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## ORIGINAL ARTICLE

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# Renal outcomes and all-cause death associated with sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL 3 Korea)

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## Abstract

**Aims:** To investigate the effectiveness of sodium-glucose co-transporter-2 (SGLT2) inhibitors on the risk of progression to end-stage renal disease (ESRD) and all-cause mortality in a broad range of patients with type 2 diabetes (T2D) using a Korean nationwide cohort.

**Materials and Methods:** Using data from the Korean National Health Insurance Service database from January 2014 to December 2017, a total of 701 674 patients were identified with T2D. We divided these patients into new users of SGLT2 inhibitors and new users of other glucose-lowering drugs (oGLDs). Using propensity scores, patients in the two groups were matched 1:1. We assessed the risk of ESRD and all-cause death.

**Results:** There were 45 016 patients in each group, and baseline characteristics were well balanced between the groups. The patients' mean age was  $58.1 \pm 10.6$  years and mean estimated glomerular filtration rate (eGFR) was  $89.2 \pm 27.4$  mL/min/1.73m<sup>2</sup>, and 8% of patients had proteinuria. We identified 167 incident ESRD cases and 1070 all-cause deaths during follow-up. Use of SGLT2 inhibitors versus oGLDs was associated with a lower risk of ESRD (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.34 to 0.65) and all-cause death (HR 0.82, 95% CI 0.73 to 0.93). In a subgroup analysis by eGFR, initiation of SGLT2 inhibitor treatment, compared with oGLD treatment, was associated with lower risk of progression to ESRD among patients with eGFR 60 to 90 mL/min/1.73m<sup>2</sup> and those with eGFR < 60 mL/min/1.73m<sup>2</sup>, and a lower risk of all-cause death was associated with SGLT2 inhibitors versus oGLDs in patients with eGFR  $\geq 90$  and 60 to 90 mL/min/1.73m<sup>2</sup>.

**Conclusion:** In this large nationwide study of Korean patients with T2D, initiation of SGLT2 inhibitors versus oGLDs was associated with lower risk of ESRD and all-cause death.

## KEYWORDS

all-cause death, ESRD, SGLT-2 inhibitor

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## 1 | INTRODUCTION

Diabetic nephropathy ranks highest, both globally and nationwide in Korea, among causes of end-stage renal disease (ESRD), and its incidence is growing exponentially.<sup>1</sup> However, no new medications had been approved for the treatment of diabetic kidney disease since the IDNT (Irbesartan in Diabetic Nephropathy Trial) and the RENAAL (Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) study, which showed beneficial effects of angiotensin II receptor blockers in patients with type 2 diabetes mellitus (T2D) and kidney disease.<sup>2</sup> Very recently, sodium-glucose co-transporter-2 (SGLT2) inhibitors have shown renoprotective effects in several large outcome trials.<sup>3–6</sup> SGLT2 inhibitor treatment inhibits the reabsorption of glucose and sodium in the proximal tubule of the kidney, resulting in glycosuria and the lowering of blood glucose independently of the action of insulin, and can also reduce body weight and blood pressure.<sup>7</sup>

The effects of SGLT2 inhibitors on kidney outcomes as novel treatment options for diabetic kidney disease have not been well described in regions outside of North America and Europe. Although previous large randomized controlled trials including the EMPA-REG OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes), the CANVAS programme (CANagliflozin cardioVascular Assessment Study), DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) and CREDENCE (Canagliflozin and Renal Event in Diabetes with Established Nephropathy Clinical Evaluation) included multiracial populations,<sup>4–6,8–10</sup> only a minority of patients (12.7%–21.0%) across these trials were recruited from Asian countries. Real-world evidence on kidney outcomes and all-cause death associated with SGLT2 inhibitors based on Asian data is also limited. The CVD-REAL 2 (Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs) study, a multinational retrospective observational study, included most of the data from Asian countries (the Republic of Korea, Japan and Singapore), but did not report on the effect of SGLT2 inhibitors on renal outcomes.<sup>11</sup> The CVD-REAL 3 (Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice) study recently published real-world evidence from the European Union, Israel and Asia, including Japan and Taiwan. It demonstrated that the initiation of SGLT2 inhibitors was associated with a slower rate of kidney function decline and a lower risk of major kidney events.<sup>12</sup> However, only approximately 11% of the total study cohort were from Asian countries. As several distinctive features are apparent in pathogenetic factors for diabetes in Asian populations,<sup>13</sup> it is important to assess whether the benefits of SGLT2 inhibitors are applicable across different ethnicities. The so-called “Asian phenotypes” in diabetes include low body mass index (BMI); greater amount of body fat, especially visceral adiposity; higher rate of central obesity and metabolic syndrome; insufficient  $\beta$ -cell response in the setting of insulin resistance; and higher risk of developing renal complications among other inter-ethnic clinical differences.<sup>14</sup> In the present study, we investigated the effects of SGLT2 inhibitors on the risk of progression to ESRD and all-cause mortality in a broad range of patients with T2D using a Korean nationwide cohort.

