first-line treatment for preventing diabetic nephropathy.

CONCLUSION

Our study supplemented data on the renoprotective effect of SGLT2i shown in RCTs by (1) conducting a head-to-head comparison of SGLT2i and o-GLM, (2) enrolling a type 2 diabetic population in routine care practice, and (3) including a variety of SGLT2i formulations to explore the “class effect” of SGLT2i. The long-term effects of SGLT2i and which patients benefit most from SGLT2i therapy are not fully answered, awaiting future research to guide better care for patients with T2DM.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: GLM = glucose-lowering medications; HbA1c = hemoglobin A1c; HCIE = Health, Clinic and Education Information Evaluation Institute; IQR = interquartile ranges; o-GLM = other classes of glucose-lowering medications; PS = propensity score; RCTs = randomized controlled trials; s-Cr = serum creatinine; SGLT2i = sodium-glucose cotransporter-2 inhibitor; T2DM = type 2 diabetes mellitus

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