**Risk of Hepatic Events Associated with Use of Sodium-Glucose Cotransporter-2 Inhibitors Versus Glucagon-Like Peptide-1 Receptor Agonists, and Thiazolidinediones Among Patients with Metabolic-Dysfunction Associated Steatotic Liver Disease**

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**What is already known on this topic**

* Emerging evidence supports the hepatic effectiveness of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).
* No head-to-head comparisons have been undertaken between SGLT-2i and guideline-recommended glucose-lowering medications, such as glucagon-like peptide 1 receptor agonists (GLP-1RA) or thiazolidinediones (TZD).

**What this study adds**

* In this nationwide cohort study, SGLT-2i was associated with a reduced risk of hepatic decompensation events in patients with MASLD compared to TZD and showed similar effectiveness to GLP1RA.
* The hepatic effectiveness of SGLT-2i was greater in female patients, and patients with aged less than 65 years.

**How this study might affect research, practice or policy**

* Given the well-established connection between type 2 diabetes and liver disease, our findings provide real-world evidence endorsing the consideration of SGLT-2i as a plausible therapeutic approach for preventing hepatic deterioration among patients with MASLD.

**Abstract**

**Objective:** To examine the hepatic effectiveness of sodium glucose cotransporter-2 inhibitors (SGLT-2i) through a head-to-head comparison with glucagon-like peptide 1 receptor agonists (GLP-1RA) or thiazolidinediones (TZD) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

**Design:** This population-based cohort study was conducted using a nationwide healthcare claims database (2014-2022) of Korea. We included individuals with MASLD (age ≥ 40 years) who initiated SGLT-2i or comparator drugs (GLP-1 RA or TZD). Primary outcome was a composite of hepatic decompensation events, including ascites, esophageal varices with bleeding, hepatic failure, or liver transplant. Liver-cause death and all-cause death were also assessed as secondary outcomes. Cox proportional hazards models were used to estimated hazard ratios (HR) with 95% confidence intervals (CI).

**Results:** After 1:1 propensity score matching, we included 22,550 patients who initiated SGLT-2i and GLP-1RA (median age=57 years, 60% male), and 191,628 patients who initiated SGLT-2i and TZD (median age=57 years, 72% male). Compared to GLP-1RA, SGLT-2i showed a similar risk of hepatic decompensation events (HR 0.93, 95% CI 0.76-1.14). Compared to TZD, SGLT-2i demonstrated a reduced risk of hepatic decompensation events (HR 0.77, 95% CI 0.72-0.82). As compared with TZD, the results of secondary analyses showed significantly lower hepatic decompensation event risks with SGLT-2i when stratified by sex (male: 0.87 [0.80-0.94]; female: 0.62 [0.55-0.69]).

**Conclusions:** In this nationwide cohort study, SGLT-2i was associated with a lowered risk of hepatic decompensation events in patients with MASLD compared to TZD, while demonstrating similar effectiveness to GLP-1RA.

**Word count of the manuscript text**: 3,522 words

**Introduction**

Metabolic-dysfunction associated steatotic liver disease (MASLD) has become a significant global health concern, particularly in patients with type 2 diabetes, where its prevalence is more than 60% (1-3). Given the asymptomatic nature of MASLD and its potential for adverse hepatic and extra-hepatic outcomes, comprehensive and multidisciplinary approach to its management is crucial (4-7). The efficacy of glucose-lowering drugs, such as metformin, is observed to be limited in addressing the challenges posed by MASLD. However, several randomized controlled trials have explored the potential benefits of glucagon-like peptide 1 receptor agonists (GLP-1RA) or thiazolidinediones (TZD), which are commonly used in the management of type 2 diabetes, in ameliorating hepatic steatosis among patients with MASLD (8-10). Although these agents have shown positive effects in the treatment of MASLD and are recommended by guidelines, there is inconclusive evidence in hepatic outcomes among patients with MASLD (11).

Sodium glucose cotransporter 2 inhibitors (SGLT-2i) inhibit glucose reabsorption at the proximal tubule of the kidney and have demonstrated cardiovascular and renal benefits beyond lowering glycemia in patients with type 2 diabetes (12-15). Data from several randomized controlled trials (RCT) have shown that SGLT-2i may have promising effects on fibrosis or steatosis, based on biological mechanisms of glucagon signaling pathways or insulin use reduction (16, 17). However, these trials had short follow-up or a small number of patients to generate clinically meaningful evidence on this issue (18). One observational study, which included patients with type 2 diabetes and liver cirrhosis, found a 11% reduced risk of hepatic decompensation events (hazard ratio [HR] 0.89, 95% confidence interval [CI], 0.62 to 1.26) among new-users of SGLT-2i compared with dipeptidyl peptidase-4 inhibitors (DPP-4i) (19). Moreover, our previous cohort study found that use of SGLT-2i versus DPP-4i was significantly associated with a lower risk of major hepatic events, a composite endpoint of liver-cause death, liver transplant, and hepatic decompensation events (HR 0.57, 95% CI 0.45 to 0.72) (20). A recent study that reported the hepatic effectiveness of glucose-lowering drugs in patients with MASLD did not include GLP-1RA, a class that is highly likely to be effective (21). Taken together, the hepatic benefits of SGLT-2i among patients with MASLD are inconclusive, warranting further investigations.

Considering the well-established association between type 2 diabetes and liver disease, it becomes crucial to identify a plausible therapeutic option for this metabolically vulnerable population. We therefore sought to address this knowledge gap by conducting a head-to-head comparison of SGLT-2i with GLP-1RA or TZD among patients with MASLD.

**Methods**

**Data Source**

This population-based cohort study utilized nationwide health administrative claims data (September 1, 2014, to December 31, 2022) obtained from the National Health Insurance Service (NHIS) of Korea. The NHIS serves as a single provider of health insurance and contains claims data for approximately 97% of the entire Korean population (> 50 million) (22). The database contains deidentified patient-level information including sociodemographic characteristics, inpatient and outpatient diagnosis, emergency room visits, prescriptions, medical procedures, and biennial health examination records. Diagnosis records were coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). The dates and causes of mortality were available from a linked dataset of death certificate records from Statistics Korea. Health examination records included anthropometric measurements, laboratory test results, self-reported alcohol consumption, and smoking behavior information. This study was approved by the Institutional Review Board of Sungkyunkwan University (IRB SKKU-2023-07-041) and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (**Supplement 2**) (23). The requirement for informed consent was waived since all the data were anonymized.

