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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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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 (aged ≥40 years) who initiated SGLT-2i or comparator drugs (GLP-1RA or TZD). Primary outcome was a composite of hepatic decompensation events, including ascites, oesophageal 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 HRs with 95% CIs.

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 with GLP-1RA, SGLT-2i showed a similar risk of hepatic decompensation events (HR 0.93, 95% CI 0.76 to 1.14). Compared with TZD, SGLT-2i demonstrated a reduced risk of hepatic decompensation events (HR 0.77, 95% CI 0.72 to 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: HR 0.87 (95% CI 0.80–0.94); female: HR 0.62 (95% CI 0.55–0.69)).

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

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 with TZD and showed similar effectiveness to GLP-1RA.

⇒ The hepatic effectiveness of SGLT-2i was greater in female patients and patients 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.

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 extrahepatic 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 randomised controlled trials (RCT) 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) restrain glucose reabsorption at the proximal tubule of the kidney and have demonstrated cardiovascular and renal benefits beyond lowering glycaemia in patients with type 2 diabetes.[12–15] Data from several RCTs have shown that SGLT-2i may have promising effects on fibrosis or steatosis, based on biological mechanisms of glucagon signalling 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 an 11% reduced risk of hepatic decompensation events (HR 0.89, 95% 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 used nationwide health administrative claims data (1 September 2014 to 31 December 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. 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 behaviour information. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline (online supplemental file 2).[23] The requirement for informed consent was waived since all the data were anonymised.

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 1 September 2014 and 31 December 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 1 September 2014, when SGLT-2i was 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 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 (online supplemental eAppendix 1, online supplemental eTable 1). Patients aged less than 40 years on the index date and those with competing liver diseases other than MASLD (eg, viral hepatitis, alcoholic liver disease, autoimmune hepatitis, haemochromatosis, Wilson's disease, Budd-Chiari syndrome) within a year prior to the index date were also excluded (online supplemental eTable 2).[26] Subsequently, we excluded patients diagnosed with end-stage renal 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 (online supplemental eFigures 1 and 2).

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 RCTs with liver histology endpoints that assessed non-alcoholic 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 glycaemic 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, discontinuation (defined as no prescription after 90 days had elapsed from the last prescription's supply), switching to or adding study drug other than index drug (within each pairwise cohort), death or the end of the study period (31 December 2022).

Outcome definition

The primary outcome was a composite of hepatic decompensation events comprising ascites, oesophageal 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. 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,

oesophageal varices or hepatic failure, respectively. Procedure codes for paracentesis, varix ligation or surgical operation were also considered to indicate ascites, oesophageal 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 (online supplemental eTable 3).

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, dipeptidyl peptidase-4 inhibitor (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 (dyslipidaemia, 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 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, non-steroidal 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 utilisation behaviour (number of hospitalisations, number of physician visits and physician specialties) were assessed a year prior to the index date (online supplemental eTable 4). Health examination results (waist circumference, fasting blood glucose, blood pressure, cholesterol level, triglycerides, serum creatinine, liver enzyme levels, estimated glomerular filtration rate (eGFR), smoking or drinking behaviours) were assessed within 3 years prior to the index date. Smoking (never, past, current, unknown), drinking (no, yes, unknown) behaviours 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 online supplemental eTable 5.

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-neighbour method with a calliper of 0.05 on the log scale. An absolute standardised 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 1000 person-years for all outcomes were calculated. The IR per 1000 person-years was calculated based on Poisson distribution. HRs and 95% CIs 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 (online supplemental eTable 6). 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 online supplemental eAppendix 2.

RESULTS

Characteristics of study cohorts

SGLT-2i versus GLP-1RA

We identified 228 666 patients for the comparison of SGLT-2i versus 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 versus GLP-1RA cohort. The treatment groups were well balanced, presenting with ASD for all covariates <0.1 (table 1).

SGLT-2i versus TZD

We identified 299 881 patients for the SGLT-2i versus 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 versus 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 versus GLP-1RA

Over a mean (SD) follow-up of 2.1 years (1.9), the IR of hepatic decompensation events per 1000 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 to 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 to 1.43); oesophageal varices with bleeding: HR 0.80 (95% CI 0.35 to 1.83); liver transplant: HR 0.25 (95% CI 0.09 to 0.70); hepatic failure: HR 0.71 (95% CI 0.50 to 1.00); liver-cause mortality: HR 0.45 (95% CI 0.15 to 1.32); all-cause mortality: HR 1.24 (95% CI 0.90 to 1.72)) (figure 1). The cumulative incidence of hepatic decompensation events was consistent with this finding (log-rank p=0.48) (figure 2).

