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End-stage renal diseases associated with SGLT2 inhibitors versus GLP-1 receptor agonists in metabolic dysfunction-associated steatotic liver disease

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A B S T R A C T

Aims: To compare the renal effectiveness of SGLT2 inhibitors (SGLT2i) versus GLP-1 receptor agonists (GLP-1RA) in metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: Using nationwide healthcare claims (2014–2023) of Korea, we constructed a cohort of MASLD patients who initiated SGLT2i or GLP-1RA. Patients were stratified on baseline status of chronic kidney disease (CKD). New-users of SGLT2i and GLP-1RA were 1:1 propensity score (PS) matched. Incidence rates (IRs) per 1,000 person-years, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for a composite of end-stage renal diseases (ESRD).

Results: Of 333,082 MASLD patients who initiated SGLT2i or GLP-1RA, a total of 1,268 SGLT2i-GLP-1RA pairs were PS-matched in cohort with CKD, while 10,996 pairs were matched in cohort without CKD. For the cohort with CKD, SGLT2i presented 33% lower risk of ESRD compared to GLP-1RA (20.3 vs. 30.0 events per 1,000 person-years; HR 0.67, 95% CI 0.45–1.00). For the cohort without CKD, SGLT2i presented a 68% lowered risk of ESRD compared to GLP-1RA (0.9 vs. 2.5 events per 1,000 person-years; HR 0.32, 95% CI 0.19–0.53).

Conclusions: The use of SGLT2i was associated with lower risk of ESRD compared to GLP-1RA in MASLD. The protective association was presented regardless of CKD status.

1. Introduction

Emerging evidence suggests that metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with chronic kidney disease (CKD).[1,2] MASLD is characterized by chronic hepatic inflammation, which exerts systemic effects, [3] including the secretion of a range of pro-inflammatory cytokines and procoagulant factors, ultimately contributing to renal inflammation and fibrosis. [4] Additionally, cardiometabolic risk factors common in MASLD, such as type 2 diabetes (T2D), obesity, hyperlipidemia, and hypertension, could further drive the CKD progression. [5] Consequently, individuals with MASLD represent a high-risk population for CKD onset and progression, [6] which underscores the need for optimized treatment strategies to mitigate renal risk and slow disease progression.

Randomized controlled trials (RCTs) have demonstrated the renal protective effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon like peptide-1 receptor agonists (GLP-1RA), initially developed as glucose-lowering agents for T2D. Based on findings from other populations, both drug classes are considered promising candidates for renal protection in MASLD patients. Landmark trials in T2D patients with atherosclerotic cardiovascular disease (ASCVD) have reported 15–24 % lowered risk of renal disease compared to placebo. [7–11] Moreover, trials dedicated to renal endpoints in patients with CKD have confirmed the efficacy of SGLT2i and GLP-1RA, showing

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24–39 % lowered risk compared to placebo. [12–14] Alongside the potential for renal effectiveness, these agents hold significant promise as a holistic approach for individuals with MASLD, who often present with multiple interrelated complications. Considering the complex risk factor profile of MASLD patients, selecting the most appropriate treatment for renal protection is particularly critical when other baseline risk factors are comparable.

However, no trials have evaluated the comparative renal effectiveness of these agents, and evidence is lacking regarding the optimal stage of disease progression at which these agents should be started. To address this knowledge gap, we conducted a nationwide cohort study to compare the renal effectiveness of SGLT2i versus GLP-1RA in individuals with MASLD. Given that baseline CKD status may influence both the incidence of end-stage renal disease (ESRD) and the distribution of risk factors, we stratified the study population by CKD status to account for potential effect modification.

2. Methods

2.1. Data Source

Nationwide health administrative claims data between September 1, 2014, and December 31, 2023, was obtained from the National Health Insurance Service (NHIS) of Korea. The NHIS is a single provider of health insurance and covers approximately 97 % of the Korean population (over 50 million people) [15]. The database includes anonymized patient-level data such as sociodemographic details, inpatient and outpatient diagnoses, emergency room visits, prescriptions, medical procedures, and biennial health examination results. Diagnoses are classified using the International Statistical Classification of Diseases, Tenth Revision (ICD-10) and the codes for Rare and Intractable Diseases (RID) registration program. In Korea, patients undergoing dialysis or renal transplantation are registered in the RID program and receive extended health insurance coverage, which reduces the costs associated with these treatments. To be registered, official documentation from a nephrologist that includes an overall clinical assessment of the patient is required. [16] Additionally, linked data from Statistics Korea provides information on mortality dates and causes. Health examination results also provide a range of key clinical variables such as serum creatinine, estimated glomerular filtration rate (eGFR), proteinuria, fasting blood glucose, and liver enzyme levels, and self-reported details on alcohol consumption and smoking behavior. The eGFR was calculated based on serum creatinine level, sex, and age using the Chronic Kidney Disease-Epidemiology Collaboration equation. [17] Finally, we conducted anonymized linkage of Kangbuk Samsung Health Study (KSHS) cohort to NHIS database, to perform validation of MASLD status in our study population (**eAppendix 1**). This study was approved by the Institutional Review Board of Sungkyunkwan University (IRB SKKU 2024–12-005) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (Supplement 2) [18].

2.2. Study population and design

Following the target trial emulation framework, [19] we emulated the design of a hypothetical trial to strengthen the validity of causal inference within an observational claims database (eTable 1). We conducted an active-comparator, new-user cohort study including patients with MASLD who initiated SGLT2i (dapagliflozin, empagliflozin, ipragliflozin, or ertugliflozin) or GLP-1RA (dulaglutide, lixisenatide, liraglutide, or exenatide), between September 1, 2014, and December 31, 2023. The index date was defined as the date of the first prescription of SGLT2i or GLP-1RA, with washout period of 1 year prior to index date, to ensure new-users of study drugs. Participants with an index date before September 1, 2014, when SGLT2i were first introduced in Korea, were excluded to ensure all study agents were available during the study period.

Among patients with T2D (ICD-10 code: E11-E14), we classified those exceeding the cut-off value of the fatty liver index (FLI) as having MASLD. [20,21] Using the linked database of NHIS-KSHS, an external validation study was performed. This linked database included results of abdominal ultrasonography performed in the fasting state to detect hepatic steatosis. Briefly, using this external dataset containing information for a subset of our study population, we took the hepatic steatosis detected by abdominal ultrasonography as the reference standard. The optimal cut-off value of FLI was calculated by receiver operating curve (ROC) analysis. We obtained a cut-off value of 53.5, with a positive predictive value of 95.4 % (**eAppendix 2**).