**Study population and Design**

This active-comparator, new-user cohort study included patients with MASLD who initiated SGLT-2i (dapagliflozin, empagliflozin, ipragliflozin, or ertugliflozin) or comparator drugs, between September 1, 2014, and December 31, 2022. We selected two active comparators, GLP-1RA (dulaglutide, lixisenatide, liraglutide, exenatide, or albiglutide) or TZD (lobeglitazone or pioglitazone), for comparison with SGLT-2i and constructed two pairwise cohorts accordingly.

We defined index date as the first prescription of SGLT-2i or comparators within each cohort, and patients with a history of using either drug within 365 days before the index date were excluded. To ensure that all the study agents were available during the study period, only participants with an index date on or after September 1, 2014, when SGLT-2i were first used in Korea, were eligible for inclusion. MASLD status was defined by the fatty liver index (FLI), with a value of 60 or higher used as a surrogate indicator of MASLD (24). Additionally, the FLI has been previously validated among the Korean population, with a positive predictive value (PPV) of 89% for detecting liver fat (25). Since we calculated the FLI using information derived from the most recent health examination results, patients without at least one health examination within 3 years prior to the index date were excluded (**eAppendix 1, eTable 1** in **Supplement 1**). Patients aged less than 40 years on the index date and those with competing liver diseases other than MASLD (e.g. viral hepatitis, alcoholic liver disease, autoimmune hepatitis, hemochromatosis, Wilson’s disease, Budd-Chiari syndrome) within a year prior to the index date were also excluded (**eTable 2** in **Supplement 1**) (26). Subsequently, we excluded patients diagnosed with end-stage kidney disease or those with procedure records for dialysis, or type 1 diabetes within a year prior to the index date. Finally, we excluded patients who initiated treatment with both SGLT-2i and the comparator drug (GLP-1RA or TZD) on the same date to avoid exposure misclassification (**eFigure 1-2** in **Supplement 1**).

**Exposures and Follow-up**

Our objective was to assess the hepatic effectiveness of SGLT-2i through a head-to-head comparison with GLP-1RA and TZD, which have already demonstrated effectiveness in hepatic steatosis and fibrosis through randomized controlled trials with liver histology end points that assessed nonalcoholic steatohepatitis resolution and change/no change in liver fibrosis (9, 10, 27). Exposure drugs (SGLT-2i) and selected active comparators (GLP-1RA or TZD) for each cohort are all recommended as second-line agents to add to metformin for glycemic management given their high efficacy of glucose lowering (28).

We applied an ‘as-treated’ approach to mitigate exposure misclassification, and patients were followed from the day after the index date until the earliest of outcome occurrence, drug discontinuation (defined as no prescription after 90 days had elapsed from the last prescription’s supply), switching to or adding other than index drug (within each pair-wise cohort), death, or the end of the study period (December 31, 2022).

**Outcome Definition**

The primary outcome was a composite of hepatic decompensation events comprising ascites, esophageal varices with bleeding, hepatic failure, or liver transplant. Secondary outcomes were the individual components of the primary composite outcome, liver-cause mortality, and all-cause mortality. In evaluating the comprehensive effect of SGLT-2i on hepatic outcomes, we also performed an exploratory analysis specifically investigating effects on hepatocellular carcinoma (HCC). All outcomes were captured through diagnosis codes in primary or secondary positions in the inpatient setting. Prescriptions for potassium-sparing diuretics, terlipressin, or lactulose were also considered to indicate ascites, esophageal varices, or hepatic failure, respectively. Procedure codes for paracentesis, varix ligation, or surgical operation were also considered to indicate ascites, esophageal varices, or liver transplant. Liver-cause mortality was defined as death caused by any liver disease based on the diagnosis codes other than viral causes (**eTable 3** in **Supplement 1**).

**Covariates**

We assessed demographic characteristics (age, sex) and calendar year on the index date. The use of glucose-lowering drugs other than study drugs (insulin, alpha-glucosidase inhibitors, meglitinides, metformin, sulfonylureas, DPP-4i) and a history of diabetic microvascular complications (retinopathy, neuropathy, nephropathy) a year prior to the index date were assessed. The levels of glucose-lowering treatments were assessed as follows: level 1, taking none or only one class of glucose-lowering drug other than insulin; level 2, taking two or more classes of glucose-lowering drugs without insulin; and level 3, taking insulin with or without other classes of glucose-lowering drugs within a year prior to the index date.

Comorbidities (dyslipidemia, hypertension, atrial fibrillation, liver cirrhosis, chronic kidney disease, dementia, hypothyroidism, hyperthyroidism, gallbladder disease, other diseases of biliary tract, chronic obstructive pulmonary disease, and peripheral vascular diseases) and Charlson Comorbidity Index (CCI) were also identified using corresponding diagnosis codes a year prior to the index date. Comedications including acetaminophen, renin-angiotensin system inhibitors, calcium channel blockers, beta-blockers, diuretics, systemic antibiotics, oral anticoagulants, oral antiplatelets, nonsteroidal anti-inflammatory drugs, opioids, systemic corticosteroids, statins, other lipid-lowering agents, vitamin E, and nitrates were identified using prescription records a year prior to the index date. Moreover, proxies for healthcare utilization behavior (number of hospitalizations, number of physician visits, and physician specialties) were assessed a year prior to the index date (**eTable 4** in **Supplement 1**). Health examination results (waist circumference, fasting blood glucose, blood pressure, cholesterol level, triglycerides, serum creatinine, liver enzyme levels, estimated glomerular filtration rate, smoking, or drinking behaviors) were assessed within 3 years prior to the index date. Smoking (never, past, current, unknown), drinking (no, yes, unknown) behaviors, and body mass index (continuous variable) were included as covariates in the propensity score (PS) model of the main analysis. Missing rates of each clinical variable from health examination results are presented in **eTable 5** in **Supplement 1**.

**Statistical Analyses**

The predicted probability of initiating each treatment for each cohort (SGLT-2i vs. GLP-1RA or SGLT-2i vs. TZD) was estimated as the PS using a multivariable logistic regression model, considering all the covariates mentioned above as independent variables. Patients in each treatment group were 1:1 PS matched using the greedy nearest-neighbor method with a caliper of 0.05 on the log scale. An absolute standardized difference (ASD) larger than 0.1 was defined as a significant imbalance in baseline covariates between the treatment groups (29). The baseline characteristics of each treatment group before and after PS matching were presented using descriptive statistics.