SGLT-2i versus TZD

Over a mean (SD) follow-up of 2.1 years (2.0), the IR of hepatic decompensation events per 1000 person-years was

Table 1 Baseline characteristics of patients initiating SGLT-2i versus GLP-1RA

	Characteristics before PS matching			Characteristics after PS matching		
	SGLT-2i	GLP-1RA	ASD	SGLT-2i	GLP-1RA	ASD
Number of patients	217 391	11 275		11 275	11 275	
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	149 148 (68.6)	6725 (59.6)		6731 (59.7)	6725 (59.6)	
Female	68 243 (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	13 375 (6.2)	130 (1.2)		131 (1.2)	130 (1.2)	
2016	23 277 (10.7)	816 (7.2)		825 (7.3)	816 (7.2)	
2017	30 010 (13.8)	2015 (17.9)		2020 (17.9)	2015 (17.9)	
2018	30 027 (13.8)	2238 (19.8)		2194 (19.5)	2238 (19.8)	
2019	35 647 (16.4)	2103 (18.7)		2163 (19.2)	2103 (18.7)	
2020	29 014 (13.3)	1323 (11.7)		1316 (11.7)	1323 (11.7)	
2021	29 604 (13.6)	1425 (12.6)		1366 (12.1)	1425 (12.6)	
2022	22 888 (10.5)	1198 (10.6)		1236 (11.0)	1198 (10.6)	
Healthcare use*						
Inpatient hospitalizations			0.20			0.00
0	171 584 (78.9)	8016 (71.1)		7978 (70.8)	8016 (71.1)	
1–2	41 005 (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	13 689 (6.3)	292 (2.6)		314 (2.8)	292 (2.6)	
≥6	196 947 (90.6)	10 878 (96.5)		10 848 (96.2)	10 878 (96.5)	
Physician specialty						
Cardiologist	32 060 (14.7)	1782 (15.8)	0.03	1775 (15.7)	1782 (15.8)	0.00
Endocrinologist	38 459 (17.7)	4478 (39.7)	0.50	4463 (39.6)	4478 (39.7)	0.00
Gastroentrologist	21 283 (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	12 762 (5.9)	591 (5.2)		537 (4.8)	591 (5.2)	
Obese I	113 746 (52.3)	5402 (47.9)		5597 (49.6)	5402 (47.9)	
Obese II	87 895 (40.4)	5126 (45.5)		5029 (44.6)	5126 (45.5)	
Smoking, No. (%)			0.14			0.00
Never	104 129 (47.9)	6160 (54.6)		6158 (54.6)	6160 (54.6)	
Past	56 186 (25.8)	2595 (23.0)		2589 (23.0)	2595 (23.0)	
Current	57 040 (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	124 073 (57.1)	7490 (66.4)		7480 (66.3)	7490 (66.4)	
Yes	93 243 (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	99 341 (45.7)	5553 (49.3)	0.07	5627 (49.9)	5553 (49.3)	0.01
Hypertension	122 736 (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