Among patients with MASLD, those with diagnosis of competing liver diseases other than MASLD (e.g. viral hepatitis, alcoholic liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, Budd-Chiari syndrome) any time before the index date were excluded (eTable 2). [22] Subsequently, we excluded patients diagnosed with ESRD or those with procedure records for renal dialysis, or type 1 diabetes, or cancer any time before the index date. Finally, we excluded patients who initiated both SGLT2i and GLP-1RA on the same date to avoid exposure misclassification. We categorized these eligible patients by baseline CKD status, defined as a single eGFR record < 60 mL/min/1.73 m^2, and conducted separate analyses for those with and without CKD (Fig. 1 and **eFig. 1**).

2.3. Exposures and follow-up

We aimed to assess the comparative renal effectiveness of SGLT2i versus GLP-1RA, both of which are recommended for cardiovascular and kidney risk reduction in high-risk individuals with T2D, and eligible option for MASLD. [23] Following an as-treated approach, patients were followed from the day after the index date until the earliest of drug discontinuation, drug switching to or adding of GLP-1RA among SGLT2i initiators or vice versa, outcome occurrence, December 31, 2023 (study end date), or death. We considered a 90-day lag period after the index date to account for protopathic bias[24]; thus, outcomes occurred in the first 90 days of follow-up were censored as nonevents. Regarding drug discontinuation, we considered a drug to be continuously used if the gap between successive prescriptions did not exceed a 90-day grace period. Duration of follow-up and censoring reasons are presented in eTable 3.

2.4. Outcome Definition

The primary outcome was a composite of ESRD comprising a diagnosis of CKD stage 5, kidney failure, dialysis, renal transplant, or renal death. As secondary outcomes, we also assessed each component of the primary outcome along with cardiovascular death, considering the fact that a large proportion of patients with ESRD die from cardiovascular disease. [25] All outcomes were captured through diagnosis or procedure codes in primary or secondary positions in the inpatient setting. [26,27] Patients undergoing dialysis or renal transplantation were identified with specific codes for RID registration program, along with diagnosis or procedure codes. Renal death and cardiovascular death were defined as death caused by any renal or cardiovascular disease based on the diagnosis codes (eTable 4). [28].

2.5. Covariates

We assessed demographic characteristics (age, sex) and calendar year on the index date. Proxies for healthcare utilization behavior (number of hospitalizations, number of physician visits, and physician specialties) were assessed a year prior to the index date. Body mass index (BMI) from health examination results were assessed within 3 years prior to the index date and stratified based on Asian categories (normal weight, <23 kg/m^2; overweight, 23 to <25 kg/m^2; obese I, 25 to <30 kg/m^2, obese II, ≥ 30 kg/m^2). [29] Also, smoking (never, past, current, unknown) and drinking (no, yes, unknown) behaviors were assessed

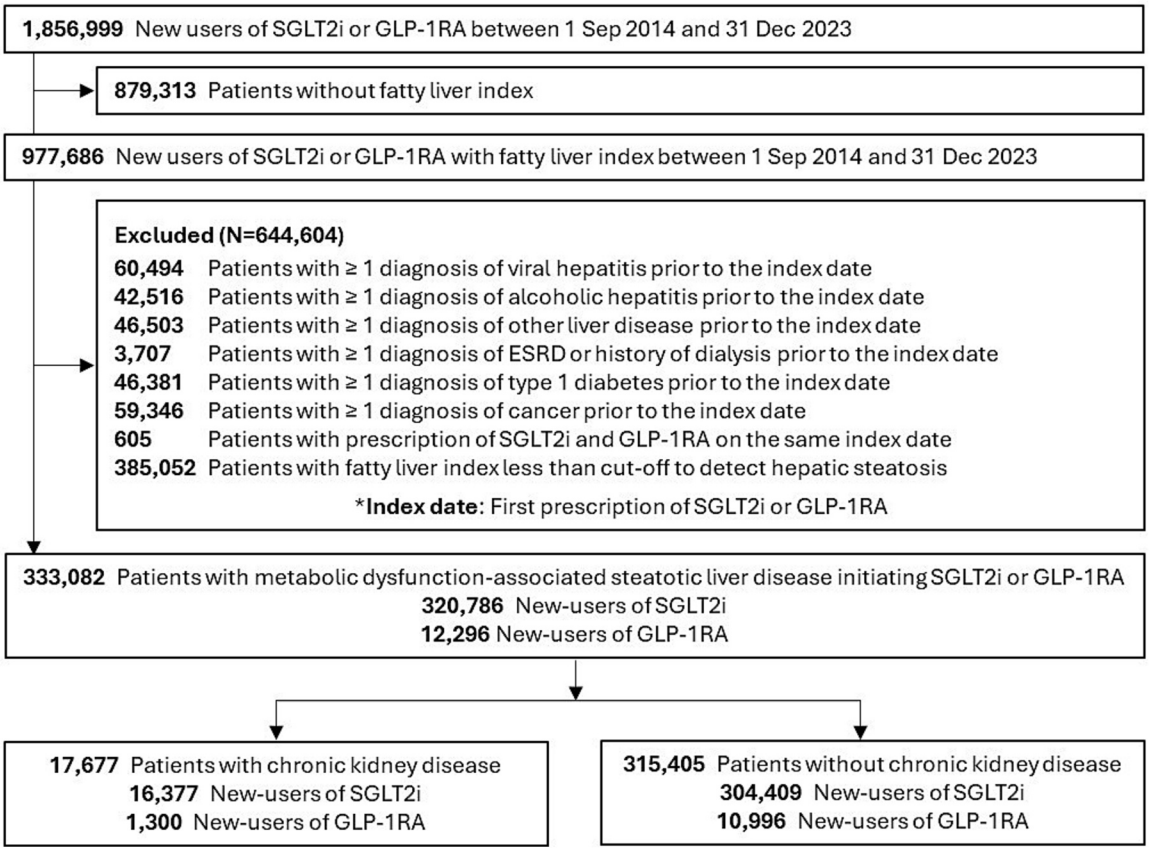

Fig. 1. Flowchart for study participants selection. **Abbreviations**: ESRD, end stage renal disease; GLP-1RA, glucagon-like peptide 1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

within 3 years prior to the index date.

Comorbidities and comedications were identified using diagnosis codes and prescription records a year prior to the index date (eTable 5). The use of antidiabetic drugs other than study drugs (insulin, alpha-glucosidase inhibitors, meglitinides, metformin, sulfonylureas, thiazolidinediones, and dipeptidyl-peptidase 4 inhibitors) and a history of diabetic microvascular complications were assessed. The levels of antidiabetic treatments were assessed as follows: level 1, taking none or only one class of antidiabetic drug other than insulin; level 2, taking two or more classes of antidiabetic drugs without insulin; and level 3, taking insulin with or without other classes of antidiabetic drugs. Charlson Comorbidity Index (CCI) were identified using corresponding diagnosis codes. A range of clinical variables (waist circumference, serum creatinine, eGFR, fasting blood glucose, blood pressure, total cholesterol, triglycerides, liver enzyme levels, and proteinuria) were obtained from health examination results. Proteinuria levels were classified based on urine dipstick test results. [30].

