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ORIGINAL ARTICLE
Prevention and epidemiology

Effect of SGLT2i on kidney outcomes of individuals with type 2 diabetes according to body mass index: nationwide cohort study

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Aims To investigate the clinical significance of the modification of the kidney protective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors by baseline body mass index (BMI).

Methods and results We included individuals with SGLT2 inhibitors or dipeptidyl peptidase-4 (DPP4) inhibitors newly prescribed for type 2 diabetes using a nationwide epidemiological cohort and performed propensity score matching (1:2). The primary outcome was the annual eGFR decline, assessed using a linear mixed-effects model, compared between individuals with SGLT2 inhibitors and DPP4 inhibitors. We investigated the interaction effect of BMI at the time of prescription using a three-knot restricted cubic spline model. We analysed 2165 individuals with SGLT2 inhibitor prescriptions and 4330 individuals with DPP4 inhibitor prescriptions. Overall, the annual decline in eGFR was less pronounced in the group treated with SGLT2 inhibitors than in those treated with DPP4 inhibitors (−1.34 mL/min/1.73 m^2 vs. −1.49 mL/min/1.73 m^2). The advantage of SGLT2 inhibitors in mitigating eGFR decline was augmented in the individuals with higher BMI (*P*-value for interaction 0.0017). Furthermore, even upon adjusting the definition of outcomes to encompass a 30 or 40% reduction in eGFR, the potential advantages of SGLT2 inhibitors over DPP4 inhibitors persisted, with a trend of augmented effects with higher BMI. This interaction effect was evident in the individuals with preserved kidney function.

Conclusion Our nationwide epidemiological study substantiated the improved kidney outcomes in the SGLT2 inhibitor users compared with the DPP4 inhibitor users across a wide range of BMI, which was pronounced for individuals with higher BMI.

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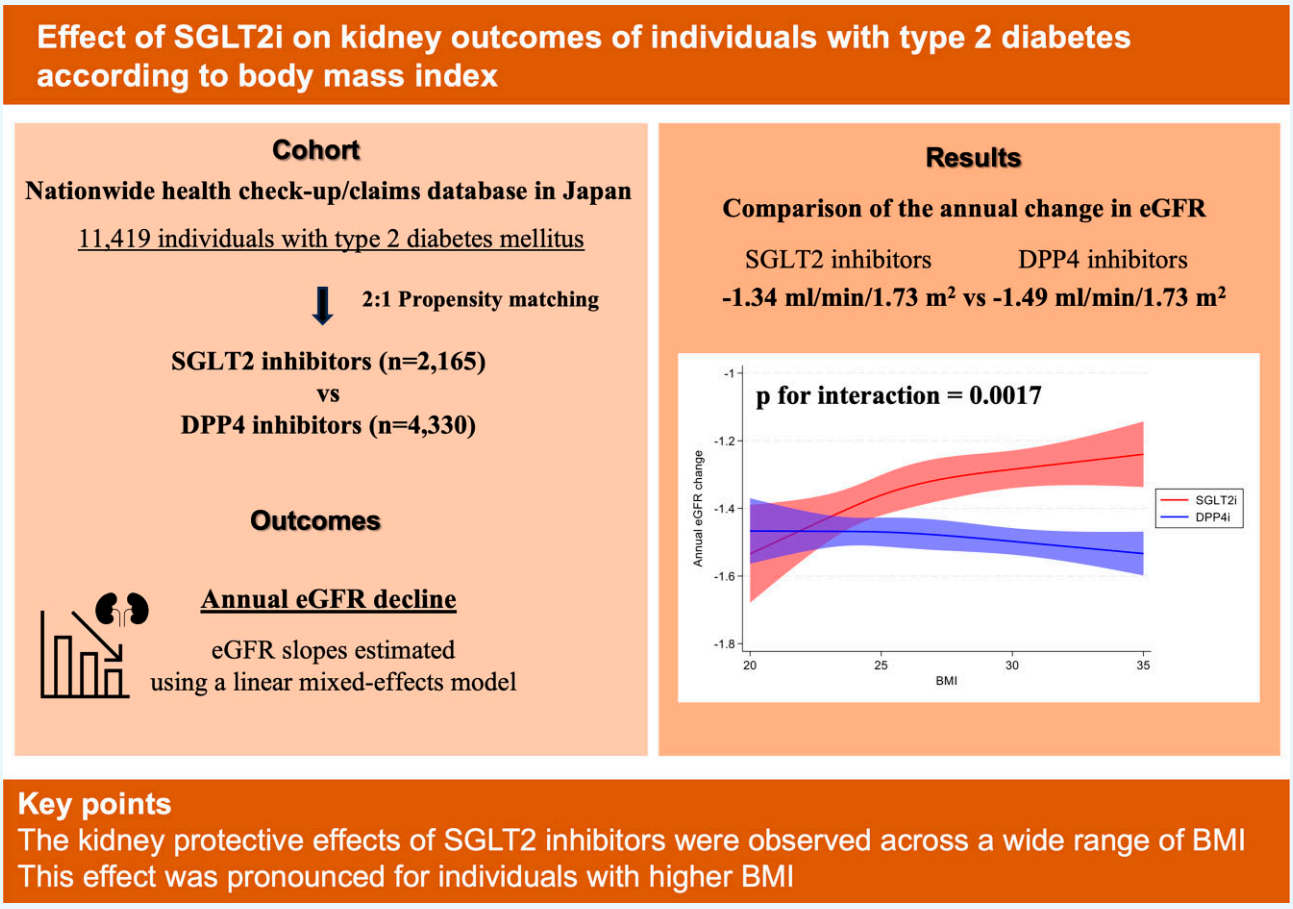
Graphical Abstract