## 2 | MATERIALS AND METHODS

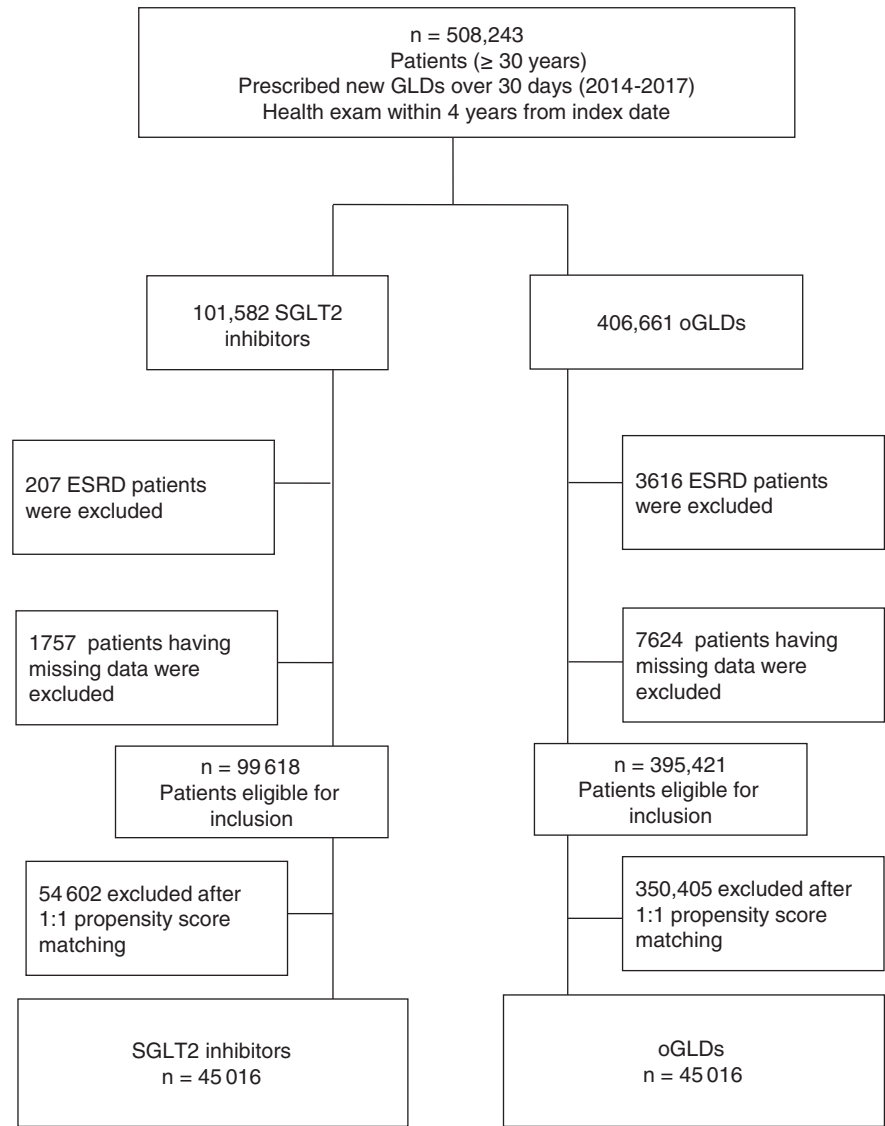
### 2.1 | Data source and study population

This study used the National Health Insurance Service (NHIS) database, which is government managed and includes patients' sociodemographic information, use of inpatient and outpatient services, and pharmacy dispensing claims. The NHIS is the only insurer providing regular health checkup programmes to the public in the Republic of Korea. Those enrolled in the NHIS are recommended to undergo health checkups at least biannually. Patients with T2D who initiated an SGLT2 inhibitor or any other glucose-lowering drug (oGLD) were identified, starting from the date of first prescription, in a time window selected from the date of the first SGLT2 inhibitor availability in this country until the last available data (from January 2014 to December 2017). Patients with known type 1 diabetes and gestational diabetes were excluded. No other *a priori* exclusion criteria were applied. We identified a total of 701 674 T2D patients who were new users of SGLT2 inhibitors or oGLDs and who had clinical and laboratory data recorded at baseline, within a time window of 30 days from the index date. Due to lack of data, we excluded 193 431 patients who had not undergone a health checkup within 4 years from the index date (Figure 1). Among the resulting 508 243 patients, those in the SGLT2 inhibitor category were defined as new users of SGLT2 inhibitors ( $n = 101\,582$ ), and those in the category of oGLD were defined as new users of oGLDs ( $n = 406\,661$ ). We then excluded 3823 patients who had already been diagnosed with ESRD and 9381 patients with missing data. Finally, 99 618 patients in the SGLT2 inhibitor category and 395 421 in the oGLD category were included for the final analysis. This study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of The Catholic University of Korea (No. SC18ZES10158). Because anonymized and deidentified information was used in the analyses, informed consent was not required.

### 2.2 | Measurements and definitions

Comorbidities were defined by a combination of medical history (International Classification of Diseases [ICD]-10 code and self-reported during health checkup questionnaires) and use of medication history for the corresponding disease. The presence of hypertension was defined as at least one claim per year under ICD-10 codes I10 or I11 and at least one claim per year for the prescription of an anti-hypertensive agent, or systolic/diastolic blood pressure  $\geq 140/90$  mmHg. The presence of dyslipidaemia was defined as at least one claim per year for the prescription of antidiyslipidaemic medication under ICD-10 code E78. The presence of cardiovascular disease (CVD) was defined as at least one claim per year under ICD-10 codes I20, I21, I22, I48, I50, G45, I60–I66, or I70–I79. Blood samples for the measurement of serum glucose, creatinine, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol levels were drawn after fasting overnight. As the serum creatinine of NHIS health checkup was measured mainly by isotope dilution mass spectrometry traceable Jaffe methods, not enzyme methods,

**FIGURE 1** CONSORT study enrolment flow diagram. ESRD, end-stage renal disease; GLD, glucose-lowering drug; oGLD, other glucose-lowering drug; SGLT2, sodium-glucose co-transporter-2



Followed from index date to the event date or until Dec 31, 2017

estimated GFR was calculated using the abbreviated Modification of Diet in Renal Disease formula: estimated glomerular filtration rate (eGFR) =  $175 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age (years)}^{-0.203} \times (0.742 \text{ if female})$ .<sup>15</sup> The presence of proteinuria was defined as having urinary protein  $\geq 1+$  on dipstick testing in fasting morning urine. The presence of diabetic retinopathy was defined according to at least one claim per year under ICD-10 code H36.0.