2.6. Statistical analyses

We fitted a multivariable logistic regression model to estimate the predicted probability of initiating SGLT2i versus GLP-1RA as the propensity score (PS), considering all the covariates mentioned above as independent variables. Regarding covariates with missing values (smoking, drinking, and proteinuria level), we used missing indicators and then included them in the PS model. [31] Patients in each treatment group were matched 1:1 using the greedy nearest-neighbor method with a 0.05 caliper on the log scale. An absolute standardized difference (ASD) greater than 0.1 was considered indicative of significant baseline covariate imbalance between treatment groups. [32] Descriptive statistics were used to present the baseline characteristics of each treatment group before and after PS matching, using mean and standard deviation (SD) for continuous variables and number and proportion (%) for categorical variables. The number of events, person-years, incidence per 1,000 person-years (IR) for the primary and secondary outcomes were calculated based on Poisson distribution in the PS-matched cohort. We fitted Cox proportional hazards model to estimate hazard ratios (HR) and 95 % confidence intervals (CI). Cumulative incidence curves were plotted using the Kaplan-Meier method and p-values for log-rank test were presented.

Subgroup analyses by age groups (<65 years, ≥65 years), sex, history of liver cirrhosis, insulin use, and renin-angiotensin-aldosterone system inhibitors (RASi) use were conducted. PS were re-estimated for each subgroup, and 1:1 PS matching (PSM) between treatment groups was conducted using the same methods as in the main analysis. Several predefined sensitivity analyses were undertaken to ensure the robustness of the main findings. First, to address potential informative censoring, the exposure was redefined using an intention-to-treat approach and patients were followed for a maximum of 3 years, regardless of drug discontinuation or switching. Second, we repeated an as-treated analysis with a shorter grace period of 60 days rather than 90-day period in the main analysis. Third, the status of MASLD was redefined using the hepatic steatosis index instead of FLI (**eAppendix 2**). Fourth, we repeated the main analysis for a restricted cohort of patients, where the FLI was calculated using data collected within a year prior to the index date. Fifth, we assessed the competing risk for death and calculated the subdistribution HR and 95 % CI using the Fine-Gray model. [33].

3. Results

3.1. Baseline characteristics of study cohorts

Of 333,082 identified patients who initiated SGLT2i or GLP-1RA, 17,677 (5.3 %) had CKD and 315,405 (94.7 %) did not have CKD at baseline. Among them, 320,786 (96.3 %) initiated SGLT2i and 12,296 (3.7 %) initiated GLP-1RA (Fig. 1). Patients were stratified by their baseline CKD status, with 1:1 PSM in each subgroup. In the cohort with CKD, 1,268 pairs of SGLT2i-GLP-1RA were matched, while 10,996 pairs were matched in the cohort without CKD. As presented in Table 1, the cohort with CKD was older, had higher proportion of hypertension, RASi, CCBs, beta-blockers, aspirin, statin, and nitrates, compared to cohort without CKD. Compared to the initiators of SGLT2i, initiators of GLP-1RA in both cohorts had higher proportion of insulin use, level of antidiabetic treatment, and diabetic complications, suggesting greater diabetes severity. Each of the treatment groups (SGLT2i vs. GLP-1RA) of the two cohorts were well balanced after 1:1 PSM, with ASD < 0.1 across all covariates, including diabetes severity, eGFR, and proteinuria status (eTable 6).

3.2. Comparative renal effectiveness

Over a mean (SD) follow-up of 591.1 (580.3) days, the risk of ESRD was 33 % lower in SGLT2i versus GLP-1RA new-users (20.3 vs. 30.0 events per 1,000 person-years; HR 0.67, 95 % CI 0.45–1.00, p-value 0.048) in the cohort with CKD. For the cohort without CKD, over a mean (SD) follow-up of 733.2 (688.5) days, SGLT2i was associated with a 68 % lowered risk of ESRD compared to GLP-1RA (0.9 vs. 2.5 events per 1,000 person-years; HR 0.32, 95 % CI 0.19–0.53) (Table 2). Cumulative incidence curves showed a lower incidence of ESRD among patients initiating SGLT2i compared to GLP-1RA in both cohorts (Fig. 2). Regarding the secondary outcomes, SGLT2i was associated with a 46 % lowered risk of progression to CKD stage 5 (HR 0.54, 95 % CI 0.32–0.91), and a 47 % lowered risk of dialysis or transplant (HR 0.53, 95 % CI 0.31–0.92) compared to GLP-1RA for the cohort with CKD. SGLT2i also presented lowered risk of CKD stage 5 (HR 0.28, 95 % CI 0.10–0.80), kidney failure (HR 0.16, 95 % CI 0.07–0.40), and dialysis or transplant (HR 0.47, 95 % CI 0.24–0.90) for the cohort without CKD. There was no association between the use of SGLT2i and risk of cardiovascular death compared to GLP-1RA in cohort with CKD (HR 2.23, 95 % CI 0.78–6.32) and without CKD (HR 0.55, 95 % CI 0.24–1.26) (Table 2).

3.3. Subgroup and sensitivity analyses

As presented in Fig. 3, effect estimates were consistent across all subgroups in the cohort with CKD. In the cohort without CKD, the magnitude of the association was stronger with male sex (HR 0.34, 95 % CI 0.19–0.60), and insulin use (HR 0.47, 95 % CI 0.25–0.86), compared to their counterparts (HR 0.54, 95 % CI 0.22–1.31; HR 0.66, 95 % CI 0.36–1.23, respectively), presenting significantly lower effect estimates for ESRD. All sensitivity analyses showed consistent results with the main analysis, except for the analysis using HSI to define MASLD, restricting patients with FLI within 1 year prior to index date, and competing risk analysis in the cohort with CKD, which might be attributed to an insufficient sample size (eTable 7–11).

4. Discussion

In this nationwide comparative effectiveness study of individuals with MASLD, we found that initiating SGLT2i was associated with a lowered risk of incident ESRD comprising chronic kidney disease stage 5, kidney failure, dialysis, renal transplant, and renal death, compared with GLP-1RA. The incidence rate of ESRD was more than 10 times higher in the cohort with CKD compared to those without CKD. SGLT2i demonstrated a beneficial effect in both cohorts, showing a lower risk of ESRD compared to GLP-1RA, regardless of baseline CKD status. Several sensitivity and subgroup analyses presented consistent results.

