Kidney outcomes in patients with diabetes mellitus did not differ between individual sodium-glucose cotransporter-2 inhibitors

Yuta Suzuki[1], Hidehiro Kaneko[1,2], Akira Okada[3], Satoshi Matsuoka[1], Katsuhito Fujiu[1,2], Nobuaki Michihata[4], Taisuke Jo[4], Norifumi Takeda[1], Hiroyuki Morita[1], Koichi Node[5], Masaomi Nangaku[6], Hideo Yasunaga[7] and Issei Komuro[1]

[1]Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan; [2]Department of Advanced Cardiology, The University of Tokyo, Tokyo, Japan; [3]Department of Prevention of Diabetes and Lifestyle-Related Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [4]Department of Health Services Research, The University of Tokyo, Tokyo, Japan; [5]Department of Cardiovascular Medicine, Saga University, Saga, Japan; [6]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan; and [7]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan

Data comparing kidney outcomes between individual sodium-glucose cotransporter-2 (SGLT2) inhibitors are limited. Here, we aimed to compare the subsequent risk of developing kidney outcomes between individual inhibitors. This would be the first study to compare kidney outcomes of patients with diabetes mellitus who were newly treated with individual SGLT2 inhibitors using a large-scale real-world dataset. To do this, we analyzed results from 12,100 patients with diabetes mellitus who were taking different SGLT2 inhibitors (2,573 with empagliflozin; 2,214 with dapagliflozin; 2,100 with canagliflozin; and 5,213 with other such inhibitors). The primary outcome was the rate of estimated glomerular filtration rate (eGFR) decline as assessed using a linear mixed-effects model with an unstructured covariance. The median age of the patients was 53 years, and 84.4% of the patients were men. The median fasting plasma glucose and HbA1c levels were 147 (interquartile range 126–178) mg/dL and 7.5 (6.9–8.4)%, respectively. The median eGFR was 78 mL/min/1.73 m^2 (interquartile range 68–90). The mean follow-up period was 773 days. The annual eGFR slopes of empagliflozin, dapagliflozin, canagliflozin, and other SGLT2 inhibitors were -1.15 (95% confidence interval, -1.33 to -0.96), -1.14 (-1.32 to -0.96), -1.24 (-1.44 to -1.04), and -1.06 (-1.18 to -0.94) ml/min/1.73 m^2, respectively. No significant interaction was detected between the SGLT2 inhibitors and time using a linear mixed-effects model. A multitude of sensitivity analyses confirmed the robustness of our primary results. Thus, we found that there was no significant difference in the annual eGFR decline slopes between patients taking different SGLT2 inhibitors.

Kidney International (2022) **102,** 1147–1153; https://doi.org/10.1016/j.kint.2022.05.031

Correspondence: *Hidehiro Kaneko, Department of Cardiovascular Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan. E-mail: kanekohidehiro@gmail.com*

Received 4 April 2022; revised 9 May 2022; accepted 20 May 2022; published online 9 August 2022

KEYWORDS: diabetes mellitus; estimated glomerular filtration rate decline; SGLT2 inhibitor

Diabetes mellitus (DM) is the leading cause of renal failure.[1] Sodium-glucose cotransporter-2 (SGLT2) inhibitors are oral antihyperglycemic medications that affect SGLT2 within the proximal tubule, inhibit glucose reabsorption, and promote urinary glucose excretion. Randomized clinical trials have shown that SGLT2 inhibitors could improve kidney outcomes in patients with DM.[2–5] For example, in patients with type 2 DM, the relative risk of the renal-specific composite of end-stage kidney disease, defined as a doubling of the creatinine level or death from renal causes, was reduced by 34% in the canagliflozin-treated group compared with the placebo group.[2] Similarly, among patients with estimated glomerular filtration rate (eGFR) 25–75 ml/min per 1.73 m^2, compared with the placebo group, dapagliflozin reduced the risk of developing a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (hazard ratio, 0.61; 95% confidence interval [CI], 0.51−0.72).[3] SGLT2 inhibitor is currently recognized as a key treatment option for DM from the perspective of the prevention of renal failure,[6,7] and there is a marked increase in the prescription of SGLT2 inhibitors for patients with DM.[8,9] Meanwhile, primarily because of the difference in SGLT2 selectivity, several studies suggested a potential difference in pharmacologic effects between individual SGLT2 inhibitors.[10–13] Nevertheless, there have been no data comparing kidney outcomes between individual SGLT2 inhibitorsusing a real-world dataset, and therefore, whether the protective effects of SGLT2 inhibitors could be considered a class effect remains unknown. In this study, we analyzed a large-scale health checkup and administrative claims dataset and sought to compare kidney outcomes among commercially available SGLT2 inhibitors in Japan.

