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 | https://doi.org/10.2337/dc21-1081

Hajime Nagasu,[1] Yuichiro Yano,[2,3] Hiroshi Kanegae,[4] Hiddo J.L. Heerspink,[5] Masaomi Nangaku,[6] Yosuke Hirakawa,[6] Yuka Sugawara,[6] Naoki Nakagawa,[7] Yuji Tani,[8] Jun Wada,[9] Hitoshi Sugiyama,[10] Kazuhiko Tsuruya,[11] Toshiaki Nakano,[12] Shoichi Maruyama,[13] Takashi Wada,[14] Kunihiro Yamagata,[15] Ichiei Narita,[16] Kouichi Tamura,[17] Motoko Yanagita,[18] Yoshio Terada,[19] Takashi Shigematsu,[20] Tadashi Sofue,[21] Takafumi Ito,[22] Hirokazu Okada,[23] Naoki Nakashima,[24] Hiromi Kataoka,[25] Kazuhiko Ohe,[26] Mihoko Okada,[27] Seiji Itano,[1] Akira Nishiyama,[28] Eiichiro Kanda,[29] Kohjiro Ueki,[30] and Naoki Kashihara[1]

OBJECTIVE

Randomized controlled trials have shown kidney-protective effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors, and clinical practice databases have suggested that these effects translate to clinical practice. However, long-term efficacy, as well as whether the presence or absence of proteinuria and the rate of estimated glomerular filtration rates (eGFR) decline prior to SGLT2 inhibitor initiation modify treatment efficacy among type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) patients, is unknown.

RESEARCH DESIGN AND METHODS

Using the Japan Chronic Kidney Disease Database (J-CKD-DB), a nationwide multicenter CKD registry, we developed propensity scores for SGLT2 inhibitor initiation, with 1:1 matching with patients who were initiated on other glucose-lowering drugs. The primary outcome included rate of eGFR decline, and the secondary outcomes included a composite outcome of 50% eGFR decline or end-stage kidney disease.

RESULTS

At baseline, mean age at initiation of the SGLT2 inhibitor ($n = 1{,}033$) or other glucose-lowering drug ($n = 1{,}033$) was 64.4 years, mean eGFR was 68.1 mL/min per 1.73 m^2, and proteinuria was apparent in 578 (28.0%) of included patients. During follow-up, SGLT2 inhibitor initiation was associated with reduced eGFR decline (difference in slope for SGLT2 inhibitors vs. other drugs 0.75 mL/min/1.73 m^2 per year [0.51 to 1.00]). During a mean follow-up of 24 months, 103 composite kidney outcomes occurred: 30 (14 events per 1,000 patient-years) among the SGLT2 inhibitors group and 73 (36 events per 1,000 patient-years) among the other drugs group (hazard ratio 0.40, 95% CI 0.26–0.61). The benefit provided by SGLT2 inhibitors was consistent irrespective of proteinuria and rate of eGFR decline before initiation of SGLT2 inhibitors ($P_{heterogeneity} \geq 0.35$).

CONCLUSIONS

The benefits of SGLT2 inhibitors on kidney function as observed in clinical trials translate to patients treated in clinical practice with no evidence that the effects are modified by the underlying rate of kidney function decline or the presence of proteinuria.

[1]*Department of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Japan*
[2]*Center for Novel and Exploratory Clinical Trials, Yokohama City University, Kanagawa, Japan*
[3]*Department of Family Medicine and Community Health, Duke University, Durham, NC*
[4]*Genki Plaza Medical Center for Health Care, Tokyo, Japan*
[5]*The George Institute for Global Health, University of New South Wales, Sydney, Australia*
[6]*Division of Nephrology and Endocrinology, University of Tokyo Graduate School of Medicine, Tokyo, Japan*
[7]*Division of Cardiology, Nephrology, Pulmonology and Neurology, Department of Internal Medicine, Asahikawa Medical University, Hokkaido, Japan*
[8]*Department of Medical Informatics and Hospital Management, Asahikawa Medical University, Hokkaido, Japan*
[9]*Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[10]*Department of Human Resource Development of Dialysis Therapy for Kidney Disease, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[11]*Department of Nephrology, Nara Medical University, Nara, Japan*
[12]*Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[13]*Department of Nephrology, Nagoya University Graduate School of Medicine, Aichi, Japan*
[14]*Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan*
[15]*Department of Nephrology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan*
[16]*Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*

Type 2 diabetes mellitus (T2DM) is the leading cause of kidney failure (1). However, few effective long-term treatments to slow nephropathy progression among T2DM patients are available. ACE inhibitors and angiotensin II receptor blockers (ARBs) have been shown to slow a decline in kidney function among T2DM patients with chronic kidney disease (CKD) (2,3). However, the efficacy of ACE inhibitors and ARBs for the kidney has not been previously characterized among T2DM and CKD patients without proteinuria.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, originally approved solely as glucose-lowering drugs for the treatment of T2DM, have increasingly been shown to have kidney- and cardiovascular-protective properties in several randomized controlled trials (RCTs) (4–7). However, little is known regarding whether the results of prior RCTs are applicable to the broader range of T2DM patients with CKD encountered in clinical practice, especially with regard to the kidney outcomes associated with SGLT2 inhibitors among T2DM and CKD patients without sev-ere albuminuria or proteinuria.

Results of an international, real-world study of T2DM patients (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors [CVD-REAL] 3) demonstrated that initiation of SGLT2 inhibitors was associated with a slower rate of estimated glomerular filtration rate (eGFR) decline in comparison with other glucose-lowering drugs (8). Another large register-based cohort study using nationwide data from routine clinical practice in Sweden, Denmark, and Norway showed that SGLT2 inhibitors lowered the risk of kidney events in comparisons with dipeptidyl peptidase 4 (DPP-4) inhibitor therapies (9). However, in both studies, CKD patients comprised $<$10% of the populations, and neither albuminuria nor proteinuria was assessed. Furthermore, no studies have assessed whether the effects of SGLT2 inhibitors on kidney function varied by the rate of kidney function decline before initiation of SGLT2 inhibitors. This is clinically relevant, since patients who have rapid decline in eGFR are at high risk for kidney failure within a short period (10).

The Japan Chronic Kidney Disease Database (J-CKD-DB) is a nationwide multicenter CKD registry (11). Using data from the J-CKD-DB, we compared the rate of eGFR decline and kidney outcomes between T2DM and CKD patients initiating SGLT2 inhibitors versus other glucose-lowering drugs, and the associations differed by the presence of proteinuria and rapid decline in eGFR before initiation of SGLT2 inhibitors. We also assessed whether the association between kidney outcomes and use of SGLT2 inhibitors differed among subgroups, defined by eGFR ($<$60 vs. $\geq$60 mL/min/1.73 m^2), age ($<$65 vs. $\geq$65 years), and the use versus nonuse of ACE inhibitors or ARBs.