Prior studies conducted among diverse populations provide grounds for comparison with our results. A prior *meta*-analysis of 23 cardiovascular outcome trials (CVOTs) showed that among patients with established ASCVD or with multiple risk factors for ASCVD, SGLT2i were superior to GLP-1RA in reducing the risk of progression to ESRD (RR 0.78, 95 % CI 0.68–0.91). [34] Another *meta*-analysis of nine RCTs showed that SGLT2i were associated with significantly lower risk of renal outcomes, such as new onset of macroalbuminuria, ESRD, or decline in eGFR, in both patients with/without albuminuria (RR 0.75, 95 % CI 0.63–0.89 and RR 0.59, 95 % CI 0.44–0.79, respectively) compared with GLP-1RA. [35] A retrospective cohort study using the Hong Kong Hospital Authority database showed that among patients with T2D, SGLT2i users had a lower risk (HR 0.77, 95 % CI 0.62–0.96) of composite kidney outcomes comprising eGFR decline, ESRD, macroalbuminuria and renal death compared with GLP-1RA. [36] Despite variations in study populations and definitions of outcome variables, the findings suggest that SGLT2i confer greater renal benefits compared to GLP-1RA. Although our study did not assess urine-based outcomes such as albuminuria or macroalbuminuria, the degree of albuminuria is known to be closely associated with CKD progression and mortality. [37] Thus, future large-scale population-based studies evaluating these outcomes in MASLD population could provide supportive evidence for our findings. Meanwhile, a recent RCT on semaglutide, a newly introduced agent in the GLP-1RA class, demonstrated a lowered risk of composite kidney disease in patients with T2D and CKD compared to placebo (HR 0.76, 95 % CI 0.66–0.88). [13] Since our study did not include this agent, future research assessing comparative effectiveness with the inclusion of semaglutide would be valuable.

Our study augments the evidence provided by prior studies of both agents, showing that SGLT2i exhibit greater renal effectiveness compared to GLP-1RA, even among individuals with MASLD. In the cohort with CKD, where the risk of ESRD was higher, the absolute magnitude of effectiveness was more pronounced. Significant renal effectiveness was also shown in the cohort without CKD, primarily driven by the prevention of kidney failure. This suggests the potential long-term protective effects of SGLT2 inhibitors, supporting the need for early intervention in individuals with MASLD. There are several biological mechanisms that could explain the lowered risk of ESRD with SGLT2i versus GLP-1RA, which include both potential direct and indirect effects of treatment. SGLT2i reduce renal tubular glucose and sodium reabsorption, thereby reducing intraglomerular pressure, and systemic blood pressure. [38,39] Meanwhile, GLP-1RA can act on intrinsic GLP1 receptor on kidney, and provide benefits by reducing cellular expression of proinflammatory and profibrotic mediators, [40] thereby potentially preventing fibrosis and mitigating kidney injury. However, while both agents have mechanistic plausibility, SGLT2i may offer more pronounced renal benefits by acting directly on the kidneys through hemodynamic mechanisms, which does not apply to GLP-1RA.

Besides the potential for direct effects on the kidney, the order and priority of antidiabetic drugs should be considered based on clustered metabolic risk factors in individuals with MASLD. Considering the well-documented cardiovascular and hepatic effectiveness of both agents in MASLD, [41,42] favorable effects on risk factors could indirectly contribute to renal protection while also addressing multiple complications. As stated in the most current clinical guideline, SGLT2i and GLP-1RA are both recommended for cardiovascular and kidney risk reduction in high-risk individuals with T2D, with SGLT2i preferred in patients with CKD and GLP-1RA preferred for weight loss and mitigating risk of MASLD. [23] The baseline characteristics of our study population indicated a majority of patients classified as obese I and II, with more than half having prevalent hypertension, and a high prevalence of statin and RASi use. Furthermore, these risk factors were already prominent in populations without CKD and were aggravated in those with CKD. Since both agents in our study have pleiotropic benefits in MASLD with

Table 1
Baseline characteristics of study participants with metabolic dysfunction-associated steatotic liver disease by chronic kidney disease status and treatment group before 1:1 propensity score matching.