For each PS-matched cohort, the number of events, person-years, incidence rates (IR), and rate differences per 1,000 person-years for all outcomes were calculated. The IR per 1,000 person-years were calculated based on Poisson distribution. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated for all outcomes using Cox proportional hazards model. The Schoenfeld residuals were calculated to examine the assumption of proportional hazards. Cumulative incidence curves for the primary outcome 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 cirrhosis, and insulin use were conducted. The effect of individual drugs of SGLT-2i was also examined for dapagliflozin and empagliflozin, the two most predominant medications (**eTable 6** in **Supplement 1**). For each subgroup, we re-estimated PS and performed 1:1 PS matching with the same methods as used in the main analysis. We also conducted a range of sensitivity analyses, which are described in **eAppendix 2** in **Supplement 1**.

**Results**

**Characteristics of Study Cohorts**

***SGLT-2i vs. GLP-1RA***

We identified 228,666 patients for the comparison of SGLT-2i vs. GLP-1RA (217,391 new users of SGLT-2i and 11,275 new users of GLP-1RA; mean [SD] age 55.8 [9.9]; 68.2% males). New users of GLP-1RA were older, had a higher proportion of females, had a higher comorbidity score, used more insulin, and more likely to have liver cirrhosis and diabetic complications. After 1:1 PS matching, 11,275 pairs were identified for SGLT-2i vs. GLP-1RA cohort. The treatment groups were well balanced, presenting with ASD for all covariates < 0.1 (**Table 1**).

***SGLT-2i vs. TZD***

We identified 299,881 patients for the SGLT-2i vs. TZD (183,485 new users of SGLT-2i and 116,396 new users of TZD; mean [SD] age 56.5 [10.2]; 70.0% males). New users of TZD were older, had higher comorbidity scores, and used metformin and sulfonylureas more frequently. After 1:1 PS matching, 95,814 pairs were identified in the SGLT-2i vs. TZD cohort. The treatment groups were well balanced, presenting with ASD for all covariates < 0.1 (**Table 2**).

**Comparative Hepatic Effectiveness for Each Cohort**

***SGLT-2i vs. GLP-1RA***

Over a mean (SD) follow-up of 2.1 years (1.9), the incidence rate of hepatic decompensation events per 1,000 person-years was 10.61 for SGLT-2i new users and 14.21 for GLP-1RA new users. Risk decrease in hepatic decompensation events for SGLT-2i compared with the GLP-1RA was not observed (HR, 0.93 [95% CI, 0.76-1.14]). Consistent with the primary outcome, all secondary outcomes were not associated with decreased risk of hepatic outcomes among SGLT-2i new users over GLP-1RA new users (ascites: HR 1.12 [95% CI, 0.88-1.43]; esophageal varices with bleeding: 0.80 [0.35-1.83]; liver transplant: 0.25 [0.09-0.70]; hepatic failure: 0.71 [0.50-1.00]; liver-cause mortality: 0.45 [0.15-1.32]; all-cause mortality: 1.24 [0.90-1.72]). (**Figure 1**). The cumulative incidence of hepatic decompensation events was consistent with this finding (log-rank *p*=0.48) (**Figure 3**).

***SGLT-2i vs. TZD***

Over a mean (SD) follow-up of 2.1 years (2.0), the incidence rate of hepatic decompensation events per 1,000 person-years was 7.64 for SGLT-2i new users and 10.18 for TZD new users. A lower risk of hepatic decompensation events was observed in the SGLT-2i compared with the TZD (HR, 0.77 [95% CI, 0.72-0.82]). Similar associations were observed for all secondary outcomes, where SGLT-2i showed decreased risk of outcomes compared to TZD (ascites: HR 0.75 [95% CI, 0.70-0.82]; esophageal varices with bleeding: 0.77 [0.60-0.98]; hepatic failure: 0.77 [0.69-0.87]; liver transplant: 0.79 [0.48-1.29]; liver-cause mortality: 0.61 [0.45-0.84]; all-cause mortality: 0.73 [0.67-0.79]) (**Figure 1**). The cumulative incidence of hepatic decompensation events was consistent with this finding (log-rank *p*<0.01) (**Figure 3**).

**Subgroup and Sensitivity Analyses**

In the SGLT-2i vs. GLP-1RA cohort, a lower risk of hepatic decompensation was observed in younger patients when stratified by age (<65 years: HR, 0.68 [95% CI, 0.52-0.90]; ≥65 years: 1.37 [1.02-1.84], *p*<0.01). In the SGLT-2i vs. TZD cohort, female patients demonstrated greater benefit from SGLT-2i (male: HR, 0.87 [95% CI, 0.80-0.94]; female: 0.62 [0.55-0.69], *p*<0.01) (**Figure 2**). The findings of a range of sensitivity analyses were consistent with those of the main analysis in both cohorts. In the analysis assessing ascites and esophageal varices restricted to those occurred after liver cirrhosis, a lower risk of hepatic decompensation events was observed in the SGLT-2i compared with the GLP-1RA (HR 0.69 [95% CI 0.52-0.93]) groups. In patients with reduced renal function (eGFR≤60 mL/min/1.73 m2), SGLT-2i were shown to have less favorable effects compared to GLP-1RAs (HR 1.45 [95% CI 1.03-2.06]). (**eTable 7-18** in **Supplement 1**).

**Discussion**

The novel results of this large nationwide cohort study suggest an association between SGLT-2i treatment and a lower risk of hepatic decompensation events, including ascites, esophageal varices with bleeding, and hepatic failure, and liver transplant in patients with MASLD when compared with TZD treatment. Notably, the hepatic effectiveness of SGLT-2i was greater in female than male patients, and in patients with aged less than 65 years. Importantly, there was no significant difference in the risk of hepatic effectiveness when comparing SGLT-2i to GLP-1RA and the robustness of these findings remained consistent across sensitivity analyses.

**Comparison with previous studies**

In a direct comparison between empagliflozin and pioglitazone, the reported findings indicated an improvement in liver steatosis and fibrosis with empagliflozin compared to pioglitazone (30). However, this study included a very small patient population (100 or fewer), and no RCTs have directly compared SGLT-2i with GLP-1RA. A meta-analysis of 25 RCTs comprising 2,237 obese patients indicated that GLP-1RA may exhibit more pronounced effects in reducing liver fat content, waist circumference, and body mass index (31). In an observational study utilizing health insurance claims data from the United States, the comparison of GLP-1RA and SGLT-2i in patients with cirrhosis and type 2 diabetes reported no statistically significant benefit in terms of hepatic decompensation events, with an HR of 0.89 (95% CI 0.62-1.28) (19). Similarly, a study utilizing the CPRD in the UK found no significant differences between GLP-1RA and SGLT-2i for acute liver injury outcomes with HR of 1.11 (95% CI 0.57–2.16) (32). The findings from our study also align with those of previous research showing the effectiveness of SGLT-2i in comparison to TZD, with no significant benefit observed in comparison to GLP-1RA.