RESEARCH DESIGN AND METHODS

Methods, Data Sources, and Study Population

J-CKD-DB is a multicenter, real-world electronic health record–based registry of patients with CKD from 21 university hospitals in Japan (clinical trial reg. no. UMIN 000026272, www.umin.ac.jp/ctr/). It was initiated in December 2014, and the database contains information on all inpatient and outpatient encounters, prescriptions, diagnostic codes, and laboratory measurements. The facilities participating in J-CKD-DB were required to have electronic health record systems that incorporated Standardized Structured Medical Information eXchange 2 (SS-MIX2) (https://www.ss-mix.org/consE/) storage and a structured data entry function that could transfer the data to the SS-MIX2 storage system (12). The SS-MIX2 specifications adopted the considerable progress made in health care information standards in Japan, including code standardization regarding laboratory data items and prescription data. A data extraction and registration system, the Multipurpose Clinical Data Registry System, has been developed and allows the efficient collection of clinical data, especially via the SS-MIX2 format (13). Data were abstracted and compiled between 1 January and 31 December 2014. For avoidance of input error and burden on physicians, all data elements were extracted automatically with use of SS-MIX2 storage and sent to the J-CKD-DB data center. Fundamental standards were adopted in SS-MIX2 regarding patient profiles (the Health Level Seven [HL7] V2.5 [ISO 27931] data format), prescriptions (national drug code in Japan, HOT code), laboratory test results (Japan Laboratory Code Version 10 [JLAC10] code), diagnoses (ICD-10), and incidence of major outcomes (14–16).

The inclusion criteria for the J-CKD-DB are as follows: *1*) age $\geq$18 years, *2*) proteinuria $\geq$1 (dipstick test), or eGFR $<$60 mL/min/1.73 m^2 (11). Therefore, the data set included individuals without proteinuria who had eGFR $<$60 mL/min/1.73 m^2. We conducted this study

[17]*Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Kanagawa, Japan*
[18]*Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[19]*Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University, Kochi, Japan*
[20]*Division of Nephrology, Rinku General Medical Center, Oosaka, Japan*
[21]*Division of Nephrology and Dialysis, Department of Cardiorenal and Cerebrovascular Medicine, Kagawa University, Kagawa, Japan*
[22]*Division of Nephrology, Faculty of Medicine, Shimane University, Shimane, Japan*
[23]*Department of Nephrology, Faculty of Medicine, Saitama Medical University, Saitama, Japan*
[24]*Medical Information Center, Kyushu University Hospital, Fukuoka, Japan*
[25]*Faculty of Health Science and Technology, Kawasaki University of Medical Welfare, Okayama, Japan*
[26]*Department of Healthcare Information Management, The University of Tokyo Hospital, Tokyo, Japan*
[27]*Institute of Health Data Infrastructure for All, Tokyo, Japan*
[28]*Department of Pharmacology, Faculty of Medicine, Kagawa University, Kagawa, Japan*
[29]*Department of Medical Science, Kawasaki Medical School, Kurashiki, Japan*
[30]*Diabetes Research Center, National Center for Global Health and Medicine, Tokyo, Japan*

Corresponding author: Yuichiro Yano, yano.yuichiro@jichi.ac.jp, yyano0817@gmail.com, or yuichiro.yano@duke.edu

Received 19 May 2021 and accepted 23 August 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.16434609.

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

under the oversight of the Ethical Committee of the Kawasaki Medical School (3173-1) and in accordance with the principles of the Declaration of Helsinki. Because of the de-identified nature of patient records, informed consent was obtained through an opt-out method on the website of each participating university hospital in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Of the 21 university hospitals in J-CKD-DB, 5 agreed to participate in the ongoing prospective longitudinal study (referred to as J-CKD-DB-Ex) between 1 January 2014 and 31 December 2018. The J-CKD-DB-Ex study was designed to identify risk factors for eGFR decline over time among CKD patients in a real-world practice setting. For the current analyses, we selected records of T2DM patients who had >1 year of continuous enrollment history in the database before initiating an SGLT2 inhibitor or other glucose-lowering drugs. The index date of treatment initiation was defined as the date a prescription was made or filled, as either an initial or add-on therapy, for any SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin) or other glucose-lowering drugs, including fixed-dose combinations, with no prior prescriptions issued for that medicine class during the preceding year. Furthermore, consistent with the methodology used in CVD-REAL 3 (8), we selected records of T2DM patients who had at least two eGFR measurements before the index date, with at least one eGFR measurement within 180 days of the index date. We additionally specified that at least 180 days between the first and last eGFR measurements before the index date were required to reliably estimate eGFR change before the index date. Patients were followed up from the index date until the end of the index treatment (on-treatment analysis only), migration or departure from the practice or database, death, or the last date of data collection.

Kidney Function and Other Measurements

Serum creatinine and spot urine specimens were collected for each participant. Serum creatinine was assayed with an enzymatic method. eGFR was derived with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation modified by a Japanese coefficient (17). Rapid decline of kidney function was defined as eGFR loss of ≥3.0 mL/min/1.73 m^2 per year (18). Urinalysis by the dipstick method was performed on spot urine specimens. Urine dipstick results were interpreted by the medical staff in each hospital and recorded as (−), (±), (1+), (2+), and (3+). The policy of the Japanese Committee for Clinical Laboratory Standards (https://jccls.org/) is that all urine dipstick tests should be manufactured so that a urine dipstick result of 1+ will correspond to a urinary protein level of 30 mg/dL. We defined proteinuria as 1+ or more.

The primary outcome was the rate of change in eGFR from the initiation of SGLT2 inhibitor or other glucose-lowering drug treatments. The secondary outcome was a composite end point of a sustained reduction in eGFR of ≥50% (confirmed by a subsequent measurement) or end-stage kidney disease (ESKD), which was defined as an eGFR of <15 mL/min/1.73 m^2 (confirmed at a subsequent measurement). In the composite end point analyses, if a participant had more than one event occur, the first event was counted as the outcome. In end point–specific analyses (sensitivity analyses), if a participant had more than one different type of event occur, all events were counted as the outcomes. For example, if a participant experienced an eGFR decline ≥50% and then was diagnosed with ESKD a month later, only an eGFR decline ≥50% was counted as the outcome in the composite end point analyses, whereas both an eGFR decline ≥50% and an ESKD event were counted as separate outcomes in the end point–specific analyses.

Statistical Analysis

Descriptive statistics are presented as mean ± SD and proportions as appropriate. A nonparsimonious propensity score using variables that might have affected treatment assignment or outcomes was developed to predict the likelihood a patient would be prescribed SGLT2 inhibitors. Variables used in the development of the propensity score included age, sex, hemoglobin A_{1c}, eGFR, the rate of change in eGFR before the index date, the presence of proteinuria at the index date, use of blood pressure–lowering medication (ACE inhibitors, ARBs, calcium channel blockers, diuretics [i.e., thiazide and aldosterone antagonist], β-blockers, and α-blockers), use of glucose-lowering medication (i.e., metformin, DPP-4 inhibitors, sulfonylureas, insulin, glucagon-like peptide 1 receptor agonists, thiazolidinedione, other drugs including acarbose and epalrestat), use of statins, and the length of follow-up (Supplementary Table 1). Patients in the two treatment groups were matched 1:1 based on propensity scores. An imbalance was considered nonnegligible if a standardized difference of >10% was present between the two groups after propensity score matching.

Two definitions of follow-up time were used. The on-treatment follow-up time frame was defined as the time from the index date to the *1*) end of index treatment, *2*) initiation of another new glucose-lowering drug or SGLT2 inhibitor, *3*) patient's departure from the practice or database, or *4*) date of last data collection—whichever occurred first. The intention-to-treat (ITT) follow-up time was defined as the time from the index date to the patient's departure from the practice or database, date of last data collection, or death—whichever occurred first. Similar to the methodology used in CVD-REAL 3 (8), the on-treatment follow-up was the primary timescale for the eGFR change analysis. The ITT follow-up was used for time-to-event analyses.