	With chronic kidney disease				Without chronic kidney disease			
	SGLT-2i	GLP-1RA	ASD		SGLT-2i	GLP-1RA	ASD	
			Before PSM	After PSM			Before PSM	After PSM
Number of patients	16,377	1300			304,409	10,996		
Age, years; mean (SD)	67.6 (10.6)	66.2 (10.7)	0.13	0.03	53.7 (11.2)	53.0 (11.8)	0.06	0.01
Sex, No. (%)			0.78	0.01			0.19	0.00
Male	9962 (60.8)	787 (60.5)			215,919 (70.9)	6798 (61.8)		
Female	6415 (39.2)	513 (39.5)			88,490 (29.1)	4198 (38.2)		
Calendar year			0.15	0.10			0.56	0.04
2014	219 (1.3)	0 (0)			4071 (1.3)	32 (0.3)		
2015	762 (4.7)	10 (0.8)			14,839 (4.9)	110 (1.0)		
2016	1146 (7.0)	84 (6.5)			25,465 (8.4)	739 (6.7)		
2017	1426 (8.7)	169 (13.0)			32,069 (10.5)	1939 (17.6)		
2018	1341 (8.2)	237 (18.2)			31,761 (10.4)	2022 (18.4)		
2019	1607 (9.8)	217 (16.7)			36,709 (12.1)	1795 (16.3)		
2020	1355 (8.3)	154 (11.8)			29,405 (9.7)	1149 (10.4)		
2021	1759 (10.7)	172 (13.2)			29,175 (9.6)	1127 (10.2)		
2022	2011 (12.3)	179 (13.8)			30,474 (10.0)	1238 (11.3)		
2023	4751 (29.0)	78 (6.0)			70,441 (23.1)	845 (7.7)		
Healthcare use								
Inpatient hospitalizations			0.08	0.02			0.17	0.02
0	11,921 (72.8)	876 (67.4)			247,630 (81.3)	8167 (74.3)		
1–2	3946 (24.1)	363 (27.9)			52,264 (17.2)	2543 (23.1)		
≥3	510 (3.1)	61 (4.7)			4515 (1.5)	286 (2.6)		
Number of physician visits			0.04	0.00			0.21	0.08
0–2	79 (0.5)	2 (0.2)			11,744 (3.9)	169 (1.5)		
3–5	394 (2.4)	16 (1.2)			23,188 (7.6)	459 (4.2)		
≥6	15,904 (97.1)	1282 (98.6)			269,477 (88.5)	10,368 (94.3)		
Physician speciality								
Cardiologist	4299 (26.3)	318 (24.5)	0.59	0.05	39,135 (12.9)	1383 (12.6)	0.35	0.00
Endocrinologist	3019 (18.4)	571 (43.9)	0.30	0.03	45,076 (14.8)	4231 (38.5)	0.55	0.03
Gastroentrologist	1752 (10.7)	163 (12.5)	0.24	0.04	25,048 (8.2)	1202 (10.9)	0.35	0.00
Body mass index; mean (SD)	29.0 (3.5)	29.4 (3.8)	0.09	0.04	29.5 (3.9)	30.1 (4.4)	0.14	0.00
Body mass index, No. (%)			0.12	0.11			0.16	0.05
Normal weight	285 (1.7)	19 (1.5)			4593 (1.5)	164 (1.5)		
Overweight	1178 (7.2)	102 (7.8)			20,325 (6.7)	652 (5.9)		
Obese I	9341 (57.0)	685 (52.7)			160,574 (52.7)	5289 (48.1)		
Obese II	5573 (34.0)	494 (38.0)			118,917 (39.1)	4891 (44.5)		
Smoking, No. (%)			0.07	0.02			0.12	0.00
Never	4485 (63.0)	352 (60.3)			52,759 (46.4)	2433 (52.0)		
Past	1573 (22.1)	135 (23.1)			24,318 (20.5)	890 (19.0)		
Current	1061 (14.9)	97 (16.6)			36,739 (32.3)	1358 (29.0)		
Drinking, No. (%)			0.00	0.00			0.14	0.00
No	4791 (67.3)	423 (72.4)			50,440 (44.3)	2542 (54.3)		
1 ~ 2 times/week	1494 (21.0)	111 (19.0)			38,913 (34.2)	1357 (29.0)		
3 ~ 4 times/week	493 (6.9)	30 (5.1)			16,586 (14.6)	521 (11.1)		
5 + times/week	341 (4.8)	20 (3.4)			7877 (6.9)	261 (5.6)		
Comorbidities								
Dyslipidemia	6437 (39.3)	536 (41.2)	0.16	0.00	138,480 (45.5)	5532 (50.3)	0.10	0.01
Hypertension	11,726 (71.6)	832 (64.0)	0.10	0.01	161,640 (53.1)	5527 (50.3)	0.06	0.00
Atrial fibrillation	901 (5.5)	44 (3.4)	0.06	0.02	4428 (1.5)	114 (1.0)	0.04	0.01
Cirrhosis	57 (0.3)	10 (0.8)	0.26	0.01	512 (0.2)	38 (0.3)	0.04	0.00
Dementia	231 (1.4)	19 (1.5)	0.01	0.01	829 (0.3)	37 (0.3)	0.01	0.01
Depression	1140 (7.0)	88 (6.8)	0.03	0.00	12,204 (4.0)	612 (5.6)	0.07	0.00
Hypothyroidism	412 (2.5)	39 (3.0)	0.00	0.03	5031 (1.7)	269 (2.4)	0.06	0.01
Hyperthyrodisim	83 (0.5)	7 (0.5)	0.01	0.03	2004 (0.7)	85 (0.8)	0.01	0.01
Gallbladder disease	409 (2.5)	34 (2.6)	0.07	0.00	5726 (1.9)	205 (1.9)	0.00	0.01
Cerebrovascular disease	1038 (6.3)	105 (8.1)	0.00	0.02	7071 (2.3)	410 (3.7)	0.08	0.00
COPD	1043 (6.4)	84 (6.5)	0.05	0.04	10,432 (3.4)	460 (4.2)	0.04	0.00
Peripheral vascular disease	1311 (8.0)	122 (9.4)	0.06	0.00	14,334 (4.7)	667 (6.1)	0.06	0.01
Heart failure	1582 (9.7)	102 (7.8)	0.01	0.02	8183 (2.7)	287 (2.6)	0.01	0.02
Ischemic heart disease	2969 (18.1)	233 (17.9)	0.04	0.04	25,972 (8.5)	960 (8.7)	0.01	0.01
Comedication								
Acetaminophen	10,508 (64.2)	856 (65.8)	0.11	0.01	174,033 (57.2)	6714 (61.1)	0.08	0.01
RAS inhibitors	13,561 (82.8)	1126 (86.6)	0.01	0.01	170,172 (55.9)	6601 (60.0)	0.08	0.00
CCB	10,276 (62.7)	808 (62.2)	0.01	0.02	125,838 (41.3)	4454 (40.5)	0.02	0.01
β-blockers	5858 (35.8)	472 (36.3)	0.05	0.03	49,960 (16.4)	1892 (17.2)	0.02	0.02
Diuretics	7892 (48.2)	657 (50.5)	0.00	0.01	65,806 (21.6)	2572 (23.4)	0.04	0.00
Systemic antibiotics	10,364 (63.3)	889 (68.4)	0.06	0.02	188,132 (61.8)	7359 (66.9)	0.11	0.01
Oral anticoagulants	1157 (7.1)	74 (5.7)	0.13	0.04	5224 (1.7)	161 (1.5)	0.02	0.03
Oral antiplatelets	4352 (26.6)	425 (32.7)	0.05	0.09	34,344 (11.3)	1635 (14.9)	0.11	0.00
NSAIDs	10,438 (63.7)	859 (66.1)	0.13	0.02	179,527 (59.0)	6873 (62.5)	0.07	0.00
Aspirin	5532 (33.8)	519 (39.9)	0.02	0.02	54,632 (17.9)	2637 (24.0)	0.15	0.01

(*continued on next page*)

Table 1 (*continued*)