The present study included individuals with SGLT2 inhibitors or DPP4 inhibitors newly prescribed for type 2 diabetes using a nationwide epidemiological cohort and performed propensity score matching (1:2). The primary outcome was the annual eGFR decline, assessed using a linear mixed-effects model. Overall, the annual decline in eGFR was suppressed in the SGLT2 inhibitors group compared with the DPP4 inhibitors group (−1.34 mL/min/1.73 m^2 vs. −1.49 mL/min/1.73 m^2). This kidney protective effect was augmented in the individuals with higher BMI (*P*-value for interaction 0.0017).
eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose cotransporter-2; DPP4, dipeptidyl peptidase-4

Keywords SGLT2 inhibitor • Body mass index • Estimated glomerular filtration rate decline • Diabetes

Introduction

Randomized controlled trials have demonstrated the kidney protective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors, establishing their crucial role in the treatment and prevention of chronic kidney disease.[1–4] Consequently, the prescription of SGLT2 inhibitors in clinical practice has been increasing, and factors influencing the effectiveness of SGLT2 inhibitors have become a subject of clinical interest. Due to their ability to inhibit the reabsorption of glucose in the proximal tubules of the kidneys, SGLT2 inhibitors exhibit effects similar to caloric restriction, leading to substantial body weight loss in many cases with SGLT2 inhibitors. In the clinical setting, SGLT2 inhibitors have been prescribed to individuals across a wide range of body mass index (BMI) spectrum. Importantly, obesity is the major risk factor for kidney dysfunction, and weight loss by lifestyle intervention or bariatric surgery improves kidney outcome.[5,6] At this point, the kidney protective effects of SGLT2 inhibitors could vary according to the BMI at the time of prescription, which should be important to understand their drug efficacies and optimize therapeutic strategies.

The modification effect of baseline BMI on the efficacy of SGLT2 inhibitors has been investigated recently. In the treatment of heart failure, the beneficial effects of SGLT2 inhibitors were consistent across a wide range of BMI levels.[7,8] Additionally, it has been reported that the kidney protective effects of SGLT2 inhibitors are observed not only in obese groups but also in non-obese groups in the subgroup analyses of randomized controlled trials.[9–11] However, no study has specifically focused on the spectrum of BMI to examine the kidney protective effects of SGLT2 inhibitors in clinical settings. Given the current widespread use of SGLT2 inhibitors across a broad patient population, verification through real-world databases encompassing a diverse range of individuals having diabetes is also of paramount importance. In this study, using a nationwide epidemiological cohort, we investigated whether the kidney outcomes would vary in individuals with SGLT2 inhibitors prescribed for type 2 diabetes compared

with dipeptidyl peptidase-4 (DPP4) inhibitors based on the BMI at the initiation of prescription.

Research design and methods

Study design and data source

Our study was a retrospective cohort analysis on a national scale, utilizing data from the expansive DeSC database provided by DeSC Healthcare Inc. in Tokyo, Japan.[12–15] This database merges extensive health checkup records with administrative claims information from April 2014 through November 2022. It compiles Japanese administrative data from three insurance types: (i) association/union-administered health insurance for salaried employees working for relatively large companies in Japan; (ii) National Health Insurance for unemployed individuals aged <75 years; and (iii) the Advanced Elderly Medical Service System for older individuals aged ≥75 years. Recognized for its comprehensive scope and dependability, the DeSC database captures data from a wide demographic, including young, middle-aged, and senior citizens in Japan. It anonymizes and collates patient information from both inpatient and outpatient services, which enables tracking of participants' health over time and across various medical institutions. Diagnoses were catalogued using ICD-10 codes. Furthermore, the database includes health checkups, incorporating lab results such as serum creatinine levels, body measurements, and lifestyle surveys. In Japan, an extensive health checkup program is conducted regularly for almost all residents, typically on an annual basis.