For inclusion in the eGFR slope analyses, at least two post–index date assessments were required, where the first measurement was obtained <120 days after the index date and the last was obtained >180 days after the first post–index date measurement. The eGFR trajectory from preindex to post-index date was displayed graphically over time. Each monthly time point was represented with the eGFR value closest to the time point of interest, within a defined interval. Time zero was indicative of the estimated intercept of the preindex slopes. The differences between post–index date eGFR slopes for patients taking SGLT2 inhibitors and slopes for those taking other glucose-lowering drugs was assessed using a linear mixed regression model, where treatment group (SGLT2 inhibitors or other glucose-lowering drugs), time (linear), and the interaction between treatment group and time were included as fixed factors. In mixed models, we used an "exchangeable" (or compound symmetry) correlation structure. We used a

compound symmetry covariance structure to model the within-subject variance, since models using other covariance structures including unstructured and spatial power structures did not converge. We tested for heterogeneity in the associations between the use of SGLT2 inhibitors and eGFR slope by each subgroup categorized according to proteinuria (yes vs. no), eGFR ($<$60 vs. $\geq$60 mL/min/1.73 m^2), age ($<$65 vs. $\geq$65 years), use of ACE inhibitors or ARBs at the index date (yes vs. no), and rapid eGFR decline before treatment initiation (yes vs. no). A statistically significant interaction was defined as P value <0.05. We also conducted the subgroup analyses noted above. We conducted three post hoc analyses. First, we exc-luded participants who were lost to follow-up within 12 months after initiating glucose-lowering drugs. Second, some participants had a quantitative urinary albumin measurement (i.e., albumin-to-creatinine ratio (ACR) with a spot urine sample. Therefore, we assessed whether the effects on kidney function of SGLT2 inhibitors versus other glucose-lowering drugs differed by the extent of ACR at the index date. Third, for propensity matching, we considered the SGLT2 inhibitors group and the other glucose-lowering drugs group as independent, an approach used in prior propensity score–matching studies (8,9). However, the estimated CIs for treatment effects may become wider because of the difference in distribution of covariates included in the propensity score model between the groups (19). Therefore, we also implemented inverse probability of treatment weighting using the propensity score (20,21).

The incidence rate for the outcomes based on patients developing a $\geq$50% eGFR decline or ESKD was assessed by treatment group. Only the first occurrence of each outcome was used for analysis, and the crude incidence rate in each group was calculated as the number of incident events divided by the overall number of person-years at risk. Time-to-first-event for SGLT2 inhibitors and other glucose-lowering drugs was compared with use of Cox proportional hazards models and presented as the hazard ratio (HR) and 95% CI for each outcome. We included the ITT population for time-to-event analyses, in which patients were followed up from the initiation of an index treatment to the occurrence of the outcome of interest or censoring date—whichever occurred first—irrespective of whether the index treatment was discontinued. In Cox models, we tested for heterogeneity in the associations between the use of SGLT2 inhibitors and outcomes by each subgroup noted above with the inclusion of multiplicative interaction terms. A statistically significant interaction was defined as P value <0.05. Stratified analyses by each subgroup were also conducted.

All statistical analyses were performed with SAS version 9.4 software (SAS Institute, Cary, NC). Statistical significance was defined as a P value <0.05 using two-sided tests.

RESULTS

Prior to matching, 1,246 new initiators of SGLT2 inhibitors and 2,492 new initiators of other glucose-lowering drugs met the study eligibility criteria (Supplementary Fig. 1). Patients initiated on an SGLT2 inhibitor were younger and had higher HbA_{1c} and eGFR measurements. The mean annual rates of eGFR change before the index date, and the prevalence of proteinuria and antihypertensive medication use, were similar between groups (Supplementary Table 2). Metformin, diuretics, ACE inhibitors, and statins were more frequently prescribed in the SGLT2 inhibitors group, whereas DPP-4 inhibitors, insulin, and sulfonylureas were less frequently prescribed.

After one-to-one propensity matching, the cohort included 1,033 new initiators of SGLT2 inhibitors and 1,033 new initiators of other glucose-lowering drugs. All baseline characteristics were well matched (Table 1), with standardized differences for all variables of $\leq$9.6%. Mean age at initiation of the SGLT2 inhibitor or other glucose-lowering drug was 64.4 years; 777 (37.6%) of 2,066 initiations were in women, mean HbA_{1c} was 61 mmol/mol (7.8%), mean eGFR was 68.1 mL/min/1.73 m^2, 549 of 2,066 initiations (26.6%) had eGFR of $\leq$60 mL/min/1.73 m^2, and proteinuria was apparent in 578 (28.0%) initiations. Of the 2,066 treatment initiations, 926 (44.8%) were in patients being treated with ACE inhibitors or ARBs at the index date (Table 1). The distributions of specific SGLT2 inhibitors in the SGLT2 inhibitors group, and the classes of index medications in the other glucose-lowering drugs group, are shown in Table 1. DPP-4 inhibitors (69.7%), metformin (54.2%), and sulfonylureas (24.8%) were the most frequently initiated other glucose-lowering drugs.

Primary Outcome

Mean ± SD follow-up time in the primary analysis was 21.0 ± 9.8 months among the SGLT2 inhibitor group and 19.5 ± 10.4 months among the other glucose-lowering drugs group. During follow-up, the median number of eGFR measurements in the SGLT2 inhibitor group and the other glucose-lowering drugs group, respectively, was 11 (interquartile range 7–16) and 10 (7–16). In the on-treatment analysis, the mean annual rate of eGFR change before initiation of index treatments was -1.3 ± 4.4 and -1.4 ± 7.2 mL/min/1.73 m^2 in the SGLT2 inhibitor and other glucose-lowering drugs groups. After initiation of SGLT2 inhibitors and other glucose-lowering drugs, the mean annual rate of eGFR change were -0.47 mL/min/1.73 m^2 per year (95% CI -0.63 to -0.31) and -1.22 (-1.41 to -1.03) (Figs. 1 and 2). The between-group difference in the rate of eGFR decline was 0.75 mL/min/1.73 m^2 per year (0.51 to 1.00), favoring SGLT2 inhibitors ($P < 0.001$). Changes in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs by proteinuria and the rate of eGFR decline prior to drug initiation are shown in Supplementary Figs. 2 and 3. Annual rate of eGFR change is shown by prespecified subgroups (Fig. 2). There was evidence of interaction between SGLT2 inhibitor use and rapid decline in eGFR before treatment initiation and use of ACE inhibitors or ARBs at the index date in associations with eGFR decline (both P for interaction <0.05) but no evidence of interaction between SGLT2 inhibitor use and proteinuria, eGFR (eGFR $<$60 vs. $\geq$60 mL/min/1.73 m^2), and age ($<$65 vs. $\geq$65 years; all P for interaction >0.34). Similar results were observed in the ITT population (Supplementary Figs. 4–7).