### 2.3 | Study outcomes and follow-up

The main outcomes for this study were newly diagnosed ESRD or all-cause death. We defined incident ESRD using the combination of ICD-10 codes (N18–N19, Z49, Z94.0, Z99.2) and initiation of renal replacement therapy for 30 days or more, and/or kidney transplantation during hospitalization. The Korean Health Insurance Review and

Assessment Service reimburses all medical care expenses for dialysis. Patients with ESRD are also registered as special medical aid beneficiaries. Therefore, we could include each ESRD patient from the whole population and analyse the data for all ESRD patients who started dialysis or had an eGFR  $< 15 \text{ mL/min/1.73 m}^2$ . Patients without ESRD or all-cause death during their follow-up periods were considered to have completed the study at the date of their death or at the end of follow-up, whichever came first. The study population was followed from baseline to the date of ESRD or all-cause death, or until December 31, 2017, whichever came first.

### 2.4 | Statistical methods

Baseline characteristics are presented as means  $\pm$  SD or n (%). The incidence rates for the primary outcomes were calculated by dividing

the number of incident cases by the total follow-up duration (patient-years). The disease-free probability of primary outcomes was calculated using Kaplan–Meier curves, and a log-rank test was performed to analyse differences between the groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) for ESRD and all-cause death were calculated using a Cox proportional hazards model for each category.

A non-parsimonious propensity score for initiating an SGLT2 inhibitor was developed for each individual episode of a new treatment initiation. Variables that could potentially affect treatment assignment or outcomes were selected: eGFR, age, sex, BMI, waist circumference, height, weight, presence of proteinuria, T2D duration, fasting blood glucose, presence of diabetic retinopathy, prior CVD, hypertension, blood pressure, dyslipidaemia, smoking, drinking, exercise, income status, Charlson Comorbidity Index, insulin treatment, glucagon-like peptide-1 receptor agonists, number of oGLDs, and index date. The propensity matching was assessed by evaluating standardized differences of patient characteristics post-match. A significant imbalance was considered to be present if a > 10% standardized difference was present between the two groups after propensity matching. An SAS (SAS Institute Inc., Cary, North Carolina) matching macro, “%OneToManyMTCH,” was used for this matching. It allows propensity-score matching from 1-to-1 to 1-to-N. We set a caliper for nearest-neighbour matching within the first four to eight digits; for example, two patients with propensity scores of 0.12345678 and 0.12347123 match on the first four digits (0.1234). The macro makes the “best” matches first and the “next-best” matches next in a hierarchical sequence until no more matches can be made. If no patient in the oGLD group has a propensity score that lies within a four-digit width of a propensity score of a patient in the SGLT2 inhibitor group, then that patient in the SGLT2 inhibitor group is left unmatched and is not used in subsequent analyses.

The primary analysis used an intention-to-treat approach, in which patients were followed from the start of an index treatment until either occurrence of the first outcome event or the censoring date (whichever was earlier), regardless of whether the index treatment was discontinued. A sensitivity analysis was performed with restriction of the follow-up period to 3 years because of the short follow-up duration of the SGLT2 inhibitor group. Also, the analyses for each outcome were conducted using an on-treatment approach, in which follow-up was censored at discontinuation of the index treatment. Statistical analyses were performed using SAS version 9.4, and a *P* value <0.05 was considered to indicate significance.

### 3 | RESULTS

#### 3.1 | Study population

Following propensity matching with 508 243 new SGLT2 inhibitor or oGLD initiation episodes, a total of 90 032 new SGLT2 inhibitor or oGLD users were identified with 45 016 in each treatment group (Table 1). The distribution of specific SGLT2 inhibitors were dapagliflozin 73.3%, empagliflozin 20.8% and ipragliflozin 6.0%,

respectively, and the mean follow-up period was  $1.49 \pm 0.85$  years. Patient characteristics were well balanced between the two groups. The mean age was 58 years and 43% were women. The mean BMI was  $26 \text{ kg/m}^2$ , and the mean duration of diabetes was 5.64 years and 5.87 years in the SGLT2 inhibitor and oGLD groups, respectively. Among the study population, 30% of patients had diabetic retinopathy. The mean eGFR values of the patients in the SGLT2 inhibitor and oGLD groups were  $89.02 \pm 25.6 \text{ mL/min/1.73 m}^2$  and  $89.44 \pm 29.18 \text{ mL/min/1.73 m}^2$ , respectively, and 8% of patients had proteinuria.

#### 3.2 | Renal outcomes: SGLT2 inhibitors versus oGLDs

During 67 133 person-years of follow-up, there were 167 cases of incident ESRD, of which 53 occurred in the SGLT2 inhibitor group (incidence rate 0.79 per 1000 patient-years) and 114 in the oGLD group (incidence rate 1.70 per 1000 patient-years). Initiation of SGLT2 inhibitors versus oGLDs was associated with a lower risk of incident ESRD (HR 0.47, 95% CI 0.34–0.65; Table 2). The incidence rate of ESRD showed a substantial decrease in the SGLT2 inhibitor group compared with the oGLD group in the Kaplan–Meier curve (*P* values by log-rank <0.0001; Figure 2A). In a subgroup analysis by eGFR, initiation of SGLT2 inhibitors versus oGLDs was associated with a lower risk of progression to ESRD among patients with eGFR 60 to 90 mL/min/1.73 m<sup>2</sup> or less than 60 mL/min/1.73 m<sup>2</sup> (HR 0.39, 95% CI 0.21–0.75 and HR 0.39, 95% CI 0.25–0.63, respectively). The results were consistent regardless of the presence or absence of proteinuria. Furthermore, a sensitivity analysis was performed to adjust for the differences in the person-years of follow-up and periods between the two groups; HR trends for ESRD were similar to the 3-year follow-up results (Table S1 and Figure S1) and those of the on-treatment analysis (Table S2 and Figure S2).