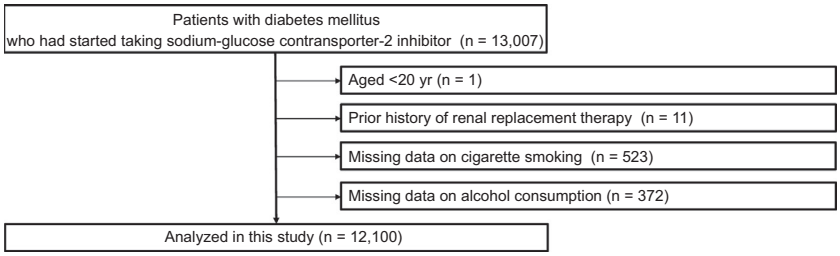

Figure 1 | Flowchart. We extracted 13,007 patients with diabetes mellitus (*International Classification of Diseases, Tenth Revision* [*ICD-10*], codes E10–E14) and available data on estimated glomerular filtration rate and proteinuria who had started taking sodium-glucose cotransporter-2 inhibitor at least 4 months after enrollment (insurance coverage). Furthermore, because we focused on estimated glomerular filtration rate decline over time, we included only individuals with repeated measures of estimated glomerular filtration rate. Because the maximum prescription period for medication is 3 months in Japan, we set a 4-month look-back period. We excluded individuals aged <20 years (n = 1), those with a prior history of renal replacement therapy (n = 11), those with missing data on cigarette smoking (n = 523), and those with missing data on alcohol consumption (n = 372). Finally, 12,100 patients were analyzed in this study.

METHODS

Study design and data source

We conducted this retrospective observational cohort study using the JMDC Claims Database (JMDC Inc.), which is a health checkup and insurance claims database, between January 2005 and April 2021.[14,15] The JMDC Claims Database includes individuals' health checkup records (e.g., body mass index [BMI], blood pressure, and laboratory data) and insurance claims data recorded using the *International Classification of Diseases, Tenth Revision* (*ICD-10*), coding. We extracted data of 13,007 patients with DM (*ICD-10* codes E10–E14) and available data on eGFR and proteinuria who had started taking SGLT2 inhibitors at least 4 months after enrollment (insurance coverage). Furthermore, we included only individuals with repeated measures of eGFR because we focused on the decline of eGFR over time. As the maximum prescription period for medication is 3 months in Japan, we set a 4-month look-back period. We excluded patients aged <20 years (n = 1), those with a history of renal replacement therapy (n = 11), those with missing data on cigarette smoking (n = 523), and those with missing data on alcohol consumption (n = 372). Finally, 12,100 patients were included in this study (Figure 1).

Ethical approval

This study was approved by the Ethics Committee of the University of Tokyo (number 2018-10862). This study was conducted following the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data included in this dataset were deidentified. Anyone who purchased it from JMDC Inc. (https://www.jmdc.co.jp/en/index) could use this database.

Measurements and definitions

We reviewed the health checkup data collected within 6 months before the SGLT2 inhibitors were prescribed. The following data were collected: BMI, blood pressure, fasting blood glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. If available, we also obtained data on hemoglobin A1c levels. We collected information on cigarette smoking (current or noncurrent) and alcohol consumption (every day or not) using a self-reported questionnaire during the health checkup. From the administrative claims records, we retrieved data on the presence of renal replacement therapy (dialysis and kidney transplantation) and diabetic complications (nephropathy, retinopathy, and neuropathy) on the prescription date of SGLT2 inhibitors. Information on medications on the date of prescription of SGLT2 inhibitors was also collected. Overweight/obesity was defined as BMI ≥25 kg/m^2. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of blood pressure–lowering medications. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, triglyceride ≥150 mg/dl, or the use of lipid-lowering medications.[16]

Outcomes

Data were obtained from January 2005 to April 2021. The primary outcome was a rate of eGFR decline estimated using a linear mixed-effects model with the unstructured covariance structure.

Statistical analysis

Continuous variables were presented as medians (quartile 1–quartile 3), and categorical variables were described as numbers (percentages). Study participants were divided into 4 groups according to individual SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, and other SGLT2 inhibitors). Considering the prescription rates, sample size, and global approval status, we combined ipragliflozin, tofogliflozin, and luseogliflozin into one group. We calculated the statistical significance of the differences between groups using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables.

A linear mixed-effects model with random slope and random intercept using the unstructured covariance structure was used to compare the slopes of eGFR over time between the individual SGLT2 inhibitors. This model included age (tertile), sex, BMI (<18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m^2), hypertension, fasting plasma glucose, dyslipidemia, cigarette smoking, alcohol consumption, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, insulin use, dipeptidyl peptidase-4 inhibitor use, glucagon-like peptide-1 receptor agonist use, biguanide use, sulfonylurea use, α-glucosidase inhibitor use, thiazolidine use, glinide use, renin-angiotensin system inhibitor use, β-blocker use, calcium channel blocker use, mineral corticoid receptor antagonist use, diuretics use, statin use, year of prescription, proteinuria (negative, trace, 1+, 2+, and 3+), time (linear), and individual SGLT2 inhibitors. We selected these covariates *a priori* because they would potentially influence the study results.[16–18] The *P* value for the interaction between time and individual SGLT2 inhibitors was calculated.