Post Hoc Analyses

First, in the on-treatment analysis, we excluded participants with a follow-up period shorter than a year (Supplementary Fig. 8). The between-group difference

Table 1—Clinical characteristics at index date after propensity score

Characteristics	SGLT-2 inhibitor group (n = 1,033)	Other glucose-lowering drugs group (n = 1,033)	Standardized mean difference (%)
Age, years	64.0 ± 11.5	64.9 ± 12.4	6.9
Women	389 (37.7)	388 (37.6)	0.2
Hemoglobin A_{1c}, %	7.8 ± 1.2	7.7 ± 1.5	6.7
Hemoglobin A_{1c}, mmol/mol	62.0 ± 13.1	60.9 ± 16.7	6.7
eGFR, mL/min/1.73 m^2	68.2 ± 17.2	68.0 ± 19.1	1.4
eGFR ≥60 mL/min/1.73 m^2	751 (71.7)	766 (74.2)	3.3
eGFR <60 mL/min/1.73 m^2	282 (27.3)	267 (25.8)	3.3
eGFR 45–59 mL/min/1.73 m^2	179 (17.3)	143 (13.8)	9.6
eGFR <45 mL/min/1.73 m^2	103 (10.0)	124 (12.0)	6.5
Rate of eGFR change prior to index, mL/min/1.73 m^2/year	−1.3 ± 5.0	−1.1 ± 9.5	2.9
Proteinuria	294 (28.5)	284 (27.5)	2.2
Glucose-lowering medications			
Canagliflozin	128 (12.4)	0	
Dapagliflozin	201 (19.5)	0	
Empagliflozin	210 (20.3)	0	
Ipragliflozin	214 (20.7)	0	
Luseogliflozin	178 (17.2)	0	
Tofogliflozin	102 (9.9)	0	
Metformin	559 (54.1)	560 (54.2)	0.2
DPP-4 inhibitor	703 (68.1)	737 (71.3)	7.2
Sulfonylurea	255 (24.7)	258 (25.0)	0.7
Insulin	206 (19.9)	219 (21.2)	3.1
GLP-1 receptor agonist	15 (1.5)	13 (1.3)	1.7
Thiazolidinedione	159 (15.4)	164 (15.9)	1.3
Others	168 (16.3)	190 (18.4)	5.6
Blood pressure–lowering medications	673 (65.2)	642 (62.1)	6.2
ACE inhibitor	76 (7.4)	62 (6.0)	5.4
ARB	396 (38.3)	408 (39.5)	2.4
Calcium channel blocker	415 (40.2)	408 (39.5)	1.4
Diuretics	106 (10.3)	100 (9.7)	1.9
β-Blocker	114 (11.0)	114 (11.0)	0.0
α-Blocker	63 (6.1)	63 (6.1)	0.0
Statins	467 (45.2)	472 (45.7)	1.0

Data are means ± SD or n (%). A standardized difference >10% is considered a nonnegligible difference. Other glucose-lowering medications include acarbose and epalrestat. Diuretics include thiazide diuretics and aldosterone antagonists. GLP-1, glucagon-like peptide 1.

in the rate of eGFR decline was 0.73 mL/min/1.73 m^2 per year (0.48 to 0.98), favoring SGLT2 inhibitors ($P < 0.001$). Second, in the SGLT2 inhibitors group (n = 1,033), ACR was measured for 903 participants. Of the 903 participants, only 15.5% had ACR > 300 mg/g. In the other glucose-lowering drugs group (n = 1,033), ACR was measured for 811 participants. Of the 811 participants, only 16.2% had ACR > 300 mg/g. Therefore, we assessed whether the effects on kidney function of SGLT2 inhibitors versus other glucose-lowering drugs differed by subgroups, with categories of above or below median levels of ACR (i.e., 76.3 mg/g) in this population. The results were consistent across the subgroups (Supplementary Figs. 9 and 10), and there was no evidence of interaction between SGLT2 inhibitor use and ACR (ACR <76.3 vs. ≥76.3 mL/min/1.73 m^2; P for interaction = 0.14). The between-group difference in the rate of eGFR decline was 0.75 mL/min/1.73 m^2 per year (0.51 to 1.00) after adjustment for time-varying ACR, favoring SGLT2 inhibitors ($P < 0.001$). Third, in inverse probability of treatment weighting analyses (on-treatment analyses), the mean annual rates of eGFR change were −0.38 mL/min/1.73 m^2 per year (95% CI −0.51 to −0.24) for the SGLT2 inhibitors group (n = 863) and −1.39 (−1.50 to −1.27) for the other glucose-lowering drugs group (n = 1,454) (Supplementary Fig. 11). The between-group difference in the rate of eGFR decline was 1.01 mL/min/1.73 m^2 per year (0.83 to 1.19), favoring SGLT2 inhibitors ($P < 0.001$).

Secondary Outcome

During follow-up, 30 composite events of a ≥50% eGFR decline and ESKD occurred in the SGLT2 inhibitor group compared with 73 in the other glucose-lowering drugs group. The cumulative incidence of composite events was higher in the other glucose-lowering drugs group than in the SGLT2 inhibitor group (Fig. 3*A*). The event rates were higher in the other glucose-lowering drug group (36/1,000 person-years) than in the SGLT2 inhibitor group (14/1,000 person-years). The cumulative

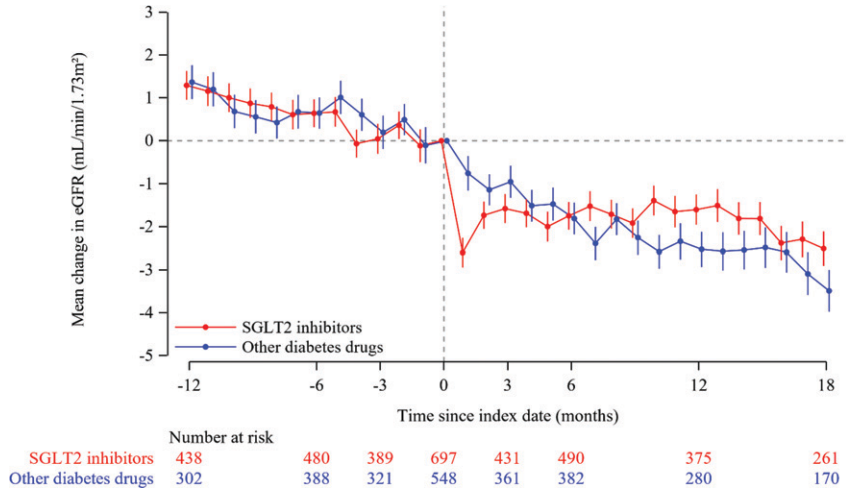

Figure 1—Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs (on-treatment analyses). Error bars show mean ± SE. Numbers below the graph refer to the number of patients at each time point. Analyses for eGFR slope were conducted from the index date and thereafter, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. *P* values were calculated using a linear mixed regression model.

incidence of composite events across groups with and without proteinuria and rapid eGFR decline is shown in Supplementary Figs. 12 and 13. Initiation of SGLT2 inhibitors versus other glucose-lowering drugs was associated with lower risk for composite events (HR 0.40, 95% CI 0.26–0.61; $P < 0.001$). There was no evidence of interaction between SGLT2 inhibitor use and proteinuria, eGFR (eGFR <60 vs. ≥60 mL/min/1.73 m^2), age (<65 vs. ≥65 years), and use of ACE inhibitors or ARBs at the index date or between SGLT2 inhibitor use and rapid decline in eGFR before treatment initiation in associations with composite events (all *P* for interaction ≥0.35) (Fig. 4).