In this study, we found significant observations in sex and age subgroup analyses that were not performed in previous studies. When stratified by sex, the hepatic effectiveness of SGLT-2i was more pronounced in female patients with MASLD compared with TZD. Considering the higher incidence of MASLD in postmenopausal women and its association with a more unfavorable prognosis due to alterations in body estrogen, the findings of this study contribute novel insights into the role of SGLT-2i among female patients with metabolically vulnerable conditions (33, 34). Moreover, SGLT-2i showed more significant hepatic effectiveness compared to GLP-1RA in patients younger than 65 years. These associations were similarly observed in our previous study comparing SGLT-2i to DPP-4i for hepatic outcomes in patients with type 2 diabetes (20). Given the escalating burden of MASLD, it is crucial to establish definitive evidence through additional studies elucidating the impact of SGLT-2i on these subgroup populations.

**Biological mechanisms**

In our study, the use of SGLT-2i was associated with a decreased risk of hepatic decompensation events compared to the use of guideline-recommended agents (GLP-1RA or TZD). The established biological mechanism supports the hepatic-protective effects of SGLT-2i in patients with MASLD. SGLT-2i may contribute positively to slowing the progression of MASLD through weight loss and enhanced insulin sensitivity, thereby improving the metabolic profiles (35-38), but further research is needed. In addition, SGLT-2i stimulate excretion of sodium and glucose by inhibiting SGLT-2 in the renal proximal tubule, augmenting sodium delivery to the macula densa, subsequently triggering a diuretic response. The diuretic effect has the potential to alleviate fluid imbalance, a prevalent concern in patients with liver cirrhosis (39, 40). An alternative potential mechanism involves glucagon stimulation, wherein SGLT-2i directly or indirectly encourage glucagon secretion, though the specific endocrinological pathway remains unclear (40). Subsequently, glucagon contributes to the improvement of adipocyte dysfunction or the reduction of liver lipotoxicity (1, 41). Moreover, the mechanism of action of SGLT-2i may be beneficial by reducing serum uric acid levels, which are known to exacerbate the progression of MASLD by inducing hepatocellular fat accumulation and insulin resistance (42, 43). It has been suggested that SGLT-2i, including empagliflozin, can lower uric acid levels by normalizing nutrient signaling pathways, which subsequently reduces purine synthesis and enhances the excretion of uric acid by the kidneys (16, 44). Lastly, although demonstrated solely in animal studies, evidence suggests that inhibiting SGLT-2 with dapagliflozin directly reduces hepatic steatosis by activating 5' AMP-activated protein kinase (AMPK) (45, 46).

We did not observe any significant differences between SGLT-2i and GLP-1RA in our study. This lack of distinction may be attributed to shared mechanisms that involve weight loss, enhancement of insulin sensitivity, and reduction in metabolic dysfunction, lipotoxicity, and liver inflammation (47). Furthermore, although controversial, it has been suggested that both classes of drugs may stimulate glucagon secretion (36, 40, 48, 49) and this may also be beneficial and supported by the potential beneficial effects of glucagon receptor agonism (50). Taken together, these biological mechanisms provide a foundation for our findings and lead us to conclude that SGLT-2i may indeed introduce significant hepatic advantages for patients with MASLD.

**Limitations**

Although our study provides valuable evidence, it is crucial to acknowledge its limitations. First, the observational nature of this study introduces the possibility of residual confounding due to unmeasured factors. Our database lacked information on key clinical variables, including the duration of diabetes, hemoglobin A1c (HbA1c) values, and severity of liver status (51). While PS matching and active-comparator new-user design were employed to address confounding effects, residual confounding cannot be completely ruled out. Second, despite the utilization of previously validated algorithms to define MASLD, there exists a potential for misclassification of MASLD status. Specifically, insulin resistance or deficiency in patients with type 2 diabetes can alter lipoprotein lipase function, which can influence triglyceride levels and potentially compromise the reliability of the FLI. However, our findings remained consistent across sensitivity analysis using hepatic steatosis index as another measure used to identify hepatic steatosis. To gain a more comprehensive understanding of this association among patients with MASLD, future studies incorporating abdominal ultrasonography, magnetic resonance imaging, or liver biopsy—acknowledged as the gold standards for assessing the spectrum of liver disease in MASLD—could offer further clarity in identifying our target population. Third, outcome misclassification remains a concern despite the use of validated diagnostic codes. Fourth, the GLP-1RAs included in this study were dulaglutide, exenatide, lixisenatide, and liraglutide and this was mainly due to reimbursement considerations in Korea; it was not possible to include semaglutide. Given the proven effects of semaglutide on the liver, particularly for MASLD through resolution of liver fibrosis and weight loss (52), caution should be exercised when interpreting the results of this study. Further research is needed to assess semaglutide, as well as newer dual and triple receptor agonists that include combinations of GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists and/or glucagon receptor agonists.

**Conclusions**

In this nationwide cohort study, use of SGLT-2i was associated with a lower risk of hepatic decompensation events in patients with MASLD compared to TZD, and importantly showed similar hepatic effectiveness to GLP-1RA. The hepatic effectiveness of SGLT-2i was greater in female patients, and in patients aged less than 65 years. Considering the established association between type 2 diabetes and liver disease, our findings provide real-world evidence supporting the role of SGLT-2i in patients with MASLD.

**Disclosures**

**Grant support:** Prof Shin was supported by a grant from the Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant No. HC23C0101). Prof Byrne is supported in part by the Southampton National Institute for Heath and Care Research Biomedical Research Centre (grant No. NIHR203319). Dr. Bea was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant No. RS-2023-00273553).

**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.

**Disclosures:** JYS received grants from the Ministry of Food and Drug Safety, the Ministry of Health and Welfare, the National Research Foundation of Korea, and pharmaceutical companies, including LG Chem, UCB, SK bioscience, and Pfizer outside the submitted work.

**Author Contributions:** -

**Ethical approval:** Ethical approval was obtained at 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-2023-07-041).

**Data sharing:** No additional data available.

**Table 1**. Baseline characteristics for patients initiating SGLT2 inhibitors (SGLT-2i) vs. GLP-1 receptor agonists (GLP-1RA).