We conducted 10 sensitivity analyses to validate the robustness of our primary finding. First, we examined the association between SGLT2 inhibitors and kidney outcomes only in patients who

Table 1 | Baseline characteristics

Characteristic	Overall (n = 12,100)	Empagliflozin (n = 2573)	Dapagliflozin (n = 2214)	Canagliflozin (n = 2100)	Other SGLT2 inhibitors (n = 5213)	*P* value
Age, yr	53 (47–58)	53 (47–58)	52 (47–57)	53 (47–58)	53 (47–58)	0.001
Men, n (%)	10,218 (84.4)	2187 (85.0)	1854 (83.7)	1811 (86.2)	4366 (83.8)	0.037
BMI, kg/m^2	27.8 (25.2–31.1)	27.7 (25.1–31.1)	28.1 (25.5–31.3)	27.6 (25–30.9)	27.8 (25.1–31.1)	0.002
SBP, mm Hg	129 (120–140)	129 (120–139)	130 (121–140)	129 (120–139)	129 (120–140)	0.27
DBP, mm Hg	81 (74–89)	81 (74–88)	82 (75–89)	81 (74–89)	81 (74–88)	0.4
Cigarette smoking, n (%)	4012 (33.2)	819 (31.8)	757 (34.2)	700 (33.3)	1736 (33.3)	0.36
Alcohol consumption, n (%)	2463 (20.4)	510 (19.8)	438 (19.8)	451 (21.5)	1064 (20.4)	0.47
Comorbidity, n (%)						
Overweight/obesity	9299 (76.9)	1983 (77.1)	1761 (79.5)	1589 (75.7)	3966 (76.1)	0.006
Hypertension	7723 (63.8)	1675 (65.1)	1434 (64.8)	1325 (63.1)	3289 (63.1)	0.22
Dyslipidemia	9922 (82.0)	2149 (83.5)	1807 (81.6)	1710 (81.4)	4256 (81.6)	0.16
Diabetic nephropathy	2020 (16.7)	460 (17.9)	348 (15.7)	321 (15.3)	891 (17.1)	0.053
Diabetic retinopathy	3002 (24.8)	684 (26.6)	515 (23.3)	448 (21.3)	1355 (26.0)	<0.001
Diabetic neuropathy	455 (3.8)	102 (4.0)	72 (3.3)	77 (3.7)	204 (3.9)	0.52
Medication, n (%)						
Insulins	1063 (8.8)	204 (7.9)	228 (10.3)	138 (6.6)	493 (9.5)	<0.001
DPP-4 inhibitor	6975 (57.6)	1448 (56.3)	1175 (53.1)	1255 (59.8)	3097 (59.4)	<0.001
GLP-1 receptor agonist	272 (2.2)	74 (2.9)	46 (2.1)	35 (1.7)	117 (2.2)	0.043
Biguanide	5746 (47.5)	1273 (49.5)	1009 (45.6)	929 (44.2)	2535 (48.6)	<0.001
Sulfonylurea	2489 (20.6)	464 (18.0)	453 (20.5)	393 (18.7)	1179 (22.6)	<0.001
α-GI	1289 (10.7)	267 (10.4)	240 (10.8)	184 (8.8)	598 (11.5)	0.008
Thiazolidine	1310 (10.8)	240 (9.3)	246 (11.1)	213 (10.1)	611 (11.7)	0.009
Glinides	370 (3.1)	92 (3.6)	53 (2.4)	61 (2.9)	164 (3.1)	0.12
Renin-angiotensin system inhibitor	4906 (40.5)	1085 (42.2)	888 (40.1)	833 (39.7)	2100 (40.3)	0.28
β-Blocker	1050 (8.7)	304 (11.8)	168 (7.6)	176 (8.4)	402 (7.7)	<0.001
Calcium channel blocker	2990 (24.7)	670 (26.0)	564 (25.5)	508 (24.2)	1248 (23.9)	0.16
Mineral corticoid receptor antagonist	229 (1.9)	66 (2.6)	37 (1.7)	39 (1.9)	87 (1.7)	0.041
Diuretics	980 (8.1)	231 (9.0)	178 (8.0)	164 (7.8)	407 (7.8)	0.32
Statin	4843 (40.0)	1085 (42.2)	860 (38.8)	796 (37.9)	2102 (40.3)	0.016
Laboratory data						
Glucose, mg/dl	147 (126–178)	147 (127–178)	148 (125–179)	146 (125–178)	147 (126–178)	0.64
HbA1c, %	7.5 (6.9–8.4)	7.4 (6.9–8.4)	7.5 (6.9–8.5)	7.4 (6.8–8.4)	7.5 (6.9–8.4)	0.35
LDL-C, mg/dl	120 (100–142)	119 (99–142)	122 (100–143)	122 (101–144)	120 (100–141)	0.014
HDL-C, mg/dl	49 (42–57)	48 (42–57)	49 (43–58)	49 (42–56)	49 (42–57)	0.11
Triglycerides, mg/dl	138 (98–204)	137 (98–198)	136 (98–203)	142 (101–206)	138 (96–205)	0.1
eGFR, ml/min per 1.73 m^2	78 (68–90)	77 (66–88)	79 (69–91)	78 (67–89)	79 (68–90)	<0.001
Proteinuria, n (%)						
Negative	8613 (71.2)	1801 (70.0)	1552 (70.1)	1466 (69.8)	3794 (72.8)	0.041
Trace	1615 (13.3)	355 (13.8)	327 (14.8)	291 (13.9)	642 (12.3)	
1+	1136 (9.4)	248 (9.6)	207 (9.3)	196 (9.3)	485 (9.3)	
2+	549 (4.5)	121 (4.7)	103 (4.7)	106 (5.0)	219 (4.2)	
3+	187 (1.5)	48 (1.9)	25 (1.1)	41 (2.0)	73 (1.4)	