#### 3.3 | All-cause death: SGLT2 inhibitors versus oGLDs

During 67 183 person-years of follow-up, there were 1070 all-cause deaths, of which 484 occurred in the SGLT2 inhibitor group (incidence rate 7.20 per 1000 patient-years) and 586 in the oGLD group (incidence rate 8.73 per 1000 patient-years). Initiation of SGLT2 inhibitors versus oGLDs was associated with a lower risk of all-cause death (HR 0.82, 95% CI 0.73–0.93; Table 2). The incidence rate of all-cause death showed a substantial decrease in the SGLT2 inhibitor group compared with the oGLD group in the Kaplan–Meier curve (*P* values by log-rank = 0.0016; Figure 2B). The results were consistent across the baseline eGFR and regardless of the presence or absence of proteinuria (Table 2). In addition, a sensitivity analysis was performed to adjust for the differences in the person-years of follow-up and periods between the two groups; HR trends for all-cause death were similar to the 3-year follow-up results (Table S1 and Figure S1) and those of the on-treatment analysis (Table S2 and Figure S2).

**TABLE 1** Baseline characteristic of patients using sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs in the total study population

	SGLT2 inhibitors (n = 45 016)	oGLDs (n = 45 016)	ASD
Age, years	58.25 ± 10.87	57.88 ± 10.38	0.0343
Sex, male, n (%)	25 832 (57.38)	25 949 (57.64)	0.0053
BMI, kg/m <sup>2</sup>	26.38 ± 3.76	26.59 ± 3.96	0.0534
Waist circumference, cm	88.12 ± 9.31	88.55 ± 9.67	0.0453
Height, cm	163.45 ± 9.1	163.62 ± 9.43	0.0185
Weight, kg	70.77 ± 13.24	71.45 ± 13.7	0.0507
eGFR, mL/min/1.73m <sup>2</sup>	89.02 ± 25.6	89.44 ± 29.18	0.0152
eGFR, n (%)			
<60 mL/min/1.73m <sup>2</sup>	3261 (7.24)	3583 (7.96)	0.0277
60–90 mL/min/1.73m <sup>2</sup>	21 527 (47.82)	20 905 (46.44)	
≥90 mL/min/1.73m <sup>2</sup>	20 228 (44.94)	20 528 (45.6)	
Presence of proteinuria, n (%)	3719 (8.26)	3827 (8.5)	0.0087
eGFR/proteinuria, n (%)			0.0400
<60 mL/min/1.73m <sup>2</sup> /absent	2751 (6.11)	2864 (6.36)	
<60 mL/min/1.73m <sup>2</sup> /present	510 (1.13)	719 (1.6)	
≥60 mL/min/1.73m <sup>2</sup> /absent	38 546 (85.63)	38 325 (85.14)	
≥60 mL/min/1.73m <sup>2</sup> /present	3209 (7.13)	3108 (6.9)	
T2D duration, years	6 (1–10)	6 (2–10)	0.0574
Glucose, mmol/L	8.76 ± 3.13	8.85 ± 3.44	0.0299
Diabetic retinopathy, n (%)	13 933 (30.95)	13 494 (29.98)	0.0212
Prior cardiovascular disease, n (%)			
Myocardial infarction	1527 (3.39)	1534 (3.41)	0.0009
Unstable angina	2482 (5.51)	2519 (5.6)	0.0036
Angina pectoris	7838 (17.41)	7885 (17.52)	0.0028
Heart failure	3284 (7.3)	3477 (7.72)	0.0163
Atrial fibrillation	1171 (2.6)	1246 (2.77)	0.0103
Stroke	5292 (11.76)	5167 (11.48)	0.0087
Hypertension, n (%)	25 706 (57.1)	25 545 (56.75)	0.0072
Systolic blood pressure, mmHg	127.86 ± 14.93	127.94 ± 14.99	0.0057
Diastolic blood pressure, mmHg	78.53 ± 9.94	78.65 ± 10.07	0.0118
Dyslipidaemia, n (%)	31 455 (69.88)	31 619 (70.24)	0.0080
Total cholesterol, mmol/L	4.84 ± 1.36	4.87 ± 1.26	0.0190
Triglycerides, mmol/L	1.68 (1.68–1.69)	1.71 (1.70–1.72)	0.0215
HDL cholesterol, mmol/L	1.28 ± 0.35	1.28 ± 0.33	0.0000
LDL cholesterol, mmol/L	2.68 ± 1.2	2.7 ± 1.15	0.0140
Smoking status, n (%)			0.0050
Non-smoker	24 426 (54.26)	24 313 (54.01)	
Ex-smoker	9363 (20.8)	9374 (20.82)	
Current smoker	11 227 (24.94)	11 329 (25.17)	
Heavy drinker, n (%)	4137 (9.19)	4268 (9.48)	0.0100
Regular exercise, n (%)	9135 (20.29)	8884 (19.74)	0.0139
Income: low 25%, n (%)	10 470 (23.26)	10 546 (23.43)	0.0040
ACE inhibitors, n (%)	1300 (2.89)	1564 (3.47)	0.0334
ARBs, n (%)	20 863 (46.35)	21 775 (48.37)	0.0406