During follow-up, 25 events for a ≥50% eGFR decline and 7 ESKD events occurred in the SGLT2 inhibitor group and 69 and 26 events occurred in the other glucose-lowering drugs group. The cumulative incidence of an ≥50% eGFR decline and ESKD was higher in the other glucose-lowering drugs group compared with the SGLT2 inhibitor group (Figs. 3*B* and *C*). Initiation of SGLT2 inhibitors versus other glucose-lowering drugs was associated with a lower relative risk for a ≥50% eGFR decline (HR 0.35, 95% CI 0.22–0.56; $P < 0.001$) and for ESKD (HR 0.26, 95% CI 0.11–0.61; $P = 0.002$) (Supplementary Figs. 14 and 15). There was no evidence of interaction between SGLT2 inhibitor use and proteinuria, eGFR (eGFR <60 vs. ≥60 mL/min/1.73 m^2), age (<65 vs. ≥65 years), or use of ACE inhibitors or ARBs at the index date or between SGLT2 inhibitor use and rapid decline in eGFR before treatment initiation in associations with an ≥50% eGFR decline or ESKD events (all *P* for interaction ≥0.35).

CONCLUSIONS

In the current analyses, using a multicenter, real-world electronic health record–based registry of T2DM patients with CKD, we found evidence that initiation of SGLT2 inhibitors versus other glucose-lowering drugs was associated with a significantly lower rate of eGFR decline. The benefit of SGLT2 inhibitors over other glucose-lowering drugs on change in eGFR was greater among patients who did not have rapid eGFR decline before initiating treatment and those who were using ACE inhibitors or ARBs at the index date. Initiation of SGLT2 inhibitors versus other glucose-lowering drugs was also associated with a significantly lower risk of a clinically important composite end point of a 50% eGFR decline or ESKD. The benefits of SGLT2 inhibitors over other glucose-lowering drugs for reducing composite kidney events were consistent among subgroups, with categories of proteinuria (yes vs. no), eGFR (<60 vs. ≥60 mL/min/1.73 m^2), age (<65 vs. ≥65 years), use of ACE inhibitors or ARBs at the index date (yes vs. no), and rapid decline before initiation of treatments (yes vs. no).

In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, investigators assessed the effects of the SGLT2 inhibitor canagliflozin on the kidney in T2DM patients with eGFR of 30 to <90 mL/min/1.73 m^2 (mean eGFR 56.2 mL/min/1.73 m^2) and severe albuminuria (median urinary ACR 927). Composite kidney outcomes, including ESKD, a doubling of the creatinine level, or death from renal causes, were significantly lower with canagliflozin compared with placebo (HR 0.66, 95% CI 0.53–0.81; $P < 0.001$) (6). The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) study included participants with severe albuminuria (median urinary ACR 949) and eGFR of 25 to <75 mL/min/1.73 m^2 (mean eGFR 43.1 mL/min/1.73 m^2) with or without T2DM. Composite kidney outcomes, including an ≥50% eGFR decline, ESKD, or death from renal causes, were significantly lower with dapagliflozin compared with placebo (HR 0.56, 95% CI 0.45–0.68) (7). Both trials excluded patients with normoalbuminuria. However, 20–50% of T2DM and CKD patients have normoalbuminuria (22,23), and the prevalence has been increasing over the last decade (1,24). The risk for adverse kidney events among T2DM patients without proteinuria is intermediate between those with albuminuria and those without CKD (i.e., normal eGFR and normoalbuminuria) (25,26). In the current study, the proportion of patients taking ACE inhibitors or ARBs appears to be one-half the percentage reported in the CREDENCE trial and the DAPA-CKD study (~40% vs. ~99%), which may be attributable to the fact that only 30% of our patients had proteinuria. The rate of eGFR decline among T2DM patients with proteinuria not taking SGLT2 inhibitors appears to be lower in the current study than in the CREDENCE trial and the DAPA-CKD study. These differences suggest that the current study population was at low risk. Since conducting an RCT in such a low-risk population may not be feasible, the current study may provide the only available evidence of the beneficial effects on kidney function of SGLT2 inhibitors over other glucose-lowering drugs among

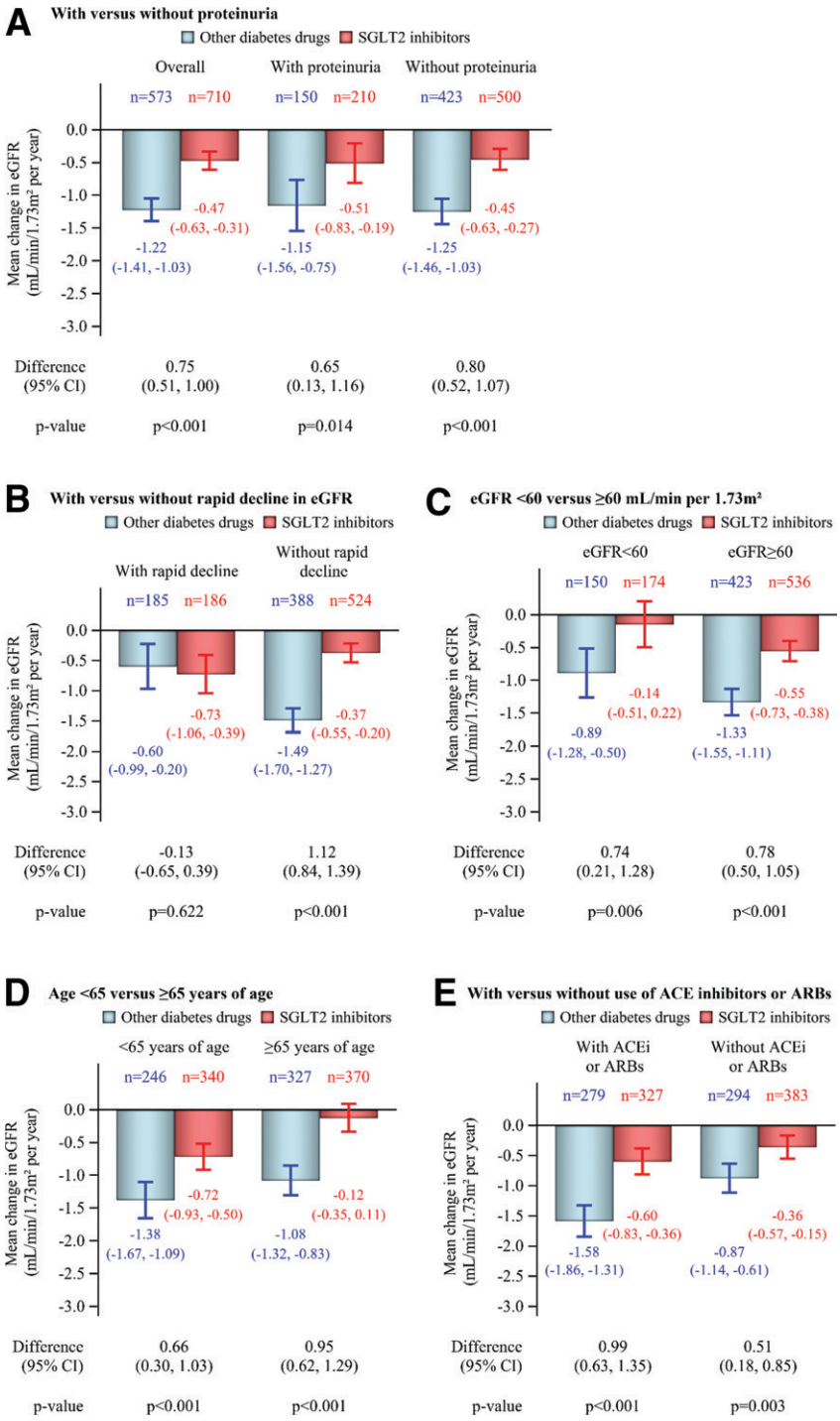

Figure 2—Annual rate of eGFR change in various subgroups (on-treatment analyses): with vs. without proteinuria at the index date (*A*), with vs. without rapid decline in eGFR before initiating treatment (*B*), eGFR <60 vs. ≥60 mL/min/1.73 m^2 at the index date (*C*), age <65 vs. ≥65 years at the index date (*D*), and with vs. without use of ACE inhibitors or ARBs at the index date (*E*). eGFR change was calculated from the postindex eGFR measurements using a linear mixed regression model. ARB, angiotensin II receptor blocker.