BMI, body mass index; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; α-GI, α-glucosidase inhibitor; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2.
Data are reported as median (interquartile range), unless otherwise indicated.

continued to use the same SGLT2 inhibitor for >3 months. Second, we analyzed individuals diagnosed with type 2 DM (*ICD-10* code E11). Third, we conducted subgroup analyses stratified by sex, age, and baseline hemoglobin A1c level. Fourth, we divided the study participants into 6 types of SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin). Fifth, we analyzed 8740 individuals with a follow-up period ≥365 days. Sixth, we defined the kidney outcome as a decrease in eGFR (≥30%) and conducted a Cox proportional hazard regression analysis to examine the association between individual SGLT2 inhibitors and the subsequent incidence of kidney outcomes. Empagliflozin was used as a reference. Model 1 included individual SGLT2 inhibitors (unadjusted model). Model 2 included individual use of the SGLT2 inhibitor, age (tertile), and sex. Furthermore, as in model 3, we added BMI (<18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m^2), hypertension, fasting plasma glucose (tertile), dyslipidemia, cigarette smoking, alcohol consumption, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, insulin use, dipeptidyl

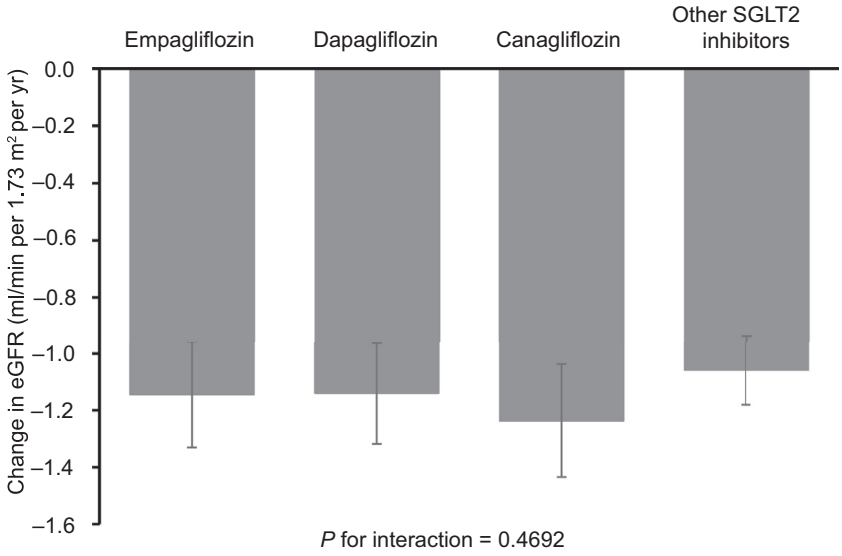

Figure 2 | Comparison of the change in estimated glomerular filtration rate (eGFR) among sodium-glucose cotransporter-2 (SGLT2) inhibitors. We performed a random slope and random intercept linear mixed-effects model to compare the annual slopes of eGFR among SGLT2 inhibitors. Model included age, sex, body mass index, hypertension, fasting plasma glucose, dyslipidemia, cigarette smoking, alcohol consumption, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, insulin use, dipeptidyl peptidase-4 inhibitor use, glucagon-like peptide-1 receptor agonist use, biguanide use, sulfonylurea use, α-glucosidase inhibitor use, thiazolidine use, glinide use, renin-angiotensin system inhibitor use, β-blocker use, calcium channel blocker use, mineral corticoid receptor antagonist use, diuretics use, statin use, year of prescription, proteinuria (negative, trace, 1+, 2+, and 3+), time (linear), and individual SGLT2 inhibitors. The *P* value for the interaction between time and individual SGLT2 inhibitors was 0.4692.