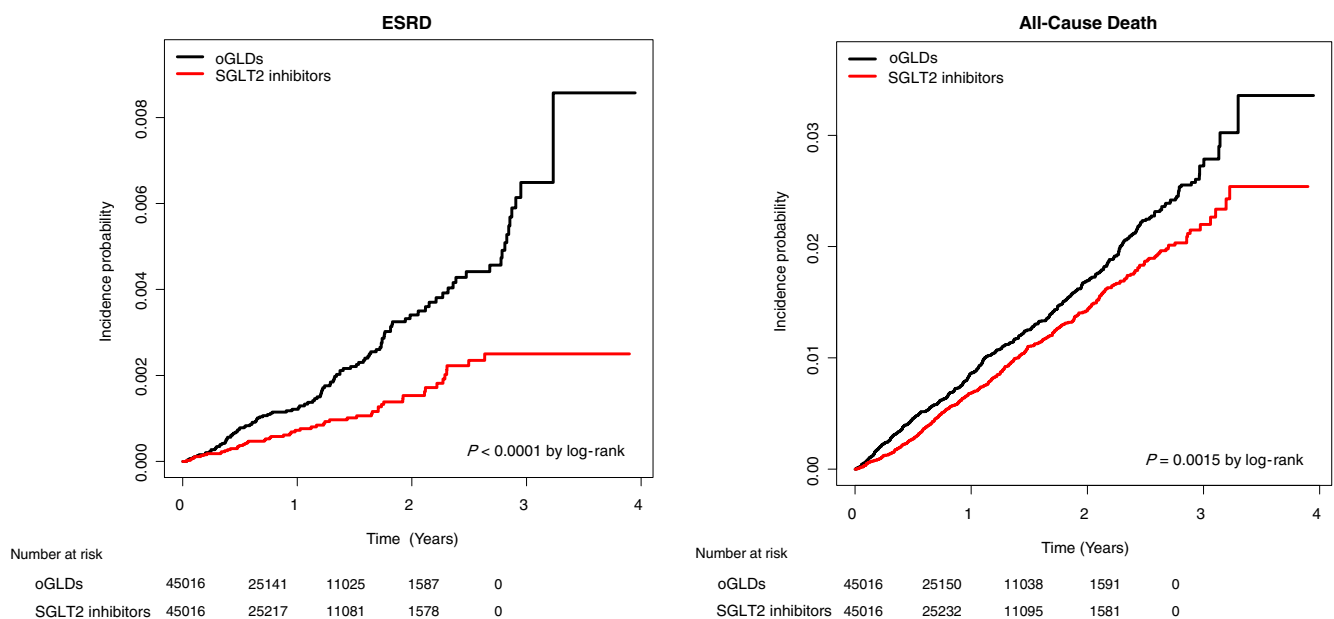
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**TABLE 1** (Continued)

	SGLT2 inhibitors (n = 45 016)	oGLDs (n = 45 016)	ASD
Loop diuretics, n (%)	2333 (5.18)	2539 (5.64)	0.0202
Thiazide diuretics, n (%)	3095 (6.88)	3374 (7.5)	0.0240
Statins, n (%)	29 042 (64.51)	30 404 (67.54)	0.0639
Beta blockers, n (%)	6960 (15.46)	7478 (16.61)	0.0313
Aldosterone, n (%)	914 (2.03)	1160 (2.58)	0.0364
Index year, n (%)			0.0000
2014	1621 (3.6)	1621 (3.6)	
2015	9621 (21.37)	9621 (21.37)	
2016	14 159 (31.45)	14 159 (31.45)	
2017	19 615 (43.57)	19 615 (43.57)	
Charlson comorbidity index	2.7 ± 1.95	2.68 ± 2.09	0.0074

Note: Values are mean ± SD or median value (interquartile range), unless otherwise indicated. Presence of proteinuria was defined as having urinary protein ≥1+ dipstick testing in fasting morning urine.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; eGFR, estimated glomerular filtration rate; oGLD, other glucose-lowering drug; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.



**FIGURE 2** Kaplan–Meier estimates of the incidence of end-stage renal disease (ESRD; left) and all-cause death (right) in patients using sodium-glucose co-transporter-2 inhibitors (SGLT2 inhibitors; red) versus other glucose lowering drugs (oGLDs; black)

### 3.4 | Subgroup analysis

To evaluate the effect of modifiers on the associations between SGLT2 inhibitors and outcomes, we conducted a stratified analysis using several factors including age, sex, BMI, abdominal obesity, diabetic retinopathy, hypertension and prior CVD (Table 3). The association of SGLT2 inhibitors versus oGLDs with lowering incident ESRD risk was stronger in obese patients (HR 0.27, 95% CI

0.16–0.44) than in non-obese patients (HR 0.80, 95% CI 0.51–1.25;  $P$  for interaction = 0.002). For all-cause death, the association was stronger in younger, female and obese patients and subgroups without hypertension or prior CVD. For example, the association of SGLT2 inhibitors versus oGLDs with lower all-cause deaths risk was stronger in female patients (HR 0.64, 95% CI 0.52–0.79) than in male patients (HR 0.94, 95% CI 0.81–1.09;  $P$  for interaction = 0.001).



**TABLE 2** Risk of end-stage renal disease and all-cause deaths associated with sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs

	N	ESRD	Person-years of follow up	Incidence rate (per 1000)	HR (95% CI)	P for interaction	Death	Person-years of follow up	Incidence rate (per 1000)	HR (95% CI)	P for interaction
Total	45 016	114	67 061	1.70	1 (ref.)		586	67 119	8.73	1 (ref.)	
	SGLT2 inhibitors	45 016	67 204	0.79	0.47 (0.34, 0.65)		484	67 247	7.20	0.82 (0.73, 0.93)	
eGFR < 60 mL/min/1.73m <sup>2</sup>	3583	70	5538	12.64	1 (ref.)	0.01	96	5576	17.22	1 (ref.)	0.10
	SGLT2 inhibitors	3261	4812	4.99	0.39 (0.25, 0.63)		91	4832	18.83	1.1 (0.83, 1.47)	
	oGLDs	20 905	31 430	1.05	1 (ref.)		284	31 443	9.03	1 (ref.)	
eGFR 60–90 mL/min/1.73m <sup>2</sup>	21 527	13	32 117	0.40	0.39 (0.21, 0.75)		239	32 127	7.44	0.82 (0.69, 0.98)	
	SGLT2 inhibitors	20 528	11	30 093	1 (ref.)		206	30 100	6.84	1 (ref.)	
	oGLDs	20 228	16	30 276	1.45 (0.67, 3.11)		154	30 288	5.08	0.74 (0.6, 0.91)	
eGFR ≥ 90 mL/min/1.73m <sup>2</sup>	41 189	57	61 426	0.93	1 (ref.)	0.12	523	61 453	8.51	1 (ref.)	0.96
	SGLT2 inhibitors	41 297	34	61 819	0.60 (0.39, 0.92)		435	61 847	7.03	0.83 (0.73, 0.94)	
	oGLDs	3827	57	5635	1 (ref.)		63	5666	11.12	1 (ref.)	
Without proteinuria	3719	19	5386	3.53	0.35 (0.21, 0.59)		49	5400	9.07	0.81 (0.56, 1.18)	
With proteinuria	2864	28	4469	6.27	1 (ref.)	0.43	77	4484	17.17	1 (ref.)	
eGFR/proteinuria	2751	11	4109	2.68	0.43 (0.21, 0.87)		73	4120	17.72	1.04 (0.76, 1.43)	
<60 mL/min/1.73m <sup>2</sup> /absent	719	42	1068	39.31	1 (ref.)		19	1092	17.40	1 (ref.)	
<60 mL/min/1.73m <sup>2</sup> /present	510	13	703	18.50	0.47 (0.25, 0.87)		18	712	25.28	1.44 (0.76, 2.75)	
≥60 mL/min/1.73m <sup>2</sup> /absent	38 325	29	56 957	0.51	1 (ref.)		446	56 969	7.83	1 (ref.)	
≥60 mL/min/1.73m <sup>2</sup> /present	38 546	23	57 710	0.40	0.79 (0.46, 1.37)		362	57 728	6.27	0.80 (0.70, 0.92)	
Total	3108	15	4566	3.28	1 (ref.)		44	4574	9.62	1 (ref.)	
	SGLT2 inhibitors	3209	6	4683	1.28	0.40 (0.15, 1.02)	31	4687	6.61	0.69 (0.43, 1.09)	

Note: Presence of proteinuria was defined as having urinary protein ≥ 1+ dipstick testing in fasting morning urine.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; oGLD, other glucose-lowering drug; SGLT2, sodium-glucose co-transporter-2 inhibitors.

**TABLE 3** Hazard ratios of end-stage renal disease and all-cause deaths for sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs in various subgroups

Subgroups	ESRD						All cause deaths					
	N	Events	Person-years of follow up	Incidence rate (per 1000)	HR (95% CI)	P for interaction	Events	Person-years of follow up	Incidence rate (per 1000)	HR (95% CI)	P for interaction	
Age, year												
<65	33 123	74	49 213	1.50	1 (ref.)	0.06	247	49 255	5.01	1 (ref.)	0.001	
	32 364	26	49 007	0.53	0.35 (0.23, 0.55)		154	49 027	3.14	0.62 (0.51, 0.76)		
≥65	11 893	40	17 847	2.24	1 (ref.)		339	17 863	18.98	1 (ref.)		
	12 652	27	18 197	1.48	0.67 (0.41, 1.09)		330	18 219	18.11	0.96 (0.82, 1.11)		
Sex												
Male	25 949	67	37 204	1.80	1 (ref.)	0.21	353	37 241	9.48	1 (ref.)	0.003	
	25 832	37	37 711	0.98	0.55 (0.37, 0.82)		337	37 739	8.93	0.94 (0.81, 1.09)		
Female	19 067	47	29 856	1.57	1 (ref.)		233	29 878	7.80	1 (ref.)		
	19 184	16	29 492	0.54	0.35 (0.20, 0.61)		147	29 507	4.98	0.64 (0.52, 0.79)		
BMI												
<25 kg/m <sup>2</sup>	16 276	42	23 851	1.76	1 (ref.)	0.002	309	23 872	12.94	1 (ref.)	0.02	
	16 641	34	24 349	1.40	0.80 (0.51, 1.25)		294	24 375	12.06	0.93 (0.79, 1.09)		
≥25 kg/m <sup>2</sup>	28 740	72	43 208	1.67	1 (ref.)		277	43 247	6.41	1 (ref.)		
	28 375	19	42 855	0.44	0.27 (0.16, 0.44)		190	42 872	4.43	0.69 (0.57, 0.83)		
Abdominal obesity												
No	21 742	45	31 909	1.41	1 (ref.)	0.003	316	31 936	9.89	1 (ref.)	0.06	
	22 205	35	32 814	1.07	0.76 (0.49, 1.19)		295	32 842	8.98	0.90 (0.77, 1.06)		
Yes	23 274	69	35 151	1.96	1 (ref.)		270	35 183	7.67	1 (ref.)		
	22 811	18	34 390	0.52	0.27 (0.16, 0.45)		189	34 405	5.49	0.72 (0.59, 0.86)		
Diabetic retinopathy												
No	31 522	42	45 688	0.92	1 (ref.)	0.38	408	45 706	8.93	1 (ref.)	0.12	
	31 083	24	46 414	0.52	0.56 (0.34, 0.93)		320	46 431	6.89	0.77 (0.67, 0.89)		
Yes	13 494	72	21 372	3.37	1 (ref.)		178	21 413	8.31	1 (ref.)		
	13 933	29	20 790	1.39	0.42 (0.27, 0.65)		164	20 815	7.88	0.95 (0.77, 1.18)		
Hypertension												
No	19 471	12	27 926	0.43	1 (ref.)	0.11	217	27 930	7.77	1 (ref.)	0.0001	
	19 310	11	28 887	0.38	0.86 (0.38, 1.96)		131	28 896	4.53	0.58 (0.47, 0.72)		
Yes	25 545	102	39 134	2.61	1 (ref.)		369	39 189	9.42	1 (ref.)		
	25 706	42	38 317	1.10	0.43 (0.30, 0.61)		353	38 350	9.20	0.98 (0.84, 1.13)		