To reduce biases related to treatment indication and other unaccounted factors, we employed a new-user, active comparator study design (as shown in Supplementary material online, *Figure S1*).[16,17] DPP4 inhibitors are prevalently used for diabetes in Japan with HbA1c lowering effects comparable to SGLT2 inhibitors, whereas the effects of DPP4 inhibitors on cardiorenal outcomes are reported to be neutral.[18–21] Therefore, our study designated individuals with diabetes who were newly prescribed DPP4 inhibitors as the reference group.

We extracted data of 24 770 individuals with type 2 diabetes who had available estimated glomerular filtration rate (eGFR) data and were newly prescribed SGLT2 inhibitors or DPP4 inhibitors at least 12 months after enrolment (insurance coverage). We excluded individuals with a prior history of kidney replacement therapy ($n = 44$), eGFR <15 mL/min/1.73 m^2 ($n = 74$), missing data on cigarette smoking ($n = 1926$), alcohol consumption ($n = 1367$), and urine protein ($n = 62$), and no repeat measurement of eGFR ($n = 9878$). Finally, we included 11 419 individuals in the present study (Supplementary material online, *Figure S2*).

Ethics

This study obtained ethical approval from the ethical committee of the University of Tokyo (2021010NI) and followed the guidelines established in the Declaration of Helsinki. Informed consent was deemed unnecessary since all information in the dataset was anonymized. The DeSC database is accessible to individuals who have acquired it from the DeSC Healthcare Inc.

Measurements and definitions

We reviewed the health check-up data before the SGLT2 or DPP4 inhibitors were prescribed. The following data were collected: BMI, blood pressure, HbA1c, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and proteinuria status (negative, trace, 1+, 2+, and 3+) assessed using urine dipstick tests. We collected information on cigarette smoking (current or noncurrent) and alcohol consumption (every day or not) using a self-reported questionnaire during the health check-up. From the claims records, we retrieved data on the presence of kidney replacement therapy (dialysis and kidney transplantation) and diabetic complications (nephropathy, retinopathy, and neuropathy) on the prescription date of SGLT2 or DPP4 inhibitors. Information on medications on the date of prescription of SGLT2 or DPP4 inhibitors was collected as well.

Outcomes

Data were obtained from April 2014 through November 2022. The primary outcome was a rate of eGFR decline after the administration of SGLT2 or DPP4 inhibitors estimated using a linear mixed-effects model with the unstructured covariance structure as described elsewhere.[22,23]

Propensity score matching

We employed a propensity score matching algorithm to create a comparable cohort for evaluating the effects of SGLT2 and DPP4 inhibitor administration. The propensity score for SGLT2 inhibitor users was calculated using a logistic regression model. This estimation incorporated variables including age, sex, BMI, systolic and diastolic blood pressure, HbA1c, lipid profile (LDL cholesterol, HDL cholesterol, triglycerides), lifestyle factors (cigarette smoking and alcohol consumption), diabetic complications (nephropathy, retinopathy, neuropathy), medication usage (insulin, GLP-1 receptor agonist, biguanide, sulfonylurea, α-glucosidase inhibitor, thiazolidine, glinide, renin-angiotensin system inhibitors, β-blocker, calcium channel blocker, mineralocorticoid receptor antagonist, diuretics, and statins). Matching was performed on a 1:2 ratio using a protocol with a calliper width equal to 0.2 standard deviations of the logit score.

Statistical analysis

The median (interquartile range) and number (percentage) were used to report descriptive statistics. We used a linear mixed-effects model for repeated measures with random intercept and slope, assuming an unstructured covariance structure, to compare the change in eGFR between SGLT2 and DPP4 inhibitors. To evaluate the potential modification effect by BMI, when individual annual eGFR slope was modelled, we incorporated covariates of SGLT2i/DPP4i in new users, BMI, and their interaction term. BMI was modelled using a restricted cubic spline with three knots placed at 23, 25, and 30 kg/m^2. We calculated the *P*-value for interaction and examined whether the difference in the annual eGFR decline rate between the groups receiving SGLT2 inhibitors and DPP4 inhibitors would be modified by baseline BMI.

We conducted four sensitivity analyses. First, we conducted subgroup analyses stratified by age, sex and baseline eGFR. Second, we analysed individuals who continued to use the SGLT2 inhibitor for more than 3 months. Third, we defined the outcome as a decrease in eGFR of 30% or more and, using DPP4 inhibitor-treated group as the reference, calculated the hazard ratio (with a 95% confidence interval) for the group treated with SGLT2 inhibitors using Cox regression analysis. We verified whether the hazard ratio was influenced by baseline BMI. Fourth, we redefined the outcome as a decrease in eGFR of 40% or more and conducted a similar analysis.