peptidase-4 inhibitor use, glucagon-like peptide-1 receptor agonist use, biguanide use, sulfonylurea use, α-glucosidase inhibitor use, thiazolidine use, glinide use, renin-angiotensin system inhibitor use, β-blocker use, calcium channel blocker use, mineral corticoid receptor antagonist use, diuretics use, statin use, year of prescription, proteinuria (negative, trace, 1+, 2+, and 3+), and eGFR to model 2. We conducted the Wald test to compare hazard ratios for kidney outcomes between individual SGLT2 inhibitors. Seventh, because we considered death to be a competing risk for kidney outcomes, we used the Fine-Gray proportional hazards model.[15] Eighth, the kidney outcome was redefined as a decrease in eGFR of ≥30% or the initiation of renal replacement therapy. Ninth, the kidney outcome was redefined as a decrease in eGFR of ≥40%. Finally, the kidney outcome was redefined as a decrease in eGFR of ≥50%.

The significance level was set at $P < 0.05$. All statistical analyses were performed with Stata v17 (StataCorp LLC).

RESULTS

Clinical characteristics

The clinical characteristics of the study participants are summarized in Table 1. The median age was 53 (quartile 1–quartile 3, 47−58) years, and 10,218 (84.4%) patients were men. The median of fasting plasma glucose and hemoglobin A1c levels were 147 (quartile 1–quartile 3, 126−178) mg/dl and 7.5 (quartile 1–quartile 3, 6.9−8.4) %, respectively. The prevalence rates of overweight/obesity, hypertension, and dyslipidemia were 76.9%, 63.8%, and 82.0%, respectively. Diabetic nephropathy, retinopathy, and neuropathy were observed in 16.7%, 24.8%, and 3.8% of the patients, respectively. More than half and 8.8% of the study participants used dipeptidyl peptidase-4 inhibitors and insulin, respectively. Study participants were classified into 4 groups according to individual SGLT2 inhibitors: empagliflozin (n = 2573), dapagliflozin (n = 2214), canagliflozin (n = 2100), and other SGLT2 inhibitors (n = 5213; 2636 for ipragliflozin, 1467 for tofogliflozin, and 1110 for luseogliflozin).

Annual eGFR slopes among individual SGLT2 inhibitors

The mean follow-up period was 773 ± 477 days. The annual eGFR slopes of empagliflozin, dapagliflozin, canagliflozin, and other SGLT2 inhibitors were –1.15 (95% CI, –1.33 to –0.96), –1.14 (95% CI, –1.32 to –0.96), –1.24 (95% CI, –1.44 to –1.04), and –1.06 (95% CI, –1.18 to –0.94) ml/min per 1.73 m^2, respectively. No significant interaction was detected between the SGLT2 inhibitors and time using a linear mixed-effects model ($P = 0.4692$; Figure 2).

Sensitivity analysis

First, the continuation rates 3 months after the first prescription were 89.5% for empagliflozin, 87.8% for dapagliflozin, 89.0% for canagliflozin, and 88.0% for other SGLT2 inhibitors. We included 10,705 participants who continued to use the same SGLT2 inhibitor for >3 months and found the annual eGFR slopes were comparable between individual SGLT2 inhibitors (Supplementary Figure S1). Second, we analyzed 8908 patients diagnosed with type 2 DM, and our primary results were unchanged (Supplementary Figure S2). Third, subgroup analyses showed the annual change in eGFR was not statistically different between individual SGLT2 inhibitors, irrespective of sex, age, and baseline hemoglobin A1c (Table 2). Fourth, there were no significant differences in

Table 2 | Subgroup analysis

Subgroups	N	Empagliflozin	Dapagliflozin	Canagliflozin	Other SGLT2 inhibitors	*P* value for interaction
Sex						
Men	10,218	−1.10 (−1.30 to −0.90)	−1.21 (−1.40 to −1.02)	−1.22 (−1.43 to −1.01)	−1.05 (−1.18 to −0.92)	0.4129
Women	1882	−1.43 (−1.95 to −0.90)	−0.71 (−1.20 to −0.22)	−1.30 (−1.83 to −0.76)	−1.08 (−1.41 to −0.76)	0.2145
Age, yr						
≥50	7801	−0.93 (−1.14 to −0.72)	−1.04 (−1.25 to −0.83)	−1.17 (−1.40 to −0.94)	−0.86 (−1.01 to −0.72)	0.1340
<50	4299	−1.47 (−1.82 to −1.13)	−1.28 (−1.60 to −0.97)	−1.37 (−1.73 to −1.02)	−1.38 (−1.60 to −1.17)	0.8857
HbA1c						
HbA1c ≥ median (7.5%)	5632	−1.81 (−2.11 to −1.51)	−1.70 (−1.99 to −1.41)	−1.78 (−2.10 to −1.46)	−1.72 (−1.91 to −1.52)	0.9502
HbA1c < median (7.5%)	5522	−0.54 (−0.79 to −0.29)	−0.61 (−0.86 to −0.37)	−0.73 (−0.99 to −0.47)	−0.49 (−0.66 to −0.32)	0.4630

eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; SGLT2, sodium-glucose cotransporter-2.
We compared the change in eGFR between individual SGLT2 inhibitors, stratified by sex, age, and baseline HbA1c level. Sex was excluded from the adjusted variables in the subgroup analysis stratified by sex. We excluded 946 individuals with missing HbA1c data from the subgroup analysis stratified by HbA1c levels.