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Characteristics before PS matching** | **Characteristics after PS matching** |
|  | SGLT-2i | GLP-1RA | ASD | SGLT-2i | GLP-1RA | ASD |
| **Number of patients** | 217391 | 11275 |  | 11275 | 11275 |  |
| **Age, years; mean (SD)** | 55.7 (9.9) | 57.0 (10.6) | 0.13  | 56.88 (10.26) | 57.04 (10.57) | 0.02  |
| **Sex, No. (%)** |  |  | 0.19  |  |  | 0.00  |
|  | Male | 149148 (68.6) | 6725 (59.6) |  | 6731 (59.7) | 6725 (59.6) |  |
|  | Female | 68243 (31.4) | 4550 (40.4) |  | 4544 (40.3) | 4550 (40.4) |  |
| **Calendar year** |  |  | 0.42  |  |  | 0.07  |
|  | 2014 | 3549 (1.6) | 27 (0.2) |  | 24 (0.2) | 27 (0.2) |  |
|  | 2015 | 13375 (6.2) | 130 (1.2) |  | 131 (1.2) | 130 (1.2) |  |
|  | 2016 | 23277 (10.7) | 816 (7.2) |  | 825 (7.3) | 816 (7.2) |  |
|  | 2017 | 30010 (13.8) | 2015 (17.9) |  | 2020 (17.9) | 2015 (17.9) |  |
|  | 2018 | 30027 (13.8) | 2238 (19.8) |  | 2194 (19.5) | 2238 (19.8) |  |
|  | 2019 | 35647 (16.4) | 2103 (18.7) |  | 2163 (19.2) | 2103 (18.7) |  |
|  | 2020 | 29014 (13.3) | 1323 (11.7) |  | 1316 (11.7) | 1323 (11.7) |  |
|  | 2021 | 29604 (13.6) | 1425 (12.6) |  | 1366 (12.1) | 1425 (12.6) |  |
|  | 2022 | 22888 (10.5) | 1198 (10.6) |  | 1236 (11.0) | 1198 (10.6) |  |
| **Healthcare use‡** |  |  |  |  |  |  |
|  |  Inpatient hospitalizations |  |  | 0.20  |  |  | 0.00  |
|  | 0 | 171584 (78.9) | 8016 (71.1) |  | 7978 (70.8) | 8016 (71.1) |  |
|  |  1-2 | 41005 (18.9) | 2800 (24.8) |  | 2837 (25.2) | 2800 (24.8) |  |
|  |  ≥3 | 4802 (2.2) | 459 (4.1) |  | 460 (4.1) | 459 (4.1) |  |
|  | Number of physician visits |  |  | 0.21  |  |  | 0.00  |
|  |  0-2 | 6755 (3.1) | 105 (0.9) |  | 113 (1.0) | 105 (0.9) |  |
|  |  3-5 | 13689 (6.3) | 292 (2.6) |  | 314 (2.8) | 292 (2.6) |  |
|  | ≥6 | 196947 (90.6) | 10878 (96.5) |  | 10848 (96.2) | 10878 (96.5) |  |
|  | Physician speciality |  |  |  |  |  |  |
|  | Cardiologist | 32060 (14.7) | 1782 (15.8) | 0.03  | 1775 (15.7) | 1782 (15.8) | 0.00  |
|  | Endocrinologist | 38459 (17.7) | 4478 (39.7) | 0.50  | 4463 (39.6) | 4478 (39.7) | 0.00  |
|  | Gastroentrologist | 21283 (9.8) | 1464 (13.0) | 0.10  | 1499 (13.3) | 1464 (13.0) | 0.01  |
| **Body mass index; mean (SD)** | 29.6 (3.7) | 30.0 (4.1) | 0.12  | 30.0 (4.1) | 30.0 (4.1) | 0.00  |
| **Body mass index, No. (%)** |  |  | 0.10  |  |  | 0.04  |
|  | Normal weight | 2988 (1.4) | 156 (1.4) |  | 112 (1.0) | 156 (1.4) |  |
|  | Overweight | 12762 (5.9) | 591 (5.2) |  | 537 (4.8) | 591 (5.2) |  |
|  | Obese I | 113746 (52.3) | 5402 (47.9) |  | 5597 (49.6) | 5402 (47.9) |  |
|  | Obese II | 87895 (40.4) | 5126 (45.5) |  | 5029 (44.6) | 5126 (45.5) |  |
| **Smoking, No. (%)** |  |  | 0.14  |  |  | 0.00  |
|  | Never | 104129 (47.9) | 6160 (54.6) |  | 6158 (54.6) | 6160 (54.6) |  |
|  | Past | 56186 (25.8) | 2595 (23.0) |  | 2589 (23.0) | 2595 (23.0) |  |
|  | Current | 57040 (26.2) | 2516 (22.3) |  | 2524 (22.4) | 2516 (22.3) |  |
|  | Unknown | 36 (0.0) | 4 (0.0) |  | 4 (0.0) | 4 (0.0) |  |
| **Drinking, No. (%)** |  |  | 0.19  |  |  | 0.00  |
|  | No | 124073 (57.1) | 7490 (66.4) |  | 7480 (66.3) | 7490 (66.4) |  |
|  | Yes | 93243 (42.9) | 3779 (33.5) |  | 3789 (33.6) | 3779 (33.5) |  |
|  | Unknown | 75 (0.0) | 6 (0.1) |  | 6 (0.1) | 6 (0.1) |  |
| **Comorbidities‡** |  |  |  |  |  |  |
|  | Dyslipidaemia | 99341 (45.7) | 5553 (49.3) | 0.07  | 5627 (49.9) | 5553 (49.3) | 0.01  |
|  | Hypertension | 122736 (56.5) | 6257 (55.5) | 0.02  | 6277 (55.7) | 6257 (55.5) | 0.00  |
|  | Atrial fibrillation | 3727 (1.7) | 166 (1.5) | 0.02  | 165 (1.5) | 166 (1.5) | 0.00  |
|  | Liver cirrhosis | 770 (0.4) | 89 (0.8) | 0.06  | 85 (0.8) | 89 (0.8) | 0.00  |
|  | Chronic kidney disease | 2968 (1.4) | 568 (5.0) | 0.21  | 482 (4.3) | 568 (5.0) | 0.04  |
|  | Dementia | 799 (0.4) | 70 (0.6) | 0.04  | 67 (0.6) | 70 (0.6) | 0.00  |
|  | Depression | 8810 (4.1) | 659 (5.8) | 0.08  | 612 (5.4) | 659 (5.8) | 0.02  |
|  | Hypothyroidism | 4695 (2.2) | 338 (3.0) | 0.05  | 324 (2.9) | 338 (3.0) | 0.01  |
|  | Hyperthyroidism | 1440 (0.7) | 79 (0.7) | 0.01  | 77 (0.7) | 79 (0.7) | 0.00  |
|  | Gallbladder disease | 4279 (2.0) | 250 (2.2) | 0.02  | 246 (2.2) | 250 (2.2) | 0.00  |
|  | Other diseases of biliary tract | 376 (0.2) | 21 (0.2) | 0.00  | 22 (0.2) | 21 (0.2) | 0.00  |
|  | COPD | 9049 (4.2) | 590 (5.2) | 0.05  | 584 (5.2) | 590 (5.2) | 0.00  |
|  | Peripheral vascular disease | 11898 (5.5) | 813 (7.2) | 0.07  | 830 (7.4) | 813 (7.2) | 0.01  |
| **Comedication‡** |  |  |  |  |  |  |
|  | Acetaminophen | 125895 (57.9) | 7145 (63.4) | 0.11  | 7193 (63.8) | 7145 (63.4) | 0.01  |
|  | RAS inhibitors | 130279 (59.9) | 7655 (67.9) | 0.17  | 7681 (68.1) | 7655 (67.9) | 0.01  |
|  | CCB | 96272 (44.3) | 5312 (47.1) | 0.06  | 5289 (46.9) | 5312 (47.1) | 0.00  |
|  | β-blockers | 40922 (18.8) | 2451 (21.7) | 0.07  | 2464 (21.9) | 2451 (21.7) | 0.00  |
|  | Diuretics | 56237 (25.9) | 3389 (30.1) | 0.09  | 3317 (29.4) | 3389 (30.1) | 0.01  |
|  | Systemic antibiotics | 137032 (63.0) | 7638 (67.7) | 0.10  | 7712 (68.4) | 7638 (67.7) | 0.01  |
|  | Oral anticoagulants | 4304 (2.0) | 246 (2.2) | 0.01  | 260 (2.3) | 246 (2.2) | 0.01  |
|  | Oral antiplatelets | 64177 (29.5) | 4542 (40.3) | 0.23  | 4541 (40.3) | 4542 (40.3) | 0.00  |
|  | NSAIDs | 131071 (60.3) | 7328 (65.0) | 0.10  | 7326 (65.0) | 7328 (65.0) | 0.00  |
|  | Opioids | 22938 (10.6) | 1533 (13.6) | 0.09  | 1501 (13.3) | 1533 (13.6) | 0.01  |
|  | Systemic corticosteroids | 103108 (47.4) | 5627 (49.9) | 0.05  | 5694 (50.5) | 5627 (49.9) | 0.01  |
|  | Statins | 139620 (64.2) | 8705 (77.2) | 0.29  | 8679 (77.0) | 8705 (77.2) | 0.01  |
|  | Other lipid-lowering agents | 57744 (26.6) | 3722 (33.0) | 0.14  | 3680 (32.6) | 3722 (33.0) | 0.01  |
|  | Vitamin E | 17804 (8.2) | 1267 (11.2) | 0.10  | 1325 (11.8) | 1267 (11.2) | 0.02  |
|  | Nitrates | 12393 (5.7) | 735 (6.5) | 0.03  | 735 (6.5) | 735 (6.5) | 0.00  |
| **Antidiabetic drugs use‡** |  |  |  |  |  |  |
|  | Insulin | 20921 (9.6) | 4613 (40.9) | 0.77  | 4549 (40.3) | 4613 (40.9) | 0.01  |
|  | α-glucosidase inhibitors | 3221 (1.5) | 240 (2.1) | 0.05  | 238 (2.1) | 240 (2.1) | 0.00  |
|  | Meglitinides | 548 (0.3) | 85 (0.8) | 0.07  | 93 (0.8) | 85 (0.8) | 0.01  |
|  | Metformin | 161228 (74.2) | 9704 (86.1) | 0.30  | 9844 (87.3) | 9704 (86.1) | 0.04  |
|  | Sulfonylureas | 86888 (40.0) | 7406 (65.7) | 0.53  | 7568 (67.1) | 7406 (65.7) | 0.03  |
|  | Thiazolidinediones | 24088 (11.1) | 2247 (19.9) | 0.25  | 2289 (20.3) | 2247 (19.9) | 0.01  |
|  | DPP4 inhibitors | 120320 (55.3) | 9077 (80.5) | 0.56  | 9127 (80.9) | 9077 (80.5) | 0.01  |
| **Diabetic complications‡** |  |  |  |  |  |  |
|  | Retinopathy | 9791 (4.5) | 1173 (10.4) | 0.23  | 1122 (10.0) | 1173 (10.4) | 0.02  |
|  | Neuropathy | 24864 (11.4) | 2303 (20.4) | 0.25  | 2296 (20.4) | 2303 (20.4) | 0.00  |
|  | Nephropathy | 32316 (14.9) | 3201 (28.4) | 0.33  | 3202 (28.4) | 3201 (28.4) | 0.00  |
|  |  Level of antidiabetic treatments**§** |  |  | 1.02  |  |  | 0.02  |
|  | 1 | 75502 (34.7) | 731 (6.5) |  | 666 (5.9) | 731 (6.5) |  |
|  | 2 | 120968 (55.6) | 5931 (52.6) |  | 6060 (53.7) | 5931 (52.6) |  |
|  | 3 | 20921 (9.6) | 4613 (40.9) |  | 4549 (40.3) | 4613 (40.9) |  |
| **CCI groups‡** |  |  | 0.36  |  |  | 0.02  |
|  | 0 | 38919 (17.9) | 1281 (11.4) |  | 1292 (11.5) | 1281 (11.4) |  |
|  | 1-2 | 98599 (45.4) | 3984 (35.3) |  | 4004 (35.5) | 3984 (35.3) |  |
|  | ≥3 | 79873 (36.7) | 6010 (53.3) |  | 5979 (53.0) | 6010 (53.3) |  |