The significance level was set at $P < 0.05$. All statistical analyses were performed with Stata v18 (StataCorp LLC, College Station, TX, USA).

Results

Clinical characteristics

Table 1 summarizes the clinical characteristics of study participants before and after propensity score matching. After 1:2 propensity score matching, 2165 well-balanced pairs were created. The median age was 65 (56–69) years for SGLT2 inhibitor users and 65 (55–69) years for DPP4 inhibitor users. In addition, 1414 (65.3%) individuals were men in SGLT2 inhibitor users, and 2813 (65.0%) individuals were men in DPP4 inhibitor users. The median eGFR was 71.8 (60.9–83.1) mL/min/1.73 m^2 in SGLT2 inhibitor users and 71.8 (61.3–82.9) mL/min/1.73 m^2 in DPP4 inhibitor users. The distribution of BMI after propensity score matching was shown in Supplementary material online, *Figure S3*, and the median BMI was 27.0 (24.2–30.3) kg/m^2.

Table 1 Baseline characteristics

	Before propensity score matching			After 1:2 propensity score matching		
	DPP4 inhibitors (*n* = 9249)	SGLT2 inhibitors (*n* = 2170)	SMD	DPP4 inhibitors (*n* = 4330)	SGLT2 inhibitors (*n* = 2165)	SMD
Age, years	68 (63–71)	65 (56–69)	−0.448	65 (55–69)	65 (56–69)	0.032
Men, *n* (%)	5633 (60.9)	1417 (65.3)	0.091	2813 (65.0)	1414 (65.3)	0.007
BMI, kg/m^2	24.6 (22.4–27.1)	27.0 (24.3–30.1)	0.601	27.0 (24.2–30.3)	26.9 (24.3–30.1)	−0.015
SBP, mmHg	133 (123–144)	132 (123–142)	−0.022	132 (122–144)	132 (123–142)	−0.022
DBP, mmHg	77 (70–84)	78 (71–86)	0.148	78 (72–86)	78 (71–86)	−0.003
Cigarette smoking, *n* (%)	1592 (17.2)	404 (18.6)	0.037	810 (18.7)	400 (18.5)	−0.006
Alcohol consumption, *n* (%)	2234 (24.2)	450 (20.7)	−0.082	872 (20.1)	450 (20.8)	0.016
Comorbidity						
Diabetic nephropathy, *n* (%)	1001 (10.8)	344 (15.9)	0.148	632 (14.6)	342 (15.8)	0.033
Diabetic retinopathy, *n* (%)	1642 (17.8)	424 (19.5)	0.046	776 (17.9)	422 (19.5)	0.040
Diabetic neuropathy, *n* (%)	291 (3.1)	70 (3.2)	0.005	129 (3.0)	69 (3.2)	0.012
Medication						
Insulins, *n* (%)	801 (8.7)	229 (10.6)	0.064	416 (9.6)	226 (10.4)	0.028
GLP1-RA, *n* (%)	40 (0.4)	101 (4.7)	0.271	137 (3.2)	96 (4.4)	0.066
Biguanide, *n* (%)	2085 (22.5)	608 (28.0)	0.126	1176 (27.2)	605 (27.9)	0.018
Sulfonylurea, *n* (%)	1069 (11.6)	191 (8.8)	−0.091	360 (8.3)	190 (8.8)	0.017
α-GI, *n* (%)	934 (10.1)	185 (8.5)	−0.054	338 (7.8)	185 (8.5)	0.027
Thiazolidine, *n* (%)	502 (5.4)	139 (6.4)	0.041	241 (5.6)	138 (6.4)	0.034
Glinides, *n* (%)	358 (3.9)	75 (3.5)	−0.022	135 (3.1)	75 (3.5)	0.019
Renin-angiotensin system inhibitor, *n* (%)	3663 (39.6)	1063 (49.0)	0.190	2110 (48.7)	1061 (49.0)	0.006
Beta-blocker, *n* (%)	906 (9.8)	339 (15.6)	0.176	633 (14.6)	338 (15.6)	0.028
Calcium channel blocker, *n* (%)	3374 (36.5)	799 (36.8)	0.007	1581 (36.5)	799 (36.9)	0.008
Mineralocorticoid receptor antagonist, *n* (%)	178 (1.9)	92 (4.2)	0.134	215 (5.0)	92 (4.2)	−0.034
Diuretics, *n* (%)	849 (9.2)	298 (13.7)	0.143	607 (14.0)	297 (13.7)	−0.009
Statin, *n* (%)	3881 (42.0)	1033 (47.6)	0.114	2092 (48.3)	1030 (47.6)	−0.015
Laboratory data						
HbA1c, %	6.9 (6.5–7.5)	6.9 (6.4–7.5)	−0.021	6.9 (6.5–7.5)	6.9 (6.4–7.5)	−0.002
LDL-C, mg/dL	120 (100–142)	117 (95–140)	−0.092	118 (98–140)	117 (95–140)	−0.041
HDL-C, mg/dL	54 (45–65)	52 (44–62)	−0.144	51 (44–61)	52 (44–62)	0.030
Triglycerides, mg/dL	126 (88–182)	135 (95–192)	0.075	135 (95–196)	135 (95–192)	0.013
eGFR, mL/min per 1.73 m^2	71.5 (61.4–82.4)	71.8 (60.9–83.3)	0.005	71.8 (61.3–82.9)	71.8 (60.9–83.1)	−0.002
Proteinuria, *n* (%)						
Negative	6936 (75.0)	1533 (70.6)	0.104	3080 (71.1)	1531 (70.7)	−0.006
Trace	1157 (12.5)	303 (14.0)		570 (13.2)	300 (13.9)	
1+	757 (8.2)	202 (9.3)		398 (9.2)	202 (9.3)	
2+	295 (3.2)	99 (4.6)		203 (4.7)	99 (4.6)	
3+	104 (1.1)	33 (1.5)		79 (1.8)	33 (1.5)	