annual eGFR slopes among patients treated with dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin compared with empagliflozin (Supplementary Figure S3). Fifth, our primary results were unchanged in individuals with a follow-up period ≥365 days (Supplementary Figure S4). Sixth, when we defined the kidney outcome as a decrease in eGFR (≥30%), 253 kidney outcomes were identified. In the multivariable-adjusted model (model 3), compared with empagliflozin, hazard ratios of dapagliflozin, canagliflozin, and other SGLT2 inhibitors for kidney outcome were 0.70 (95% CI, 0.46–1.07), 1.03 (95% CI, 0.69–1.54), and 0.77 (95% CI, 0.54–1.09), respectively. Wald tests did not show significant differences in kidney outcomes among individual SGLT2 inhibitors ($P = 0.1682$; Figure 3). Seventh, the results shown in the sixth sensitivity analysis remained unchanged after a competing risks analysis (Supplementary Figure S5). Eighth, the outcome was redefined as a decrease in eGFR of ≥30% or the initiation of renal replacement therapy, and the Wald test showed that there was no significant difference in the risk of developing kidney outcomes between individual SGLT2 inhibitors (Supplementary Figure S6). Ninth, kidney outcome was defined as a decrease in eGFR of ≥40%. According to this definition, the risk of kidney outcomes was comparable among individual SGLT2 inhibitors (Supplementary Figure S7). Tenth, we defined the outcome as a decrease in eGFR of ≥50%, and the risk for this kidney outcome did not differ between individual SGLT2 inhibitors under this definition (Supplementary Figure S8).

DISCUSSION

In this study, we analyzed 12,100 patients with DM who had newly taken SGLT2 inhibitors and found that there was no significant difference in the annual eGFR slopes between patients taking empagliflozin, dapagliflozin, canagliflozin, and other SGLT2 inhibitors. We confirmed the robustness of our results through various sensitivity analyses. To the best of our knowledge, the present study is the first to compare the kidney outcomes of patients with DM who were newly treated with individual SGLT2 inhibitors using a large-scale, real-world dataset.

A growing body of evidence supports the use of SGLT2 inhibitors in the treatment of DM and chronic kidney disease. Not only randomized controlled trials,[2–5] but analyses of real-world data also support the clinical benefit of SGLT2 inhibitors.[16–18] An analysis of Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL), an international,

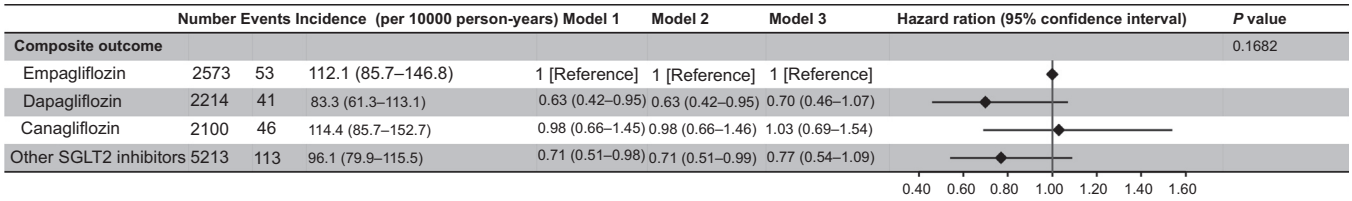

Figure 3 | Risk of kidney outcome, defined as a decrease in estimated glomerular filtration rate (eGFR; ≥30%) among individual sodium-glucose cotransporter-2 (SGLT2) inhibitors. We defined the kidney outcome as a decrease in eGFR (≥30%) and conducted a Cox proportional hazard regression analysis to examine the association between individual SGLT2 inhibitors and the subsequent incidence of kidney outcomes. Empagliflozin was used as a reference. Model 1 included individual SGLT2 inhibitors (unadjusted model). Model 2 included individual use of the SGLT2 inhibitor, age (tertile), and sex. Furthermore, as in model 3, we added body mass index (<18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m^2), hypertension, fasting plasma glucose (tertile), dyslipidemia, cigarette smoking, alcohol consumption, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, insulin use, dipeptidyl peptidase-4 inhibitor use, glucagon-like peptide-1 receptor agonist use, biguanide use, sulfonylurea use, α-glucosidase inhibitor use, thiazolidine use, glinide use, renin-angiotensin system inhibitor use, β-blocker use, calcium channel blocker use, mineral corticoid receptor antagonist use, diuretics use, statin use, year of prescription, proteinuria (negative, trace, 1+, 2+, and 3+), and eGFR to model 2. We performed the Wald test to compare hazards for kidney outcomes between individual SGLT2 inhibitors, and the *P* value was 0.1682.