**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 system; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter 2 inhibitors

§Stratified by Asian body mass index categories: Normal weight, <23 kg/m2; Overweight, 23 to <25 kg/m2; Obese I, 25 to <30 kg/m2, Obese II, ≥30 kg/m2

**Table 2**. Baseline characteristics for patients initiating SGLT2 inhibitors (SGLT-2i) vs. Thiazolidinediones (TZD).

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Characteristics before PS matching** | **Characteristics after PS matching** |
|  | SGLT-2i | TZD | ASD | SGLT-2i | TZD | ASD |
| **Number of patients** | 183485 | 116396 |  | 95814 | 95814 |  |
| **Age, years; mean (SD)** | 55.4 (9.8) | 58.4 (10.6) | 0.30 | 57.4 (9.9) | 57.4 (10.4) | 0.00 |
| **Sex, No. (%)** |  |  | 0.10 |  |  | 0.00 |
|  | Male | 125373 (68.3) | 84627 (72.7) |  | 68412 (71.4) | 68578 (71.6) |  |
|  | Female | 58112 (31.7) | 31769 (27.3) |  | 27402 (28.6) | 27236 (28.4) |  |
| **Calendar year** |  |  | 0.48 |  |  | 0.00 |
|  | 2014 | 2962 (1.6) | 5557 (4.8) |  | 2803 (2.9) | 2962 (3.1) |  |
|  | 2015 | 11128 (6.1) | 18622 (16.0) |  | 9955 (10.4) | 10053 (10.5) |  |
|  | 2016 | 18974 (10.3) | 17481 (15.0) |  | 13782 (14.4) | 13597 (14.2) |  |
|  | 2017 | 24795 (13.5) | 16544 (14.2) |  | 14740 (15.4) | 14567 (15.2) |  |
|  | 2018 | 24941 (13.6) | 16784 (14.4) |  | 14732 (15.4) | 14698 (15.3) |  |
|  | 2019 | 30151 (16.4) | 13922 (12.0) |  | 13167 (13.7) | 13279 (13.9) |  |
|  | 2020 | 25128 (13.7) | 11144 (9.6) |  | 10708 (11.2) | 10645 (11.1) |  |
|  | 2021 | 25731 (14.0) | 9558 (8.2) |  | 9280 (9.7) | 9335 (9.7) |  |
|  | 2022 | 19675 (10.7) | 6784 (5.8) |  | 6647 (6.9) | 6678 (7.0) |  |
| **Healthcare use‡** |  |  |  |  |  |  |
|  |  Inpatient hospitalizations |  |  | 0.00 |  |  | 0.07 |
|  | 0 | 145643 (79.4) | 91451 (78.6) |  | 75771 (79.1) | 75787 (79.1) |  |
|  |  1-2 | 34077 (18.6) | 21893 (18.8) |  | 17716 (18.5) | 17770 (18.5) |  |
|  |  ≥3 | 3765 (2.1) | 3052 (2.6) |  | 2327 (2.4) | 2257 (2.4) |  |
|  | Number of physician visits |  |  | 0.15 |  |  | 0.00 |
|  |  0-2 | 6501 (3.5) | 2709 (2.3) |  | 2411 (2.5) | 2468 (2.6) |  |
|  |  3-5 | 12589 (6.9) | 6002 (5.2) |  | 5278 (5.5) | 5356 (5.6) |  |
|  | ≥6 | 164395 (89.6) | 107685 (92.5) |  | 88125 (92.0) | 87990 (91.8) |  |
|  | Physician speciality |  |  |  |  |  |  |
|  | Cardiologist | 27543 (15.0) | 10523 (9.0) | 0.18 | 9767 (10.2) | 9791 (10.2) | 0.00 |
|  | Endocrinologist | 31432 (17.1) | 16566 (14.2) | 0.08 | 14524 (15.2) | 14364 (15.0) | 0.01 |
|  | Gastroentrologist | 17887 (9.7) | 10798 (9.3) | 0.02 | 9047 (9.4) | 8950 (9.3) | 0.00 |
| **Body mass index; mean (SD)** | 29.6 (3.7) | 28.3 (3.4) | 0.35 | 28.6 (3.3) | 28.6 (3.4) | 0.01 |
| **Body mass index, No. (%)** |  |  | 0.35 |  |  | 0.04 |
|  | Normal weight | 2507 (1.4) | 3699 (3.2) |  | 1989 (2.1) | 2341 (2.4) |  |
|  | Overweight | 10883 (5.9) | 12273 (10.5) |  | 7895 (8.2) | 8687 (9.1) |  |
|  | Obese I | 96323 (52.5) | 68935 (59.2) |  | 56901 (59.4) | 55769 (58.2) |  |
|  | Obese II | 73772 (40.2) | 31489 (27.1) |  | 29029 (30.3) | 29017 (30.3) |  |
| **Smoking, No. (%)** |  |  | 0.09 |  |  | 0.00 |
|  | Never | 87785 (47.8) | 52561 (45.2) |  | 43935 (45.9) | 43995 (45.9) |  |
|  | Past | 47582 (25.9) | 29529 (25.4) |  | 24320 (25.4) | 24274 (25.3) |  |
|  | Current | 48087 (26.2) | 34269 (29.4) |  | 27535 (28.7) | 27522 (28.7) |  |
|  | Unknown | 31 (0.0) | 37 (0.0) |  | 24 (0.0) | 23 (0.0) |  |
| **Drinking, No. (%)** |  |  | 0.08 |  |  | 0.00 |
|  | No | 104309 (56.8) | 61467 (52.8) |  | 51682 (53.9) | 51523 (53.8) |  |
|  | Yes | 79116 (43.1) | 54867 (47.1) |  | 44094 (46.0) | 44245 (46.2) |  |
|  | Unknown | 60 (0.0) | 62 (0.1) |  | 38 (0.0) | 46 (0.0) |  |
| **Comorbidities‡** |  |  |  |  |  |  |
|  | Dyslipidaemia | 83360 (45.4) | 50969 (43.8) | 0.03 | 42784 (44.7) | 42797 (44.7) | 0.00 |
|  | Hypertension | 102203 (55.7) | 69067 (59.3) | 0.07 | 55789 (58.2) | 55720 (58.2) | 0.00 |