TABLE 3 (Continued)

Subgroups	N	ESRD				All cause deaths				P for interaction		
		Events	Person-years of follow up	Incidence rate (per 1000)	HR (95% CI)	Events	Person-years of follow up	Incidence rate (per 1000)	HR (95% CI)			
Prior CVD												
No		23 166	26	33 561	0.77	1 (ref.)	0.70	193	33 572	5.75	1 (ref.)	0.004
SGLT2 inhibitors		22 683	14	34 168	0.41	0.54 (0.28, 1.04)		124	34 178	3.63	0.63 (0.50, 0.79)	
Yes		21 850	88	33 500	2.63	1 (ref.)		393	33 547	11.71	1 (ref.)	
SGLT2 inhibitors		22 333	39	33 036	1.18	0.45 (0.31, 0.66)		360	33 069	10.89	0.93 (0.80, 1.07)	

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; ESRD, end-stage renal disease; HR, hazard ratio; oGLD, other glucose-lowering drug; SGLT2, sodium-glucose co-transporter-2 inhibitors.

## 4 | DISCUSSION

The results of the present study suggest that initiation of SGLT2 inhibition as compared with oGLD treatment had a statistically significant and clinically relevant association with lower risk of ESRD and all-cause death in patients with T2D in a general population of patients with T2D in Korea, evidence that is complementary to and consistent with what has been already observed in previous randomized controlled trials for this class of compounds. T2D patients in the SGLT2 inhibitor group had a significantly lower risk of incident ESRD and all-cause death compared with patients in the oGLD group. Although ESRD and all-cause death are rare events in the general population and would be unexpected in those with near-normal baseline eGFR, due to the large sample size, we were able to accrue a substantial number of these events to demonstrate that initiation of SGLT2 inhibitors was significantly associated with a lower risk of these outcomes compared with oGLDs. Recent randomized clinical trials demonstrated a lower risk of renal composite events and all-cause death with SGLT2 inhibitors in T2D patients; however, results showing the beneficial effect of SGLT2 inhibitors on ESRD and all-cause death in routine clinical care are scarce.<sup>3,4,6</sup> The present report complements the results from the CVD REAL 3 study,<sup>12</sup> providing further evidence from an Asian patient population from the nationwide Korean registry including ~80 000 patients with T2D and with ~67 000 patient-years of follow-up.

It is noteworthy that the present study assessed the effect of SGLT2 inhibition on risk of incident ESRD and all-cause death stratified by renal function including eGFR and presence of proteinuria, and the overall results were consistent across these subgroups. The patients with eGFR 60 to 90 mL/min/1.73 m<sup>2</sup> or <60 mL/min/1.73 m<sup>2</sup> were observed to have a lower risk of progression to ESRD with SGLT2 inhibitors versus oGLDs, whereas those with eGFR ≥90 mL/min/1.73 m<sup>2</sup> were not. We interpret the results with caution because the discordance may be dependent on how renal events were defined and because of the relatively short follow-up period for incident ESRD in these real-world data. There were few ESRD events in the subgroup with eGFR ≥90 mL/min/1.73 m<sup>2</sup>, which had a relatively low risk for ESRD development considering the clinical natural course of chronic kidney disease progression. CREDENCE is the only published randomized controlled trial to examine a population with diabetic kidney disease, especially in terms of the outcomes of eGFR subgroups. The CREDENCE study population had more advanced chronic kidney disease; their mean eGFR was 56.2 mL/min/1.73 m<sup>2</sup> and 99% of the patients had a microalbuminuria level > 30 mg/g and a mean T2D duration of 15.8 years, while the population in our real-world study had an eGFR level of 89.2 mL/min/1.73 m<sup>2</sup>, an 8% rate of proteinuria, and a mean T2D duration of 6 years. In CREDENCE, patients in the eGFR 45 to 60 mL/min/1.73 m<sup>2</sup> subgroup had an HR of 0.47 (95% CI 0.31–0.72) for the risk of a renal composite outcome. Interestingly, the results were comparable with our real-world data, in which the HR for incident ESRD was 0.39 (95% CI 0.25–0.63) in the subgroup with an eGFR level < 60 mL/min/1.73 m<sup>2</sup>. As for all-cause death, the patients with eGFR 60 to 90 and ≥ 90 mL/min/1.73 m<sup>2</sup>

were observed to have a lower risk of all-cause deaths with SGLT2 inhibitors versus oGLDs, whereas those with eGFR  $<60$  mL/min/1.73 m<sup>2</sup> were not. However, it is difficult to draw any firm conclusions around this segment because there were relatively low numbers of patients and events in the subgroup with eGFR  $<60$  mL/min/1.73 m<sup>2</sup>, and the *P* for interaction was not statistically significant.