Data are reported as medians (interquartile range) or numbers (percentage), where appropriate.
DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose co-transporter-2; BMI, body mass index; SBP, systolic blood pressure; SMD, standardized mean difference; DBP, diastolic blood pressure; GLP1-RA, glucagon-like peptide-1 receptor agonist; α-GI, α-glucosidase inhibitor; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Change in eGFR among SGLT2 and DPP4 inhibitors

The median follow-up period was 633 (388–963) days. *Figure 1* shows the annual eGFR decline rate of individuals prescribed SGLT2 or DPP4 inhibitors according to the baseline BMI.

Overall, the annual rate of eGFR decline was significantly lowered in the group prescribed SGLT2 inhibitors compared with DPP4 inhibitors (−1.34 mL/min/1.73 m^2 vs. −1.49 mL/min/1.73 m^2, $P < 0.0001$). In addition, the lowering of annual eGFR decline in the SGLT2 inhibitor group was augmented with higher BMI (*P*-value for interaction 0.0017).

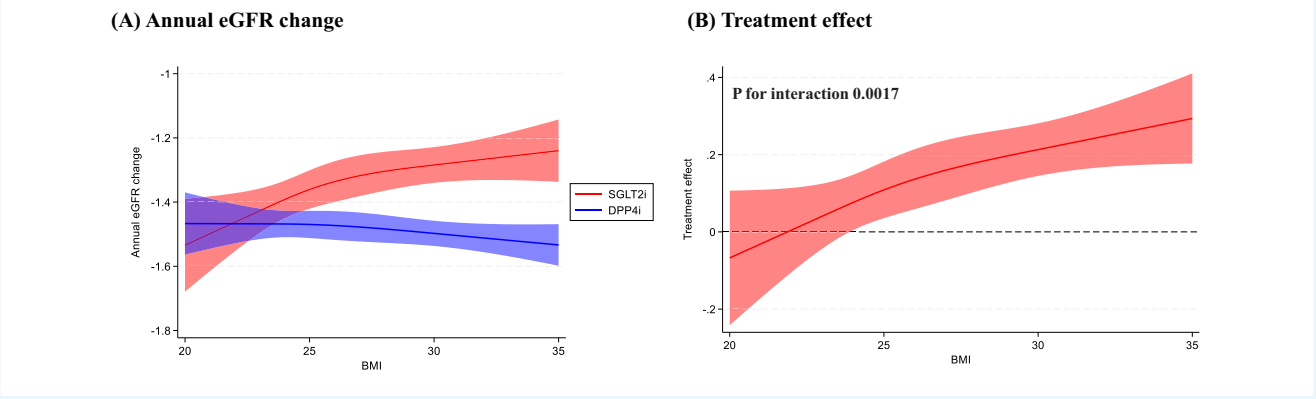


Figure 1 Annual rate of eGFR decline in the SGLT2 inhibitor or DPP4 inhibitor users across the BMI spectrum. (*A*) Annual eGFR change over the spectrum of BMI. The lines correspond to the annual eGFR change assessed using a linear mixed-effects model of the SGLT2 inhibitor group and the DPP4 inhibitor group. The shaded area represents the 95% confidence interval. (*B*) Treatment effect of SGLT2 inhibitors over DPP4 inhibitors on annual eGFR change over the spectrum of BMI. The treatment effect was calculated by the differences in annual eGFR change between the SGLT2 inhibitor group and the DPP4 inhibitor group, shown with a 95% confidence interval. eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose cotransporter-2; DPP4, dipeptidyl peptidase-4; BMI, body mass index.