	With chronic kidney disease				Without chronic kidney disease			
	SGLT-2i	GLP-1RA	ASD		SGLT-2i	GLP-1RA	ASD	
			Before PSM	After PSM			Before PSM	After PSM
Opioids	2002 (12.2)	167 (12.8)	0.05	0.02	27,541 (9.0)	1193 (10.8)	0.06	0.00
Systemic corticosteroids	8462 (51.7)	642 (49.4)	0.22	0.01	141,480 (46.5)	5268 (47.9)	0.03	0.00
Statins	12,814 (78.2)	1124 (86.5)	0.07	0.02	189,196 (62.2)	8044 (73.2)	0.24	0.01
Other lipid-lowering agents	5628 (34.4)	489 (37.6)	0.23	0.02	85,486 (28.1)	3556 (32.3)	0.09	0.02
Vitamin E	1159 (7.1)	182 (14.0)	0.02	0.00	17,958 (5.9)	987 (9.0)	0.12	0.02
Nitrates	1694 (10.3)	144 (11.1)	0.90	0.07	14,760 (4.8)	490 (4.5)	0.02	0.01
Antidiabetic drugs use								
Insulin	2637 (16.1)	719 (55.3)	0.04	0.00	22,202 (7.3)	3929 (35.7)	0.74	0.03
α-glucosidase inhibitors	351 (2.1)	35 (2.7)	0.00	0.03	3241 (1.1)	201 (1.8)	0.06	0.01
Meglitinides	86 (0.5)	20 (1.5)	0.10	0.00	496 (0.2)	54 (0.5)	0.06	0.01
Metformin	11,927 (72.8)	890 (68.5)	0.41	0.02	219,231 (72.0)	9575 (87.1)	0.38	0.03
Sulfonylureas	8486 (51.8)	925 (71.2)	0.18	0.04	109,888 (36.1)	6815 (62.0)	0.54	0.03
Thiazolidinediones	2502 (15.3)	291 (22.4)	0.45	0.02	31,983 (10.5)	2116 (19.2)	0.25	0.00
DPP4 inhibitors	11,239 (68.6)	1131 (87.0)	0.39	0.05	167,227 (54.9)	8490 (77.2)	0.48	0.03
Diabetic complications								
Nephropathy	2043 (12.5)	359 (27.6)	0.26	0.03	12,718 (4.2)	1016 (9.2)	0.20	0.01
Neuropathy	3307 (20.2)	408 (31.4)	0.33	0.01	35,121 (11.5)	2349 (21.4)	0.27	0.01
Retinopathy	3882 (23.7)	502 (38.6)	0.36	0.01	40,546 (13.3)	2749 (25.0)	0.30	0.00
Level of antidiabetic treatments			0.34	0.07			0.88	0.07
1	3773 (23.0)	42 (3.2)			113,291 (37.2)	1065 (9.7)		
2	9967 (60.9)	539 (41.5)			168,916 (55.5)	6002 (54.6)		
3	2637 (16.1)	719 (55.3)			22,202 (7.3)	3929 (35.7)		
CCI groups			0.31	0.03			0.27	0.02
0	1681 (10.3)	113 (8.7)			61,675 (20.3)	1633 (14.9)		
1–2	5212 (31.8)	236 (18.2)			146,304 (48.1)	4400 (40.0)		
≥3	9484 (57.9)	951 (73.2)			96,430 (31.7)	4963 (45.1)		
Health examination results; mean (SD)								
Waist circumference [cm]	96.4 (8.1)	97.9 (8.9)	0.18	0.03	95.9 (9.7)	97.3 (9.7)	0.15	0.00
Serum creatinine [mg/dL]	1.5 (1.9)	1.6 (0.6)	0.06	0.01	0.9 (0.2)	0.9 (0.2)	0.08	0.01
eGFR [mL/min/1.73 m^2]	49.9 (9.0)	46.0 (10.6)	0.39	0.00	95.7 (15.8)	95.9 (16.9)	0.01	0.01
Fasting blood glucose [mg/dL]	149.0 (55.3)	165.3 (66.5)	0.27	0.01	161.6 (55.8)	177.3 (65.6)	0.26	0.01
Systolic blood pressure [mmHg]	132.1 (16.8)	131.1 (16.0)	0.06	0.06	131.3 (14.9)	130.5 (14.9)	0.05	0.01
Diastolic blood pressure [mmHg]	77.7 (10.8)	76.0 (10.3)	0.16	0.09	81.4 (10.5)	80.3 (10.3)	0.11	0.01
Total cholesterol [mg/dL]	178.2 (48.9)	171.5 (44.6)	0.15	0.04	196.4 (54.6)	186.6 (54.8)	0.18	0.02
Triglycerides [mg/dL]	222.7 (169.7)	228.9 (155.8)	0.04	0.01	245.3 (211.3)	241.7 (199.4)	0.02	0.00
GGT [IU/L]	60.5 (72.9)	54.7 (59.1)	0.09	0.05	76.8 (88.3)	68.4 (72.1)	0.10	0.01
Proteinuria; n (%)			0.25	0.07			0.25	0.10
Negative	11,179 (68.3)	749 (57.6)			247,560 (81.3)	8480 (77.1)		
Trace	997 (6.1)	80 (6.2)			20,624 (6.8)	773 (7.0)		
1+	1640 (10.0)	157 (12.1)			20,512 (6.7)	867 (7.9)		
2+	1360 (8.3)	156 (12.0)			10,410 (3.4)	551 (5.0)		
3+	800 (4.9)	117 (9.0)			3639 (1.2)	214 (1.9)		
4+	280 (1.7)	30 (2.3)			985 (0.3)	61 (0.6)		
Unknown	121 (0.7)	11 (0.8)			679 (0.2)	50 (0.5)		

Abbreviations: ASD, absolute standardized difference; CCB, calcium-channel blockers; CCI, charlson comorbidity index; DPP4, dipeptidyl-peptidase 4; GLP-1RA, glucagon-like peptide 1 receptor agonists; NSAIDs, non-steroidal anti-inflammatory drugs; PS, propensity score; RAS, renin angiotensin aldosterone system; SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitors.
*Stratified by Asian body mass index categories: Normal weight, <23 kg/m^2; Overweight, 23 to < 25 kg/m^2; Obese I, 25 to < 30 kg/m^2, Obese II, ≥30 kg/m^2.

metabolic dysfunction associated with features of the metabolic syndrome, [43,44] our findings have clinical implications in that they may serve as evidence, particularly in patients where renal protection should be the main goal.

4.1. Strength & limitations

To our knowledge, this is the first study to evaluate the comparative renal effectiveness of SGLT2i and GLP-1RA in individuals with MASLD, a population for whom these two agents could be prescribed and could have clinically relevant benefits. Our database provided information on a range of clinical variables, such as serum creatinine levels, proteinuria level, or fasting glucose level, enabling adjustment for important confounders. Although we cannot prove causality with this study, our active-comparator, new-user design strengthens the causal inference of this cohort study. We also applied lag period to delicately address the potential impact of protopathic bias.

Our study has several limitations. First, since we conducted an observational study utilizing healthcare claims, the potential for unmeasured confounders cannot be ruled out. Although we incorporated extensive baseline clinical covariates in the PS model to adjust for the severity of T2D and CKD, it is important to interpret our findings with caution, considering that the unadjusted population showed a higher disease severity among patients receiving GLP-1RA. Second, the mean duration of follow-up was relatively short (around 1.6 years for cohort with CKD, and 2.0 years for cohort without CKD) due to high rates of drug discontinuation (eTable 2). However, regardless of baseline CKD status, the consistent direction of point estimates across outcomes along the disease trajectory—from stage 5 CKD to kidney failure, transplantation, and renal death—suggests that our findings may cautiously indicate potential long-term implications, which should be validated in studies with longer follow-up. Moreover, the survival curves from landmark RCTs have shown the separation of curves within one year for renal endpoints. Therefore, we believe the duration of follow-up was sufficient to show the effects of treatments and our results represent what would be expected in real-world clinical practice where strict adherence to the index treatment is not guaranteed. Third, identifying ESRD through ICD-10 codes in the claims database lacks validation.

Table 2
Risk of end-stage renal diseases in individuals with metabolic dysfunction-associated steatotic liver disease initiating SGLT2 inhibitors versus GLP-1 receptor agonists by chronic kidney disease status.