Continued

Table 1 Continued

	Characteristics before PS matching			Characteristics after PS matching		
	SGLT-2i	GLP-1RA	ASD	SGLT-2i	GLP-1RA	ASD
COPD	9049 (4.2)	590 (5.2)	0.05	584 (5.2)	590 (5.2)	0.00
Peripheral vascular disease	11 898 (5.5)	813 (7.2)	0.07	830 (7.4)	813 (7.2)	0.01
Comedication*						
Acetaminophen	125 895 (57.9)	7145 (63.4)	0.11	7193 (63.8)	7145 (63.4)	0.01
RAS inhibitors	130 279 (59.9)	7655 (67.9)	0.17	7681 (68.1)	7655 (67.9)	0.01
CCB	96 272 (44.3)	5312 (47.1)	0.06	5289 (46.9)	5312 (47.1)	0.00
β-blockers	40 922 (18.8)	2451 (21.7)	0.07	2464 (21.9)	2451 (21.7)	0.00
Diuretics	56 237 (25.9)	3389 (30.1)	0.09	3317 (29.4)	3389 (30.1)	0.01
Systemic antibiotics	137 032 (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	64 177 (29.5)	4542 (40.3)	0.23	4541 (40.3)	4542 (40.3)	0.00
NSAIDs	131 071 (60.3)	7328 (65.0)	0.10	7326 (65.0)	7328 (65.0)	0.00
Opioids	22 938 (10.6)	1533 (13.6)	0.09	1501 (13.3)	1533 (13.6)	0.01
Systemic corticosteroids	103 108 (47.4)	5627 (49.9)	0.05	5694 (50.5)	5627 (49.9)	0.01
Statins	139 620 (64.2)	8705 (77.2)	0.29	8679 (77.0)	8705 (77.2)	0.01
Other lipid-lowering agents	57 744 (26.6)	3722 (33.0)	0.14	3680 (32.6)	3722 (33.0)	0.01
Vitamin E	17 804 (8.2)	1267 (11.2)	0.10	1325 (11.8)	1267 (11.2)	0.02
Nitrates	12 393 (5.7)	735 (6.5)	0.03	735 (6.5)	735 (6.5)	0.00
Antidiabetic drugs use*						
Insulin	20 921 (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	161 228 (74.2)	9704 (86.1)	0.30	9844 (87.3)	9704 (86.1)	0.04
Sulfonylureas	86 888 (40.0)	7406 (65.7)	0.53	7568 (67.1)	7406 (65.7)	0.03
Thiazolidinediones	24 088 (11.1)	2247 (19.9)	0.25	2289 (20.3)	2247 (19.9)	0.01
DPP4 inhibitors	120 320 (55.3)	9077 (80.5)	0.56	9127 (80.9)	9077 (80.5)	0.01
Diabetic complications*						
Nephropathy	9791 (4.5)	1173 (10.4)	0.23	1122 (10.0)	1173 (10.4)	0.02
Neuropathy	24 864 (11.4)	2303 (20.4)	0.25	2296 (20.4)	2303 (20.4)	0.00
Retinopathy	32 316 (14.9)	3201 (28.4)	0.33	3202 (28.4)	3201 (28.4)	0.00
Level of antidiabetic treatments*			1.02			0.02
1	75 502 (34.7)	731 (6.5)		666 (5.9)	731 (6.5)	
2	120 968 (55.6)	5931 (52.6)		6060 (53.7)	5931 (52.6)	
3	20 921 (9.6)	4613 (40.9)		4549 (40.3)	4613 (40.9)	
CCI groups*			0.36			0.02
0	38 919 (17.9)	1281 (11.4)		1292 (11.5)	1281 (11.4)	
1–2	98 599 (45.4)	3984 (35.3)		4004 (35.5)	3984 (35.3)	
≥3	79 873 (36.7)	6010 (53.3)		5979 (53.0)	6010 (53.3)	

*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.
†Assessed a year prior to the index date.
ASD, absolute standardised difference; CCB, calcium channel blocker; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; NSAID, non-steroidal anti-inflammatory drug; PS, propensity score; RAS, renin-angiotensin system; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

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 to 0.82). Similar associations were observed for all secondary outcomes, where SGLT-2i showed decreased risk of outcomes compared with TZD (ascites: HR 0.75 (95% CI 0.70 to 0.82); oesophageal varices with bleeding: HR 0.77 (95% CI 0.60 to 0.98); hepatic failure: HR 0.77 (95% CI 0.69 to 0.87); liver transplant: HR 0.79 (95% CI 0.48 to 1.29); liver-cause mortality: HR 0.61 (95% CI 0.45 to 0.84); all-cause mortality: HR 0.73 (95% CI 0.67 to 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 versus 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 to 0.90); ≥65 years: HR 1.37 (95% CI 1.02 to 1.84), p<0.01). In the SGLT-2i versus TZD cohort, female patients demonstrated greater benefit from SGLT-2i (male: HR 0.87 (95% CI 0.80 to 0.94); female: HR 0.62 (95% CI 0.55 to 0.69), p<0.01) (figure 2). The findings of a range of sensitivity analyses were consistent with those