T2DM and CKD patients without proteinuria or those not taking ACE inhibitors or ARBs.

In kidney biopsy studies, only a subset of patients with T2DM have purely diabetic glomerulopathy (30–50%), whereas others have tubulointestinal or vascular disease with or without diabetic glomerulopathy (27). It remains to be determined whether T2DM patients with different structural lesions may respond differently to SGLT2 inhibitors. T2DM and CKD patients without proteinuria have less typical diabetic glomerulopathy but disproportionally damaged intestinal and vascular damage (28,29). Nodular lesions and mesangiolysis have been reported among T2DM patients who have rapid decline in eGFR (30). In the current analyses, initiation of SGLT2 inhibitors versus other glucose-lowering drugs was associated with a significantly lower risk of composite kidney outcomes irrespective of the rate of eGFR decline before treatment initiation. Conversely, the benefit of SGLT2 inhibitors over other glucose-lowering drugs in slowing eGFR decline was greater among patients who did not have rapid eGFR decline before treatment initiation. The difference may be related to a regression to the mean effect; i.e., patients with versus without rapid eGFR decline before treatment initiation appear to have slower decline after treatment irrespective of the treatment group.

The cumulative incidence of composite kidney events was similar among T2DM patients with proteinuria taking SGLT2 inhibitors versus those without proteinuria not taking SGLT2 inhibitors. The mechanisms underlying the potential disease-modifying effects of SGLT2 inhibitors among T2DM and CKD patients are largely unknown, but in recent post hoc analyses from the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial it was suggested that short-term reduction in albuminuria had a statistically significant association with a decreased risk of long-term renal function decline (31). Thus, it is possible that eGFR decline is alleviated by correction of glomerular hyperfiltration and subsequent reduction in proteinuria (32,33). In the current study, we did not adjust for values of ACR obtained during follow-up because statistical power was affected by limited availability of ACR measures. Therefore, it remains uncertain whether the kidney function benefits of SGLT2 inhibitors compared with other glucose-lowering drugs are independent of differences in changes in proteinuria after treatment initiation.

Strengths of this study include the consistency of several subgroup analyses, and the availability of multiple eGFR measurements before and after treatment initiation, which enabled us to match patients based on their rate of kidney function

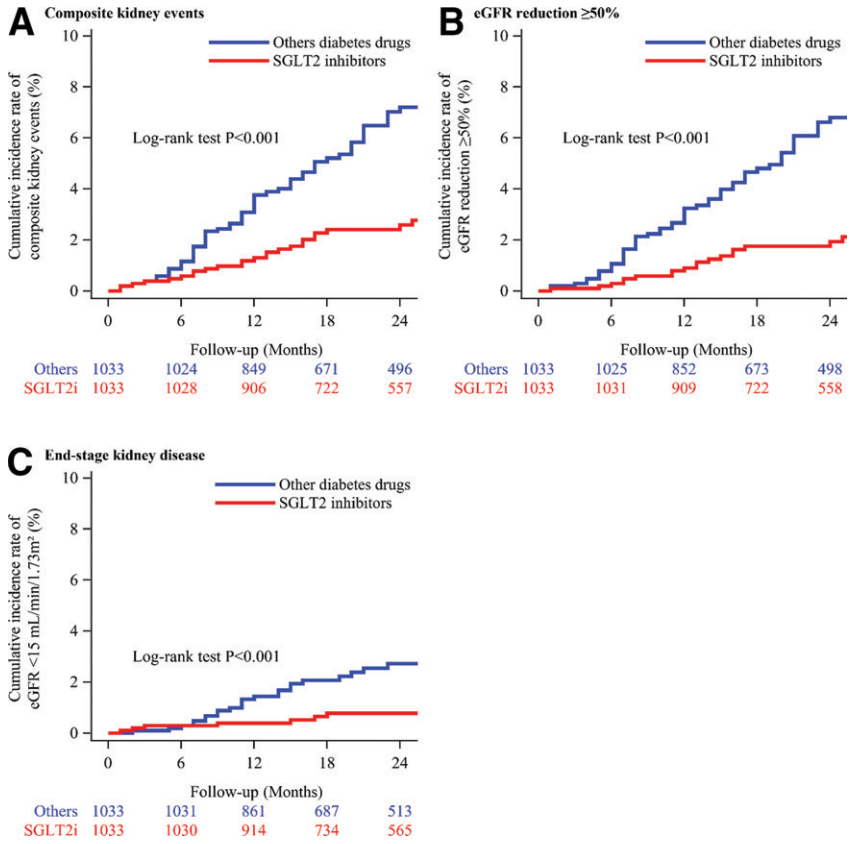

Figure 3—Cumulative incidence of kidney events among the SGLT2 inhibitors group and other glucose-lowering drugs group (ITT analyses) The cumulative probability of composite kidney events (*A*), an ≥50% eGFR decline (*B*), and ESKD (*C*) among the SGLT2 inhibitors group and the other glucose-lowering drugs group was calculated with the Kaplan-Meier method. Composite kidney events included a sustained reduction in eGFR of ≥50% and ESKD (i.e., eGFR <15 mL/min/1.73 m^2). The log-rank test was used to calculate the *P* value, and the value was <0.001. The median length of follow-up for each group was as follows: for the SGLT2 inhibitors group 25 months (interquartile range 15–32 and the other glucose-lowering drugs group 23 months (14–32) in composite kidney events analyses and in the eGFR reduction ≥50% analyses and for the SGLT2 inhibitors group 25 months (16–32) and the other glucose-lowering drugs 23 months (14–32) months in the ESKD analyses.

decline before initiation of an SGLT2 inhibitor or other glucose-lowering drug. SGLT2 inhibitors were being used in a broad and low-risk population, which more closely mirrors the use of SGLT2 inhibitors in clinical practice. In Japan, universal health coverage is achieved, and therefore, economic factors unlikely had a large effect on the selection of patients for initiation of SGLT2 inhibitors versus other glucose-lowering drugs.