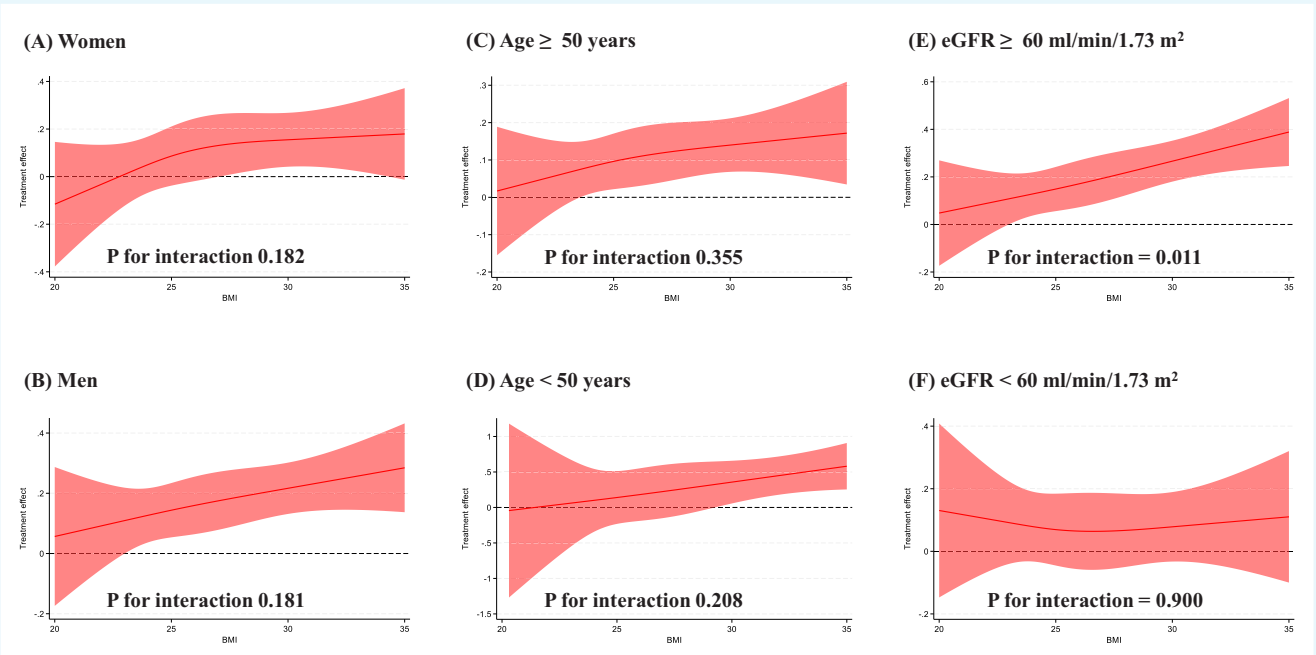


Figure 2 Subgroup analysis. Treatment effect of SGLT2 inhibitors over DPP4 inhibitors on annual eGFR change according to the subgroups: (*A*) women, (*B*) men, (*C*) age ≥50 years, (*D*) age <50 years, (*E*) eGFR ≥60 mL/min/1.73 m^2, (F) eGFR <60 mL/min/1.73 m^2. eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose cotransporter-2; DPP4, dipeptidyl peptidase-4.

Sensitivity analysis

First, we conducted a subgroup analysis (*Figure 2*). The annual decline of eGFR was consistently lowered in the SGLT2 inhibitor group. Of note, a significant augmentation with higher BMI was observed in individuals with eGFR ≥60 mL/min/1.73 m^2, whereas this augmentation was diminished in individuals with eGFR <60 mL/min/1.73 m^2. Second, we included 10 470 individuals who continued to use the SGLT2 inhibitor for more than 3 months, and 2021 pairs were created. We found annual eGFR decline was significantly lowered in the SGLT2 inhibitor group, which was augmented with higher BMI (Supplementary material online, *Figure S4*). Third, we defined the kidney outcome as a decrease in eGFR (≥30% and ≥40%). Overall, the incidence of eGFR decline event was significantly lower in the SGLT2 inhibitor group compared with the DPP4 inhibitor group ($P < 0.001$ for each), which was apparent in individuals with higher BMI (*Figure 3*).