real-world study of patients with type 2 DM, demonstrated that the initiation of SGLT2 inhibitors could slow the decline of kidney function compared with the initiation of other glucose-lowering medications.[16] Similarly, another cohort study in Sweden, Denmark, and Norway reported that the risk of developing adverse kidney outcomes was reduced in patients with DM using SGLT2 inhibitors versus those using dipeptidyl peptidase-4 inhibitors.[17] These results of preceding studies may suggest a class effect of SGLT2 inhibitors from the perspective of renal protective effects.

Meanwhile, given the differences between individual SGLT2 inhibitors (e.g., selectivity of SGLT2 and duration of action[12,19]), there could be a difference in clinical outcomes between individual SGLT2 inhibitors, and several studies have shown a potential difference between individual SGLT2 inhibitors. For example, although SGLT2 inhibitors are also known to have a cardiovascular benefit,[20–22] a recent analysis of a retrospective cohort in Taiwan showed that dapagliflozin use had a more favorable effect on heart failure than empagliflozin use.[10] An analysis of a cohort that included patients with type 2 DM and heart failure showed that plasma aldosterone concentration was significantly increased in patients treated with empagliflozin and canagliflozin compared with those treated with dapagliflozin, and plasma noradrenaline was significantly increased in patients treated with empagliflozin compared with those treated with canagliflozin and dapagliflozin, suggesting the potential difference in neurohumoral response among individual SGLT2 inhibitors.[13] Given these backgrounds, there could be a difference in kidney outcomes between individual SGLT2 inhibitors. Furthermore, a network meta-analysis of randomized trials suggested a potential advantage in renal protection of dapagliflozin and empagliflozin over canagliflozin.[23] However, data on comparisons of kidney outcome risk between individual SGLT2 inhibitors are scarce. SGLT2 inhibitors were first launched in Japan in 2014 and included 6 commercially available SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin). Considering the widespread use of SGLT2 inhibitors in clinical practice, it is essential to evaluate the comparability of kidney outcomes between individual SGLT2 inhibitors.

The present study is distinguishable from previous studies in that we compared kidney outcomes (mainly changes in eGFR) between commercially available SGLT2 inhibitors in Japan using a nationwide, real-world dataset and showed that there were no statistically significant differences in kidney outcomes between individual SGLT2 inhibitors. Furthermore, our finding is in line with a recent study presenting comparable cardiovascular outcomes among individual SGLT2 inhibitors.[24] Although we performed a multitude of sensitivity analyses and confirmed the robustness of our primary findings, further investigation is needed to validate our results. The present study showed comparable kidney outcomes between the individual SGLT2 inhibitors. However, because of the relatively short follow-up period, the number of patients requiring renal replacement therapy was small (n = 12). The mean follow-up period was relatively short, and therefore, analysis of other independent datasets with longer follow-up periods is required.

There are several limitations to this study. Although we performed multivariate Cox regression analyses, the possibility of unmeasured confounders could not be eliminated. For example, the duration of DM or information on socioeconomic status could have influenced the results of this study. However, these data were not available in the JMDC Claims Database. Given that the study participants enrolled in the JMDC Claims Database are covered by "kempo," which is a health insurance system for employees, and most of the individuals registered in our dataset are employees (or their family members) who work for relatively large Japanese companies, the socioeconomic status of the participants in the JMDC Claims Database would not be so largely different. However, we must consider that the lack of these data is a major study limitation. Because the JMDC Claims Database does not include individuals aged >75 years, it is unknown whether our primary results could be applicable to elderly individuals. More than 80% of study participants were men, which might decrease the generalizability of the findings of the present study. Finally, the dose of medications (e.g., each SGLT2 inhibitor) was not considered in this study.

In conclusion, our analysis of a nationwide, real-world dataset demonstrated that the kidney outcomes of patients with DM were comparable between individual SGLT2 inhibitors.

DISCLOSURE

Research funding and scholarship funds (HK and KF) were provided by Medtronic Japan, Biotronik Japan, SIMPLEX QUANTUM, Boston Scientific Japan, and Fukuda Denshi, Central Tokyo. AO 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. MN received consulting fees, 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. All the other authors declared no competing interests.

DATA STATEMENT

The JMDC Claims Database is available for purchase from JMDC, Inc. (https://www.jmdc.co.jp/en/index).

ACKNOWLEDGMENTS

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (21AA2007), and the Ministry of Education, Culture, Sports, Science and Technology, Japan (20H03907, 21H03159, and 21K08123). The funding sources had nothing regarding the current study.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Comparison of the change in estimated glomerular filtration rate (eGFR) among sodium-glucose cotransporter-2 (SGLT2) inhibitors (continuous prescription group).