Limitations

Due to the observational nature of the study, and despite robust statistical techniques, including propensity-matching and multiple sensitivity analyses, a possibility of residual, unmeasured confounding cannot be excluded. For example, some patients might discontinue SGLT2 inhibitors during the initial weeks of treatment, which could lead to an increase in eGFR among the SGLT2 inhibitor group. Furthermore, measurements of blood pressure levels and adiposity parameters (e.g., BMI) at and after initiation of glucose-lowering drugs were not available in the current study, although both might affect kidney function during follow-up. However, reductions in blood pressure and weight have been shown to insufficiently account for all of the observed benefits of SGLT2 inhibitors for kidney function (34,35). Indeed, prior studies suggested that the benefits of SGLT2 inhibitors for kidney function were evident regardless of patients' blood pressure levels and BMI (7,36). Serum creatinine was assayed with an enzymatic method, which was not calibrated (traceable) to isotope dilution-liquid chromatography–mass spectrometry (IDLCMS). In the current study, serum creatinine was assayed with an enzymatic method, which was not calibrated (traceable) to IDLCMS. Although enzymatic methods have been shown to comply with the National Kidney Disease Education Program (NKDEP) working group–recommended limits of bias (37,38), the accuracy of serum creatinine with use of an enzymatic method may be limited. Bias might result from creatinine measurements being made in clinical practice because of incident ill health as well as regular, more routine follow-up. However, this situation reflects real-world clinical practice and presents the only way to assess eGFR change over time. Ascertainment bias because of the retrospective nature of data is also a possibility. However, frequency of creatinine measurements between users and nonusers was similar. As conducted in EMPA-REG OUTCOME and CVD-REAL 3 (8,31), we calculated eGFR slope using a linear model. However, a linear model might not be optimal to capture the eGFR trajectory after initiation of SGLT2 inhibitors. Furthermore, bias in mixed-model inferences for fixed effects might also occur if the compound symmetry assumption was not verified or the method for determining whether missing data were ignorable was not appropriate. We did not impute missing values because the number of missing measurements was substantial—4,962 of 8,700 individuals (57%) had missing values for eGFR, hemoglobin A_{1c}, or proteinuria, and the number of eGFR measurements during follow-up substantially differed by individuals. It is possible that the pattern of missingness depends on the severity of the disease and that missing values more frequently occur among patients with a faster eGFR decline. This could bias our estimates and should be considered in interpreting these results. We did not have comorbidity information (e.g., history of cardiovascular disease and blood pressure levels) and were thus unable to include this in propensity score matching. Selection bias in matching or excluding patients also cannot be ruled out. Additionally, bias might result from eGFR assessment, which requires a certain number of observations before and after treatment initiation. Our approach was consistent with the methodology used in CVD-REAL 3 (8). We focused on kidney outcomes only and did not examine safety. Information regarding other

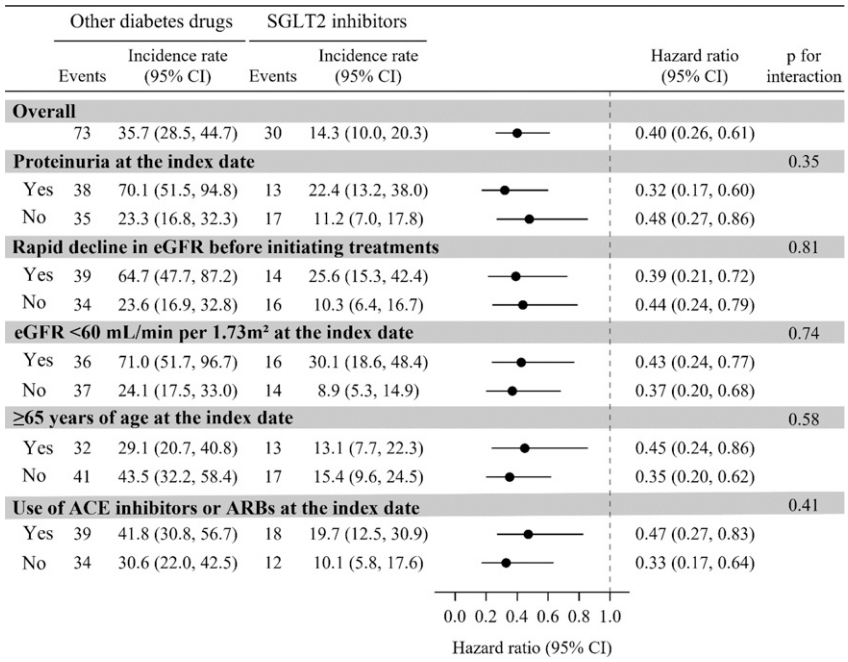

Figure 4—The frequency of events, the corresponding incidence rates, and HRs for composite kidney events among the SGLT2 inhibitors group and other glucose-lowering drugs group (ITT analyses) Composite kidney events included a sustained reduction in eGFR of ≥50% and ESKD (i.e., eGFR <15 mL/min/1.73 m^2). The incidence rate is per 1,000 person-years. Time to first event for the SGLT2 inhibitors group and the other glucose-lowering drugs group was compared by use of Cox proportional hazard models and is presented as the HR and 95% CI for composite kidney events separately by the subgroups. We tested for heterogeneity in the association between SGLT2 inhibitor use and outcomes by each subgroup with the inclusion of multiplicative interaction terms, and a statistically significant interaction was defined as *P* value <0.05.

microvascular complications of diabetes, including retinopathy and neuropathy, was not available in the current study. Therefore, it remains uncertain whether the kidney function benefits of SGLT2 inhibitors differ by the presence of retinopathy and neuropathy. The proportion of individuals with eGFR <45 mL/min/1.73 m^2 was only 10.0% in the SGLT2 inhibitor group and only 12.0% in the other glucose-lowering drugs group. Therefore, we did not test whether the benefits of SGLT2 inhibitor treatment over other glucose-lowering drugs are consistent across subgroups categorized as eGFR <45 vs. ≥45 mL/min/1.73 m^2. Lastly, longer follow-up data from observational studies are required to assess whether the effects of SGLT2 inhibitors are sustained over time.

Conclusion

In routine clinical practice, T2DM patients with CKD who received SGLT2 inhibitors had significantly better kidney outcomes than those who received other glucose-lowering drugs, irrespective of the presence or absence of proteinuria and the rate of eGFR decline before treatment initiation. These data complement findings from randomized trials and suggest that the benefits of SGLT2 inhibitors on kidney function as observed in clinical trials may be applicable to a broader patient population in routine clinical practice.

Funding. This work was supported in part by grants from Development of Comprehensive Database of Chronic Kidney Disease, Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare of Japan, awarded to N.K. (19AC1002), and Japan Agency for Medical Research and Development, Practical Research Project for Life-Style related Diseases including Cardiovascular Diseases and Diabetes Mellitus and Platform Program for Promotion of Genome Medicine in the form of grants awarded to N.K. (20ek0210135h0001, 19ek0210095h0003, 20km0405210h0003).