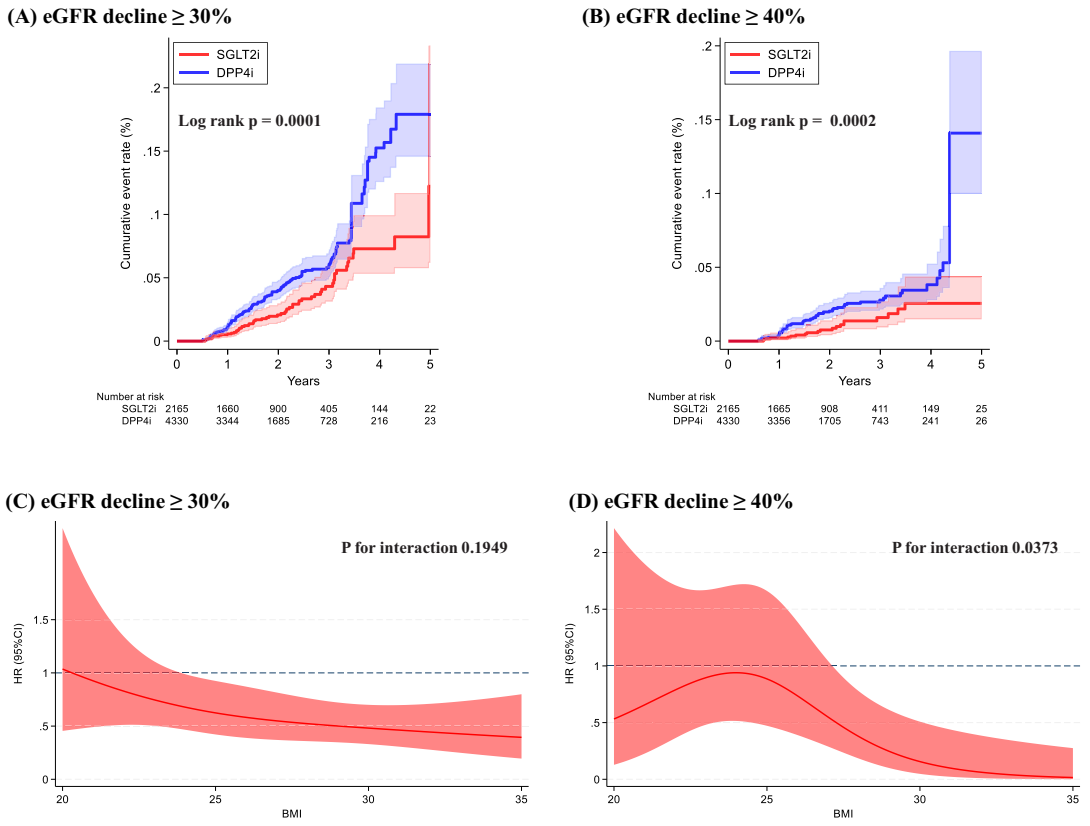


Figure 3 Incident of eGFR decline between the SGLT2 inhibitor and DPP4 inhibitor users. (*A*) (*B*) Kaplan–Meier curves of the incidence of eGFR decline ≥30% (*A*) and the incidence of eGFR decline ≥40% (*B*). The shaded area represents the 95% confidence interval. (*C*) (*D*), the effect of SGLT2 inhibitors over DPP4 inhibitors on the incidence of eGFR decline ≥30% (*C*) and the incidence of eGFR decline ≥40% (*D*). Hazard ratio is shown with a 95% confidence interval. eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose cotransporter-2; DPP4, dipeptidyl peptidase-4.

Discussion

Using a large-scale epidemiological dataset, we analysed 11 419 individuals with diabetes who had newly taken SGLT2 inhibitors or DPP4 inhibitors and substantiated the advantage of SGLT2 inhibitors on kidney outcomes of individuals with type 2 diabetes over DPP4 inhibitors in the real-world setting encompassing a diverse range of individuals. Further, the annual eGFR decline was prominently lowered with SGLT2 inhibitors in individuals with a higher BMI, particularly in overweight and obese individuals with preserved kidney function. To the best of our knowledge, this is the first investigation to show the effect of SGLT2i on kidney outcomes according to BMI using a large-scale real-world dataset.

We believe that our investigation has the following novelties and clinical implications. This is the first study investigating the kidney outcomes for individuals with SGLT2 inhibitors in real-world clinical settings. Improved kidney outcomes were observed across various subgroups of individuals with SGLT2 inhibitors, including preserved kidney function. This result underscores the benefit of SGLT2 inhibitors for individuals with type 2 diabetes in the scope of kidney protection in clinical settings.