	SGLT2 inhibitors			GLP-1 receptor agonists			Rate differences (95 % CI)	Hazard ratio (95 % CI)	p-value
	No./ total No.	Person-years	Incidence per 1000 person-years (95 % CI)	No./ total No.	Person-years	Incidence per 1000 person-years (95 % CI)			
With chronic kidney disease									
Primary outcome									
Composite end-stage renal diseases	44/1268	2172.61	20.25 (15.07 to 27.21)	58/1268	1931.59	30.03 (23.21 to 38.84)	−9.77 (−19.5 to −0.00)	0.67 (0.45–1.00)	0.048
Secondary outcomes									
Chronic kidney disease, Stage 5	22/1268	2202.47	9.99 (6.58 to 15.17)	36/1268	1978.03	18.20 (13.13 to 25.23)	−8.21 (−15.5 to −0.95)	0.54 (0.32–0.91)	0.022
Kidney failure	18/1268	2184.04	8.24 (5.19 to 13.08)	22/1268	1958.19	11.23 (7.40 to 17.06)	−2.99 (−9.04 to 3.05)	0.73 (0.39–1.36)	0.320
Renal dialysis or transplant	21/1268	2205.46	9.52 (6.21 to 14.60)	35/1268	1986.11	17.62 (12.65 to 24.54)	−8.10 (−15.2 to −0.98)	0.53 (0.31–0.92)	0.023
Renal death	0/1268	N/A	N/A	1/1268	2002.60	0.50 (0.07 to 3.54)	N/A	N/A	N/A
Cardiovascular death	12/1268	2212.53	5.42 (3.08 to 9.55)	5/1268	2002.60	2.50 (1.04 to 6.00)	2.93 (−0.84 to 6.70)	2.23 (0.78–6.32)	0.133
Without chronic kidney disease									
Primary outcome									
Composite end-stage renal diseases	22/ 10996	25609.07	0.86 (0.57 to 1.30)	47/ 10996	18534.87	2.54 (1.91 to 3.37)	−1.68 (−2.49 to −0.87)	0.32 (0.19–0.53)	0.000
Secondary outcomes									
Chronic kidney disease, Stage 5	5/10996	25631.43	0.20 (0.08 to 0.47)	11/ 10996	18589.72	0.59 (0.33 to 1.07)	−0.40 (−0.79 to −0.01)	0.28 (0.10–0.80)	0.018
Kidney failure	6/10996	25613.85	0.23 (0.11 to 0.52)	25/ 10996	18546.00	1.35 (0.91 to 1.99)	−1.11 (−1.67 to −0.55)	0.16 (0.07–0.40)	0.000
Renal dialysis or transplant	15/ 10996	25628.93	0.59 (0.35 to 0.97)	22/ 10996	18586.42	1.18 (0.78 to 1.80)	−0.60 (−1.17 to −0.02)	0.47 (0.24–0.90)	0.023
Renal death	1/10996	25633.08	0.04 (0.01 to 0.28)	0/10996	N/A	N/A	N/A	N/A	N/A
Cardiovascular death	10/ 10996	25633.08	0.39 (0.21 to 0.73)	13/ 10996	18597.91	0.70 (0.41 to 1.20)	−0.31 (−0.76 to 0.14)	0.55 (0.24–1.26)	0.156

Abbreviations: CI, confidence interval; GLP-1, glucagon-like peptide 1; SGLT2, sodium-glucose cotransporter 2.

However, we defined the outcome using diagnosis codes identified in the inpatient setting and verified through the RID program, thereby enhancing specificity. We also expect the outcome misclassification to be non-differential between the treatment groups. Fourth, we used semi-quantitative urine dipstick test results to assess proteinuria rather than specific measures of albuminuria. However, the distribution of urine dipstick test results was well balanced between the treatment groups after PS matching. Therefore, the bias resulting from the inability to accurately measure albuminuria is also presumed to be non-differential between the treatment groups. Fifth, baseline CKD status was defined using a single eGFR measurement obtained during a health screening rather than for diagnostic purposes. Since urine-based markers, such as the albumin-to-creatinine ratio, were not incorporated, misclassification of CKD status may have occurred. Finally, due to reimbursement policies in Korea, we were unable to include agents with higher glucose-lowering and weight loss efficacy, such as semaglutide, [13] in our analysis. Novel potent GLP-1RA are expected to improve multiple risk factors in the MASLD population—including glycemic control, blood pressure, and body weight—thereby conferring renal benefits. If these agents had been included in our study, the magnitude of the effect estimates might have been more modest.

5. Conclusions

In this nationwide cohort study, SGLT2i presented significantly lowered risk of ESRD compared to GLP-1RA in individuals with MASLD. The protective association was presented regardless of baseline CKD status, suggesting that SGLT2i may be a preferred option over GLP-1RA at any stage of the disease course. However, given the multifaceted metabolic risk factors in MASLD, it is crucial to assess the benefits of each agent while considering the patient's individual risk profile for various complications. Further studies with more potent GLP-1RA would also be highly beneficial.

6. Disclosures

6.1. Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

6.2. Disclosures

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Ethical approval

Ethical approval was obtained from the Institutional Review Board of Sungkyunkwan University, where requirement of informed consent was waived as this study used anonymized administrative data (IRB No. SKKU-2024–12-005).

Author Contributions

HYK: study concept and design; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript. BH, SB, JHB, YMC, YC, SR and CDB: study concept and design; interpretation