|  | Atrial fibrillation | 3147 (1.7) | 1221 (1.0) | 0.06 | 1093 (1.1) | 1099 (1.1) | 0.00 |
|  | Liver cirrhosis | 604 (0.3) | 524 (0.5) | 0.02 | 415 (0.4) | 401 (0.4) | 0.00 |
|  | Chronic kidney disease | 2226 (1.2) | 2186 (1.9) | 0.05 | 1512 (1.6) | 1452 (1.5) | 0.01 |
|  | Dementia | 627 (0.3) | 811 (0.7) | 0.05 | 505 (0.5) | 481 (0.5) | 0.00 |
|  | Depression | 7234 (3.9) | 5053 (4.3) | 0.02 | 4067 (4.2) | 3991 (4.2) | 0.00 |
|  | Hypothyroidism | 3998 (2.2) | 1898 (1.6) | 0.04 | 1709 (1.8) | 1686 (1.8) | 0.00 |
|  | Hyperthyroidism | 1234 (0.7) | 653 (0.6) | 0.01 | 560 (0.6) | 575 (0.6) | 0.00 |
|  | Gallbladder disease | 3651 (2.0) | 2036 (1.7) | 0.02 | 1730 (1.8) | 1728 (1.8) | 0.00 |
|  | Other diseases of biliary tract | 317 (0.2) | 277 (0.2) | 0.01 | 203 (0.2) | 207 (0.2) | 0.00 |
|  | COPD | 7451 (4.1) | 5894 (5.1) | 0.05 | 4571 (4.8) | 4526 (4.7) | 0.00 |
|  | Peripheral vascular disease | 9599 (5.2) | 7484 (6.4) | 0.05 | 5810 (6.1) | 5830 (6.1) | 0.00 |
| **Comedication‡** |  |  |  |  |  |  |
|  | Acetaminophen | 105358 (57.4) | 69281 (59.5) | 0.04 | 56565 (59.0) | 56366 (58.8) | 0.00 |
|  | RAS inhibitors | 107446 (58.6) | 69686 (59.9) | 0.03 | 57055 (59.5) | 56999 (59.5) | 0.00 |
|  | CCB | 80378 (43.8) | 52566 (45.2) | 0.03 | 42758 (44.6) | 42680 (44.5) | 0.00 |
|  | β-blockers | 34415 (18.8) | 19337 (16.6) | 0.06 | 16161 (16.9) | 16125 (16.8) | 0.00 |
|  | Diuretics | 45815 (25.0) | 31676 (27.2) | 0.05 | 25086 (26.2) | 25141 (26.2) | 0.00 |
|  | Systemic antibiotics | 114888 (62.6) | 74939 (64.4) | 0.04 | 61183 (63.9) | 61098 (63.8) | 0.00 |
|  | Oral anticoagulants | 3600 (2.0) | 1471 (1.3) | 0.06 | 1296 (1.4) | 1340 (1.4) | 0.00 |
|  | Oral antiplatelets | 51244 (27.9) | 37294 (32.0) | 0.09 | 29409 (30.7) | 29466 (30.8) | 0.00 |
|  | NSAIDs | 109751 (59.8) | 71448 (61.4) | 0.03 | 58490 (61.0) | 58337 (60.9) | 0.00 |
|  | Opioids | 19114 (10.4) | 12418 (10.7) | 0.01 | 10118 (10.6) | 10088 (10.5) | 0.00 |
|  | Systemic corticosteroids | 86960 (47.4) | 55885 (48.0) | 0.01 | 45760 (47.8) | 45669 (47.7) | 0.00 |
|  | Statins | 113509 (61.9) | 73738 (63.4) | 0.03 | 61273 (63.9) | 61121 (63.8) | 0.00 |
|  | Other lipid-lowering agents | 47351 (25.8) | 29329 (25.2) | 0.01 | 24956 (26.0) | 24869 (26.0) | 0.00 |
|  | Vitamin E | 14366 (7.8) | 10511 (9.0) | 0.04 | 8525 (8.9) | 8406 (8.8) | 0.00 |
|  | Nitrates | 10435 (5.7) | 4401 (3.8) | 0.09 | 3936 (4.1) | 4005 (4.2) | 0.00 |
| **Antidiabetic drugs use‡** |  |  |  |  |  |  |
|  | Insulin | 16190 (8.8) | 11936 (10.3) | 0.05 | 9507 (9.9) | 9461 (9.9) | 0.00 |
|  | α-glucosidase inhibitors | 2603 (1.4) | 3106 (2.7) | 0.09 | 2023 (2.1) | 2047 (2.1) | 0.00 |
|  | Meglitinides | 404 (0.2) | 540 (0.5) | 0.04 | 317 (0.3) | 326 (0.3) | 0.00 |
|  | Metformin | 131146 (71.5) | 96152 (82.6) | 0.27 | 77600 (81.0) | 77293 (80.7) | 0.01 |
|  | Sulfonylureas | 67199 (36.6) | 55606 (47.8) | 0.23 | 44058 (46.0) | 43708 (45.6) | 0.01 |
|  | GLP-1 receptor agonists | 1534 (0.8) | 420 (0.4) | 0.06 | 469 (0.5) | 414 (0.4) | 0.01 |
|  | DPP4 inhibitors | 93614 (51.0) | 79927 (68.7) | 0.37 | 63427 (66.2) | 62978 (65.7) | 0.01 |
| **Diabetic complications‡** |  |  |  |  |  |  |
|  | Retinopathy | 7407 (4.0) | 5987 (5.1) | 0.05 | 4619 (4.8) | 4540 (4.7) | 0.00 |
|  | Neuropathy | 18812 (10.3) | 15687 (13.5) | 0.10 | 11976 (12.5) | 12000 (12.5) | 0.00 |
|  | Nephropathy | 25013 (13.6) | 17826 (15.3) | 0.05 | 14393 (15.0) | 14306 (14.9) | 0.00 |
|  |  Level of antidiabetic treatments**§** |  |  | 0.43 |  |  | 0.01 |
|  | 1 | 74165 (40.4) | 24584 (21.1) |  | 23095 (24.1) | 23539 (24.6) |  |
|  | 2 | 93130 (50.8) | 79876 (68.6) |  | 63212 (66.0) | 62814 (65.6) |  |
|  | 3 | 16190 (8.8) | 11936 (10.3) |  | 9507 (9.9) | 9461 (9.9) |  |
| **CCI groups‡** |  |  | 0.21 |  |  | 0.00 |
|  | 0 | 35872 (19.6) | 14734 (12.7) |  | 13090 (13.7) | 13369 (14.0) |  |
|  | 1-2 | 84028 (45.8) | 53535 (46.0) |  | 44784 (46.7) | 44767 (46.7) |  |
|  | ≥3 | 63585 (34.7) | 48127 (41.3) |  | 37940 (39.6) | 37678 (39.3) |  |