In addition, we demonstrated that the advantages of SGLT2 inhibitors were further pronounced in individuals with a higher BMI. Considering the effects of SGLT2 inhibitors, which include an increase in urinary glucose excretion akin to caloric restriction, and the associated mechanisms, it is reasonable to expect beneficial outcomes in kidney function for patients with overweight or obesity. Additionally, we recently reported that greater body weight reduction after SGLT2 inhibitors prescription was associated with better kidney outcomes.[24] These studies underscore the clinical importance of the assessment of body weight for individuals prescribed SGLT2 inhibitors. Nevertheless, SGLT2 inhibitors have various pharmacological mechanisms beyond the increase in urinary glucose excretion akin to caloric restriction, such as the reduction in intraglomerular pressure through tubule-glomerular feedback, enhancement of tubular oxygenation, mitigation of inflammation, and increased stimulation of erythropoiesis. Even in individuals without overweight or obesity, it is postulated that SGLT2 inhibitors exert kidney protective effects through these multifactorial mechanisms, which could be particularly important for individuals with impaired kidney function. Previous studies assessing the impact of BMI on the kidney protective effects of SGLT2 inhibitors focused on patients with chronic kidney disease, concluding that the kidney protective effects were consistent across BMI categories.[9–11] In this study, individuals with preserved eGFR constituted 80% of the total population. Subgroup analyses indicated that the interaction effects of the BMI spectrum were mainly driven by the individuals with preserved kidney function. Further, leveraging the real-world data analysis, our study included more individuals with lower BMI compared with the past studies which primarily focused on subpopulation analysis of randomized clinical trials.[25] By studying individuals with a more diverse range of BMI, we were able to analyse the association with SGLT2 inhibitor efficacy more sensitivity, which may also explain the

divergence between our results and those previously reported. This finding necessitates further discussion.

We acknowledge several limitations in the present study. First, although this is the largest study to analyse the kidney outcome in individuals with SGLT2 inhibitors using real-world data, individuals with lower BMI, especially under 23 kg/m^2, consisted of a small proportion (Supplementary material online, *Figure S3*). It might be challenging to conclude the effect of SGLT2 inhibitors on this population solely based on our study. Second, we used a new-user, active comparator study design, which reduces the sample size.[16,26] Especially, DPP4 inhibitors were the most prevalent medication for diabetes in Japan.[21] In this entire cohort, the number of SGLT2 inhibitor users was 381 838, and a large proportion of individuals were excluded because of not meeting the new user criteria for both SGLT2 inhibitors and DPP4 inhibitors. There could be a risk of selection bias and reduced statistical power, whereas this study design enabled the handling of pre-treatment cofounding factors, which was crucial for the present study. Finally, the presence of unmeasured confounding factors cannot be ruled out due to the nature of observational cohort studies. For instance, information on the duration of diabetes, which could affect the clinical outcomes, was not available in our dataset.

In conclusion, the present study using a nationwide epidemiological database substantiated the improved kidney outcomes in individuals with type 2 diabetes who were prescribed SGLT2 inhibitors compared with DPP4 inhibitors, over a wide range of BMI spectrum. Further, the advantages of SGLT2 inhibitors on kidney outcomes were more pronounced in individuals with an elevated BMI, especially among those who are overweight or obese yet retain kidney function.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

Author contributions

T.J. and H.K. were involved in the conception, design, and conduct of the analysis and interpretation of the results. Y.S. and A.O. contributed to conduct of the analysis and interpretation of the results. T. A., T.K., K.F., N.T., H.M. K.H., T.Y., K.N., I.K., H.Y., M.N., and N.T. contributed to interpretation of the results and critical revision of the manuscript. T.J. wrote the first draft of the manuscript, and all authors edited and approved the final version of the manuscript. H.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest. Research funding and scholarship funds (H.K. and K.F.) were provided by Medtronic Japan, Biotronik Japan, SIMPLEX QUANTUM, Boston Scientific Japan, and Fukuda Denshi, Central Tokyo. A.O. is a member of the Department of Prevention of Diabetes and Lifestyle-related Diseases, a cooperative program between the University of Tokyo and the Asahi Mutual Life Insurance Company. The authors have no conflicts of interest to declare. M.N. received consulting fees or speaking honorarium or both from Mitsubishi Tanabe Pharma, Astellas, Kyowa Kirin, AstraZeneca, JT, and Boehringer Ingelheim and has received research grants from Daiichi Sankyo, Mitsubishi Tanabe Pharma, Kyowa Kirin, JT, Takeda, Chugai Pharmaceutical, and Torii.

Data availability

The DeSC database is available for purchase from DeSC Healthcare Inc.

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