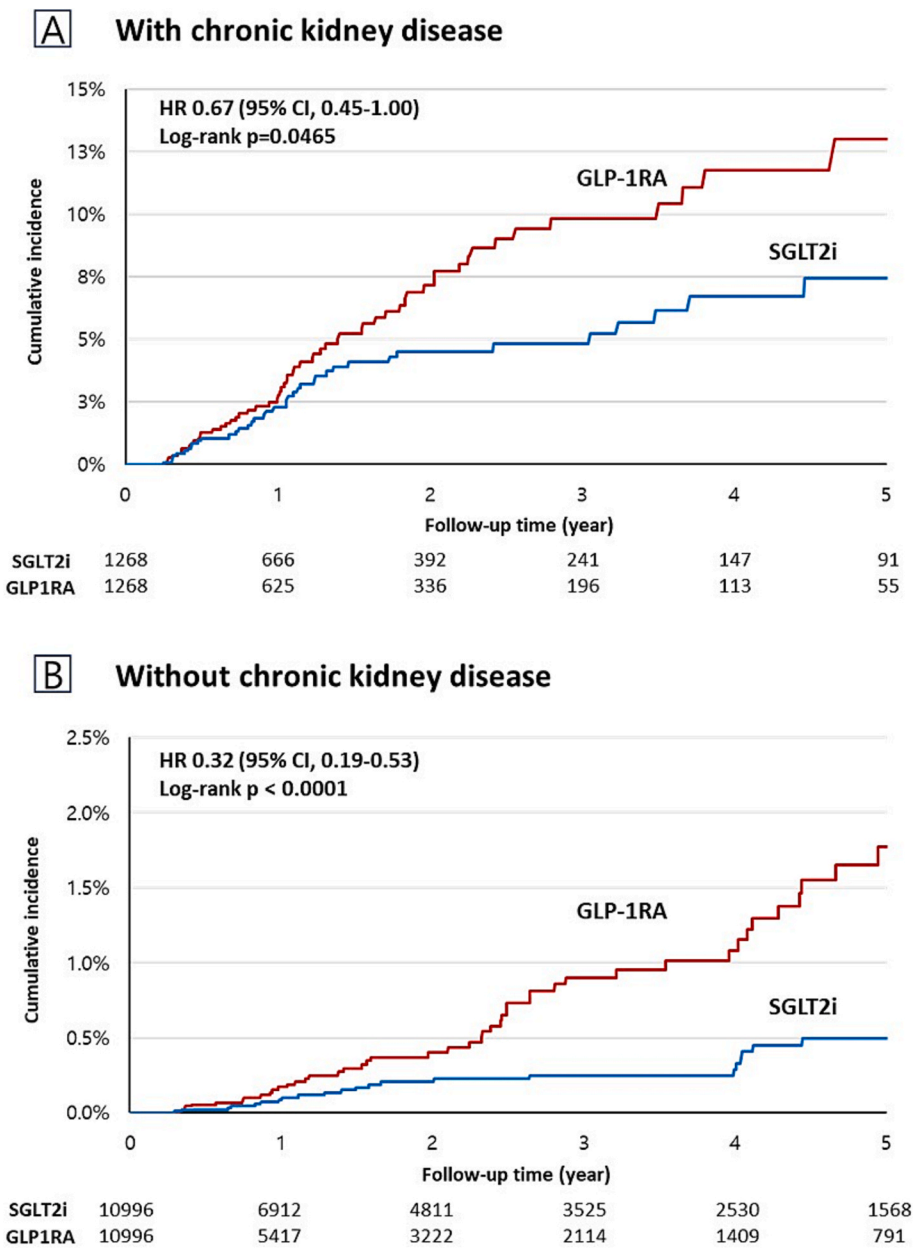

Fig. 2. Cumulative incidence of end-stage renal diseases in 1:1 propensity score matched initiators of SGLT2 inhibitors versus GLP-1 receptor agonists. **Abbreviations**: CI, confidence interval; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

of data and critical revision of the manuscript. JYS: study concept and design; interpretation of data; technical or material support; critical revision of the manuscript; and study supervision. JYS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JYS is the guarantor.

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CRediT authorship contribution statement

Hwa Yeon Ko: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bin Hong:** Methodology, Investigation, Conceptualization. **Sungho Bea:** Methodology, Investigation, Conceptualization. **Jae Hyun Bae:** Supervision, Methodology, Investigation, Conceptualization. **Young Min Cho:** Supervision, Methodology, Investigation, Conceptualization. **Yoosoo Chang:** Supervision, Resources, Methodology, Investigation, Conceptualization. **Seungho Ryu:** Supervision, Resources, Methodology, Investigation, Conceptualization. **Christopher D Byrne:** Supervision, Methodology, Investigation, Conceptualization. **Ju-Young Shin:** Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

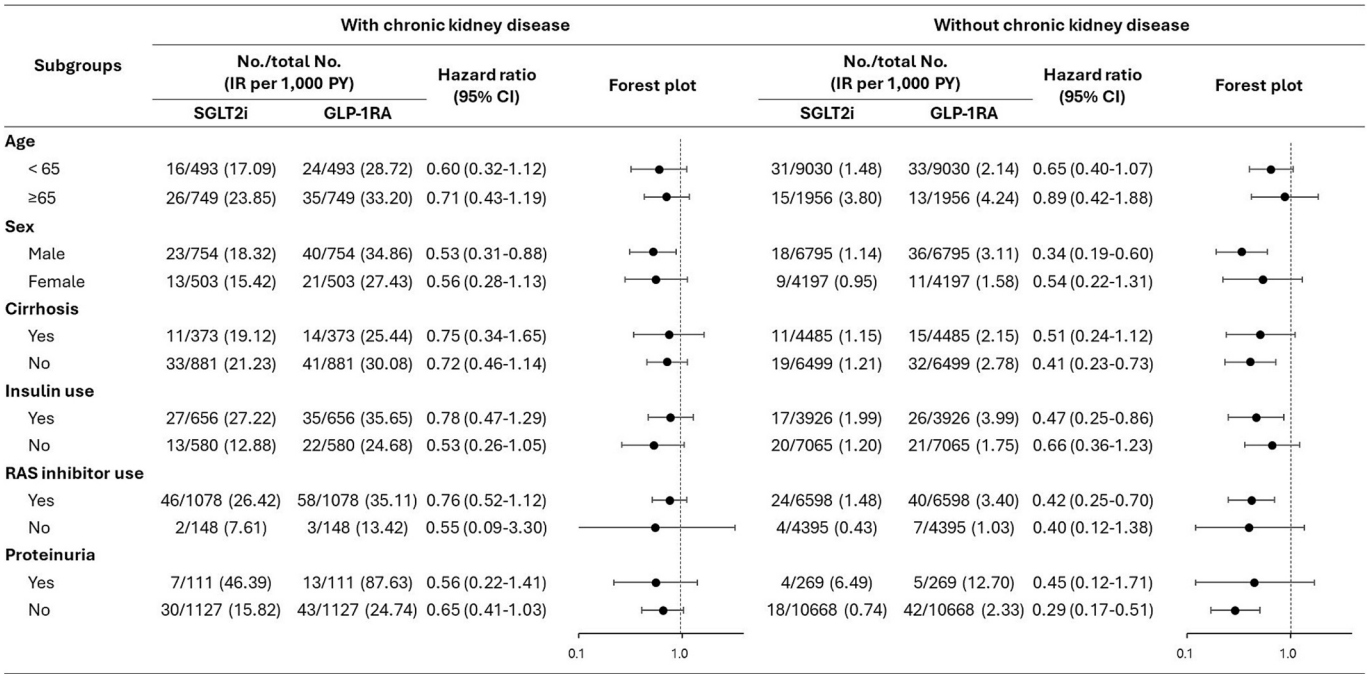

Fig. 3. Results of subgroup analyses for end-stage renal diseases in 1:1 propensity score matched initiators of SGLT2 inhibitors versus GLP-1 receptor agonists. **Abbreviations**: CI, confidence interval; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2025.112921.

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