Duality of Interest. H.N. and N.K. received research support from AstraZeneca, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, and Daiichi Sankyo. Y.Y. received research grants from Boehringer Ingelheim and consulting fees from AstraZeneca. H.J.L.H. is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, CSL Pharma, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe Pharma, Novo Nordisk, and Travere Therapeutics. H.J.L.H. received research grants from Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen. 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. Y.H. received joint research fees from Mitsubishi Tanabe Pharma. K.Ts. received consulting fees or speaking honoraria or both from Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Kowa, Mitsubishi Tanabe Pharma, and Ono. T.W. received personal fees from Sanwa Chemical, Kyowa Kirin, Baxter Limited, Bayer Yakuhin, Teijin Pharma Limited, Nippon Boehringer Ingelheim, Taisho Pharmaceutical, Ono, Eli Lilly, AstraZeneca, Miyarisan Pharmaceutical, Fujirebio, and Vifor Pharma. T.W. received grants and personal fees from Chugai Pharmaceutical, Astellas, Merck Sharp & Dohme (MSD), Kowa, Mochida Pharmaceutical, Daiichi Sankyo, Takeda, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Torii, Terumo, Kissei Pharmaceutical, Sanofi, GlaxoSmithKline, Hayashidera Medinol, and Asahi Kasei Pharma. I.N. received consulting fees or speaking honorarium or both from Kyowa Kirin, Otsuka Pharmaceutical, Sanofi, Daiichi Sankyo, and Sumitomo Dainippon and received operating funds from Asteras, Terumo, Baxter, Otsuka Pharmaceutical, Chugai Pharmaceutical, Sanofi, Kyowa Kirin, Daiichi Sankyo, Sumitomo Dainippon, Takeda, Ono, Kaneka, and Bayer. T.Sh. received lecturer fees from Boehringer Ingelheim, Ono, and Kowa and received consulting fee and lecturer fees from AstraZeneca. A.N. received consulting fees or speaking honorarium or both from Novartis, Boehringer Ingelheim, AstraZeneca, Taisho Pharmaceutical, and Daiichi Sankyo and received operating funds from Boehringer Ingelheim, Bayer, Taisho Pharmaceutical, and Daiichi Sankyo. K.U. received lecture fees from Takeda, Novo Nordisk, Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, AstraZeneca, MSD, Ono, Sumitomo Dainippon Pharma, Sanofi, and Astellas. K.U. received research grants from Novo Nordisk, Eli Lilly, Nippon Boehringer Ingelheim, Abbott Japan, and MSD and endowments from Takeda, Astellas, Novo Nordisk, Sumitomo Dainippon Pharma, Sanofi, Kyowa Kirin, Mitsubishi Tanabe Pharma, Daiichi Sankyo, and Ono. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. H.N., Y.Y., H.K., H.J.L.H., and N.K. contributed to study conception and design. H.K. performed analysis of data. H.N., Y.Y., H.K., H.J.L.H., M.N., Y.H., Y.S., N.N., Y.T., J.W., H.S., K.Ts., T.N., S.M., T.W., K.Y., I.N., K.Ta., M.Y., Y.T., T.Sh., T.So., T.I., H.O., N.N., H.K., K.O., M.O., S.I., A.N., E.K., K.U., and N.K. interpreted data. H.N. and Y.Y. drafted the manuscript. H.J.L.H., M.N., Y.H., Y.S., N.N., Y.T., J.W., H.S., K.Ts., T.N., S.M., T.W., K.Y., I.N., K.Ta., M.Y., Y.T., T.Sh., T.So., T.I., H.O., N.N., H.K., K.O., M.O., S.I., A.N., E.K., K.U., and N.K. critically revised the manuscript for important intellectual content. H.N., Y.Y., H.K, H.J.L.H., M.N., Y.H., Y.S., N.N., Y.T., J.W., H.S., K.Ts.,

T.N., S.M., T.W., K.Y., I.N., K.Ta., M.Y., Y.T., T.Sh., T.So., T.I., H.O., N.N., H.K., K.O., M.O., S.I., A.N., E.K., K.U., and N.K. gave final approval of the submitted manuscript. H.N., Y.Y., H.K., and N.K. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
3. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860
4. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
5. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
6. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
7. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–1446
8. 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
9. 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
10. Levey AS, Coresh J. Chronic kidney disease. Lancet 2012;379:165–180
11. Nakagawa N, Sofue T, Kanda E, et al. J-CKD-DB: a nationwide multicentre electronic health record-based chronic kidney disease database in Japan. Sci Rep 2020;10:7351
12. Kimura M, Nakayasu K, Ohshima Y, et al. SS-MIX: a ministry project to promote standardized healthcare information exchange. Methods Inf Med 2011;50:131–139
13. Sugiyama T, Miyo K, Tsujimoto T, et al. Design of and rationale for the Japan Diabetes compREhensive database project based on an Advanced electronic Medical record System (J-DREAMS). Diabetol Int 2017;8:375–382
14. Rajeev D, Staes CJ, Evans RS, et al. Development of an electronic public health case report using HL7 v2.5 to meet public health needs. J Am Med Inform Assoc 2010;17:34–41
15. Kawazoe Y, Imai T, Ohe K. A querying method over RDF-ized health level seven v2.5 messages using life science knowledge resources. JMIR Med Inform 2016;4:e12
16. Kume N, Suzuki K, Kobayashi S, Araki K, Yoshihara H. Development of unified lab test result master for multiple facilities. Stud Health Technol Inform 2015;216:1050
17. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis 2010;56:32–38
18. Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med 2008;168:2212–2218
19. Austin PC. Comparing paired vs non-paired statistical methods of analyses when making inferences about absolute risk reductions in propensity-score matched samples. Stat Med 2011;30:1292–1301
20. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424
21. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med 2004;23:2937–2960
22. Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care 2010;33:1536–1543
23. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–3277
24. Kume S, Araki SI, Ugi S, et al. Secular changes in clinical manifestations of kidney disease among Japanese adults with type 2 diabetes from 1996 to 2014. J Diabetes Investig 2019;10:1032–1040
25. Ninomiya T, Perkovic V, de Galan BE, et al.; ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009;20:1813–1821
26. Rigalleau V, Lasseur C, Raffaitin C, et al. Normoalbuminuric renal-insufficient diabetic patients: a lower-risk group. Diabetes Care 2007;30:2034–2039
27. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol 2007;27:195–207
28. Shimizu M, Furuichi K, Toyama T, et al.; Kanazawa Study Group for Renal Diseases and Hypertension. Long-term outcomes of Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy. Diabetes Care 2013;36:3655–3662
29. Ekinci EI, Jerums G, Skene A, et al. Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care 2013;36:3620–3626
30. Furuichi K, Shimizu M, Yamanouchi M, et al. Clinicopathological features of fast eGFR decliners among patients with diabetic nephropathy. BMJ Open Diabetes Res Care 2020;8:e001157
31. Waijer SW, Xie D, Inzucchi SE, et al. Short-term changes in albuminuria and risk of cardiovascular and renal outcomes in type 2 diabetes mellitus: a post hoc analysis of the EMPA-REG OUTCOME trial. J Am Heart Assoc 2020;9:e016976
32. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752–772
33. Bakris GL. Slowing nephropathy progression: focus on proteinuria reduction. Clin J Am Soc Nephrol 2008;3(Suppl. 1):S3–S10
34. Scheen AJ, Delanaye P. Effects of reducing blood pressure on renal outcomes in patients with type 2 diabetes: focus on SGLT2 inhibitors and EMPA-REG OUTCOME. Diabetes Metab 2017;43:99–109
35. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol 2021;17:319–334
36. Ji Q, Ji L, Mu Y, et al. Effect of empagliflozin on cardiorenal outcomes and mortality according to body mass index: a subgroup analysis of the EMPA-REG OUTCOME trial with a focus on Asia. Diabetes Obes Metab 2021;23:1886–1891
37. Hoste L, Deiteren K, Pottel H, Callewaert N, Martens F. Routine serum creatinine measurements: how well do we perform? BMC Nephrol 2015;16:21
38. Jassam N, Weykamp C, Thomas A, et al. Post-standardization of routine creatinine assays: are they suitable for clinical applications. Ann Clin Biochem 2017;54:386–394