Figure S2. Comparison of the change in estimated glomerular filtration rate (eGFR) among sodium-glucose cotransporter-2 (SGLT2) inhibitors for patients diagnosed with type 2 diabetes mellitus (DM).
Figure S3. Comparison of the change in estimated glomerular filtration rate (eGFR) among 6 sodium-glucose cotransporter-2 (SGLT2) inhibitors.
Figure S4. Comparison of the change in estimated glomerular filtration rate (eGFR) among sodium-glucose cotransporter-2 (SGLT2) inhibitors for patients with a follow-up period ≥365 days.
Figure S5. Risk of kidney outcome, defined as a decrease in estimated glomerular filtration rate (eGFR; ≥30%) among individual sodium-glucose cotransporter-2 (SGLT2) inhibitors (competing risks model).
Figure S6. Risk of composite kidney outcome, defined as a decrease in estimated glomerular filtration rate (eGFR; ≥30%) or the initiation of renal replacement therapy among individual sodium-glucose cotransporter-2 (SGLT2) inhibitors.
Figure S7. Risk of kidney outcome, defined as a decrease in estimated glomerular filtration rate (eGFR; ≥40%) among individual sodium-glucose cotransporter-2 (SGLT2) inhibitors.
Figure S8. Risk of kidney outcome, defined as a decrease in estimated glomerular filtration rate (eGFR; ≥50%) among individual sodium-glucose cotransporter-2 (SGLT2) inhibitors.

REFERENCES

1. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA*. 2016;316:602–610.
2. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
3. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446.
4. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334.
5. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:2099.
6. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2020;43:487–493.
7. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: management of hyperglycaemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2020;63:221–228.
8. Eberly LA, Yang L, Eneanya ND, et al. Association of race/ethnicity, gender, and socioeconomic status with sodium-glucose cotransporter 2 inhibitor use among patients with diabetes in the US. *JAMA Netw Open*. 2021;4:e216139.
9. Bouchi R, Sugiyama T, Goto A, et al. Retrospective nationwide study on the trends in first-line antidiabetic medication for patients with type 2 diabetes in Japan. *J Diabetes Investig*. 2022;13:280–291.
10. Shao SC, Chang KC, Lin SJ, et al. Differences in outcomes of hospitalizations for heart failure after SGLT2 inhibitor treatment: effect modification by atherosclerotic cardiovascular disease. *Cardiovasc Diabetol*. 2021;20:213.
11. Lin YH, Huang YY, Hsieh SH, et al. Renal and glucose-lowering effects of empagliflozin and dapagliflozin in different chronic kidney disease stages. *Front Endocrinol (Lausanne)*. 2019;10:820.
12. Tager T, Frankenstein L, Atar D, et al. Influence of receptor selectivity on benefits from SGLT2 inhibitors in patients with heart failure: a systematic review and head-to-head comparative efficacy network meta-analysis. *Clin Res Cardiol*. 2022;111:428–439.
13. Nakagaito M, Joho S, Ushijima R, et al. Comparison of canagliflozin, dapagliflozin and empagliflozin added to heart failure treatment in decompensated heart failure patients with type 2 diabetes mellitus. *Circ Rep*. 2019;1:405–413.
14. Kaneko H, Itoh H, Yotsumoto H, et al. Association of isolated diastolic hypertension based on the cutoff value in the 2017 American College of Cardiology/American Heart Association blood pressure guidelines with subsequent cardiovascular events in the general population. *J Am Heart Assoc*. 2020;9:e017963.
15. Kaneko H, Yano Y, Itoh H, et al. Association of blood pressure classification using the 2017 American College of Cardiology/American Heart Association blood pressure guideline with risk of heart failure and atrial fibrillation. *Circulation*. 2021;143:2244–2253.
16. Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol*. 2020;8:27–35.
17. Pasternak B, Wintzell V, Melbye M, et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian cohort study. *BMJ*. 2020;369:m1186.
18. Nagasu H, Yano Y, Kanegae H, et al. Kidney outcomes associated with SGLT2 inhibitors versus other glucose-lowering drugs in real-world clinical practice: the Japan Chronic Kidney Disease Database. *Diabetes Care*. 2021;44:2542–2551.
19. Kurosaki E, Ogasawara H. Ipragliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors in the treatment of type 2 diabetes: preclinical and clinical data. *Pharmacol Ther*. 2013;139:51–59.
20. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
21. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
22. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
23. Wei XB, Wei W, Ding LL, Liu SY. Comparison of the effects of 10 GLP-1 RA and SGLT2 inhibitor interventions on cardiovascular, mortality, and kidney outcomes in type 2 diabetes: a network meta-analysis of large randomized trials. *Prim Care Diabetes*. 2021;15:208–211.
24. Suzuki Y, Kaneko H, Okada A, et al. Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus. *Cardiovasc Diabetol*. 2022;21:67.