**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 system; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones

§Stratified by Asian body mass index categories: Normal weight, <23 kg/m2; Overweight, 23 to <25 kg/m2; Obese I, 25 to <30 kg/m2, Obese II, ≥30 kg/m2

**Figure legends**

**Figure 1**. Hepatic decompensation events in 1:1 propensity score matched initiators of (A) SGLT2 inhibitors vs. GLP-1 receptor agonists, and (B) SGLT-2 inhibitors vs. Thiazolidinediones.

**Abbreviations**: CI, confidence interval; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; IR, incidence rate; PY, person-year; RD, rate difference; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones

**Figure 2**. Results of subgroup analyses for hepatic decompensation events in 1:1 propensity score matched initiators of (A) SGLT2 inhibitors vs. GLP-1 receptor agonists, and (B) SGLT-2 inhibitors vs. Thiazolidinediones.

**Abbreviations**: CI, confidence interval; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; IR, incidence rate; PY, person-year; RD, rate difference; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones

**Figure 3**. Cumulative incidence of hepatic decompensation events in 1:1 propensity score matched initiators of (A) SGLT2 inhibitors vs. GLP-1 receptor agonists, and (B) SGLT-2 inhibitors vs. Thiazolidinediones.

**Abbreviations**: CI, confidence interval; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones

**References**

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