The glucose-lowering effects of SGLT2 inhibitors decrease as renal function declines, which raises the possibility that the magnitude of benefit on glycaemia might be somewhat attenuated in patients with lower baseline eGFR levels mediated by reduced available nephron mass and diminished glucose reabsorption capacity.<sup>16–18</sup> However, SGLT2 inhibitors consistently decrease the risk of incident ESRD regardless of baseline eGFR, which indicates that the effects of SGLT2 inhibitors are partly mediated via non glucosuric-dependent mechanisms.<sup>19–21</sup> Although pleiotropic effects of SGLT2 inhibitors have been inferred, improvement of glycaemic control, lowering of systemic blood pressure and intraglomerular pressure, reduction in albuminuria, and amelioration of volume overload are all plausible protective mechanisms with the possibility of a more comprehensive interactive effect.<sup>5,22,23</sup> SGLT2 inhibitors induce natriuresis, which activates tubulo-glomerular feedback, reducing glomerular hypertension and hyperfiltration to limit kidney damage. The proposal of the haemodynamic mechanism of SGLT2 inhibitors is supported by the transient decline of eGFR after initiation of SGLT2 inhibitors followed by spontaneous recovery.<sup>8</sup> In this regard, the renoprotective mechanism of SGLT2 inhibitors can be linked in part to the renin-angiotensin system blockade-induced improvement of diabetic nephropathy, mainly by lowering intraglomerular pressure.<sup>24</sup> Furthermore, the impact of SGLT2 inhibitors on the risk of ESRD differed according to BMI in the present study, although a few cases of incident ESRD developed. Thus, obese patients (BMI  $\geq 25$  kg/m<sup>2</sup>) experienced a greater benefit of lowering the risk of ESRD compared to those with BMI  $<25$  kg/m<sup>2</sup>. These findings suggest that the renal benefits of SGLT2 inhibitors may be amplified especially in obesity-associated glomerular hyperfiltration in patients with T2D, although this issue warrants further investigation.<sup>25</sup> Another proposed mechanism of SGLT2 inhibitors is mediated by metabolic effects. SGLT2 inhibitors appear to decrease energy demand by reducing sodium transport and ameliorate cellular stress by enhancing AMPK/SIRT1, eventually leading to protection from functional and structural tubular injury by diabetes.<sup>26</sup> In addition, SGLT2 inhibitors could limit the activity of transforming growth factor  $\beta 1$ , a known intrarenal cytokine associated with progressive kidney failure and lowering of the expression of inflammatory molecules.<sup>27,28</sup>

The findings of the present study should be interpreted in the context of several potential limitations. First, due to the observational nature of the study, we cannot exclude the possibility of unmeasured confounding factors, which cannot be overcome by propensity-score matching. Confounders such as socio-economic factors, or metabolic variables that were not measured after baseline in this study, could have affected both the choice of glucose-lowering medication and the outcomes. A novel drug may also be more readily prescribed to healthier patients, and those with relatively uncontrolled diabetes in

the early post-marketing period in the real world.<sup>29</sup> Second, an immortal time bias can arise if some proportion of the follow-up time is excluded or misclassified. Third, renal function, including eGFR and the presence of proteinuria, was measured only at enrolment; therefore, subtle changes in renal function could not be included in the analyses. The presence of proteinuria was evaluated using a semi-quantitative dipstick test, which has an approximately 30% false-negative rate for microalbuminuria. Fourth, the follow-up period was relatively short considering the clinical course of renal outcomes in patients with T2D, and there was no information about the precise cause of ESRD or mortality, or uric acid levels (which can be reduced by SGLT2 inhibitors).<sup>30</sup> Finally, these results have a limited generalizability to other (non-Korean) populations.

The strengths of the present study include a large sample size, which encompassed the entire South Korean population, and the inclusion of several types of subgroup analyses, especially focused on the stratified renal function with eGFR and presence of proteinuria. These observational findings can be considered as complementary to the other large renal outcome trials of SGLT2 inhibitors including the CREDENCE trial,<sup>4</sup> the DAPA-CKD<sup>31,32</sup> and ongoing EMPA-Kidney trials.<sup>33</sup> Nevertheless, the vast majority of participants in these trials were recruited in the United States and Europe, thereby restricting the generalizability of the results. The present study reflects the utilization of SGLT2 inhibitors in clinical practice in an East Asian population. Thus, our findings suggest that the renal benefits of SGLT2 inhibitors may extend across different ethnic backgrounds.

In conclusion, the results of the present study suggest that SGLT2 inhibition had a statistically significant and clinically relevant association with lower risk of ESRD and all-cause death in patients with T2D in a general Korean population of patients with T2D, evidence that is complementary to and consistent with what has been already observed in previous randomized controlled trials for this class of compounds. This benefit was consistent across the spectrum of eGFR at baseline. Findings from ongoing SGLT2 inhibitor trials will provide further evidence regarding how best to integrate these therapies into the care of patients with chronic kidney disease to improve outcomes. Moreover, longer-duration studies in patients with renal dysfunction will ultimately inform the long-term safety of SGLT2 inhibitor use.

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## CONFLICTS OF INTEREST

E.S.K., K.D.H., S.J.Y., H.S.K. received research grant from AstraZeneca. Y.S.N., E.T.W., P.F. are AstraZeneca employees. M.K. has served on advisory boards for Amarin, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, Glytec, Janssen, Merck (Diabetes), Novartis, Novo Nordisk, and Sanofi; served as a consultant for Amgen, Applied Therapeutics, AstraZeneca, Bayer,

Boehringer Ingelheim, GlaxoSmithKline, Intarcia, Novo Nordisk, and Sanofi, and received research grants from AstraZeneca and Boehringer Ingelheim. H.J.L.H. has consultancy agreements with Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, Fresenius, Gilead and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, and has a policy of honoraria going to his employer. He has also received grant support from Boehringer Ingelheim, AstraZeneca and Janssen (funding to his employer).

### CONTRIBUTION STATEMENT

E.S.K., K.D.H., P.F., M.K., H.J.L.H. and H.S.K. contributed to the development of the study concept and design. E.S.K., K.D.H. and H.S.K. contributed to data collection and analysis, interpretation of the data, and writing of the article. Y.S.N., E.W. and S.J.Y. contributed to the interpretation of the data and critical review and revision of the article. P.F., M.K. and H.J.L.H. contributed to interpretation of the data, data report finalization, and critical review and revision of the article.

### PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14239>.

### DATA AVAILABILITY STATEMENT

Data are available through the Korean National Health Insurance Sharing Service (NHISS). Researchers who wish to access the data can apply at <https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do>.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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