Table 2 Baseline characteristics of patients initiating SGLT-2i versus TZD

	Characteristics before PS matching			Characteristics after PS matching		
	SGLT-2i	TZD	ASD	SGLT-2i	TZD	ASD
Number of patients	183 485	116 396		95 814	95 814	
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	125 373 (68.3)	84 627 (72.7)		68 412 (71.4)	68 578 (71.6)	
Female	58 112 (31.7)	31 769 (27.3)		27 402 (28.6)	27 236 (28.4)	
Calendar year			0.48			0.00
2014	2962 (1.6)	5557 (4.8)		2803 (2.9)	2962 (3.1)	
2015	11 128 (6.1)	18 622 (16.0)		9955 (10.4)	10 053 (10.5)	
2016	18 974 (10.3)	17 481 (15.0)		13 782 (14.4)	13 597 (14.2)	
2017	24 795 (13.5)	16 544 (14.2)		14 740 (15.4)	14 567 (15.2)	
2018	24 941 (13.6)	16 784 (14.4)		14 732 (15.4)	14 698 (15.3)	
2019	30 151 (16.4)	13 922 (12.0)		13 167 (13.7)	13 279 (13.9)	
2020	25 128 (13.7)	11 144 (9.6)		10 708 (11.2)	10 645 (11.1)	
2021	25 731 (14.0)	9558 (8.2)		9280 (9.7)	9335 (9.7)	
2022	19 675 (10.7)	6784 (5.8)		6647 (6.9)	6678 (7.0)	
Healthcare use*						
Inpatient hospitalizations			0.00			0.07
0	145 643 (79.4)	91 451 (78.6)		75 771 (79.1)	75 787 (79.1)	
1–2	34 077 (18.6)	21 893 (18.8)		17 716 (18.5)	17 770 (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	12 589 (6.9)	6002 (5.2)		5278 (5.5)	5356 (5.6)	
≥6	164 395 (89.6)	107 685 (92.5)		88 125 (92.0)	87 990 (91.8)	
Physician specialty						
Cardiologist	27 543 (15.0)	10 523 (9.0)	0.18	9767 (10.2)	9791 (10.2)	0.00
Endocrinologist	31 432 (17.1)	16 566 (14.2)	0.08	14 524 (15.2)	14 364 (15.0)	0.01
Gastroentrologist	17 887 (9.7)	10 798 (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	10 883 (5.9)	12 273 (10.5)		7895 (8.2)	8687 (9.1)	
Obese I	96 323 (52.5)	68 935 (59.2)		56 901 (59.4)	55 769 (58.2)	
Obese II	73 772 (40.2)	31 489 (27.1)		29 029 (30.3)	29 017 (30.3)	
Smoking, No. (%)			0.09			0.00
Never	87 785 (47.8)	52 561 (45.2)		43 935 (45.9)	43 995 (45.9)	
Past	47 582 (25.9)	29 529 (25.4)		24 320 (25.4)	24 274 (25.3)	
Current	48 087 (26.2)	34 269 (29.4)		27 535 (28.7)	27 522 (28.7)	
Unknown	31 (0.0)	37 (0.0)		24 (0.0)	23 (0.0)	
Drinking, No. (%)			0.08			0.00
No	104 309 (56.8)	61 467 (52.8)		51 682 (53.9)	51 523 (53.8)	
Yes	79 116 (43.1)	54 867 (47.1)		44 094 (46.0)	44 245 (46.2)	
Unknown	60 (0.0)	62 (0.1)		38 (0.0)	46 (0.0)	
Comorbidities*						
Dyslipidaemia	83 360 (45.4)	50 969 (43.8)	0.03	42 784 (44.7)	42 797 (44.7)	0.00
Hypertension	102 203 (55.7)	69 067 (59.3)	0.07	55 789 (58.2)	55 720 (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

Continued

Table 2 Continued

	Characteristics before PS matching			Characteristics after PS matching		
	SGLT-2i	TZD	ASD	SGLT-2i	TZD	ASD
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	105 358 (57.4)	69 281 (59.5)	0.04	56 565 (59.0)	56 366 (58.8)	0.00
RAS inhibitors	107 446 (58.6)	69 686 (59.9)	0.03	57 055 (59.5)	56 999 (59.5)	0.00
CCB	80 378 (43.8)	52 566 (45.2)	0.03	42 758 (44.6)	42 680 (44.5)	0.00
β-blockers	34 415 (18.8)	19 337 (16.6)	0.06	16 161 (16.9)	16 125 (16.8)	0.00
Diuretics	45 815 (25.0)	31 676 (27.2)	0.05	25 086 (26.2)	25 141 (26.2)	0.00
Systemic antibiotics	114 888 (62.6)	74 939 (64.4)	0.04	61 183 (63.9)	61 098 (63.8)	0.00
Oral anticoagulants	3600 (2.0)	1471 (1.3)	0.06	1296 (1.4)	1340 (1.4)	0.00
Oral antiplatelets	51 244 (27.9)	37 294 (32.0)	0.09	29 409 (30.7)	29 466 (30.8)	0.00
NSAIDs	109 751 (59.8)	71 448 (61.4)	0.03	58 490 (61.0)	58 337 (60.9)	0.00
Opioids	19 114 (10.4)	12 418 (10.7)	0.01	10 118 (10.6)	10 088 (10.5)	0.00
Systemic corticosteroids	86 960 (47.4)	55 885 (48.0)	0.01	45 760 (47.8)	45 669 (47.7)	0.00
Statins	113 509 (61.9)	73 738 (63.4)	0.03	61 273 (63.9)	61 121 (63.8)	0.00
Other lipid-lowering agents	47 351 (25.8)	29 329 (25.2)	0.01	24 956 (26.0)	24 869 (26.0)	0.00
Vitamin E	14 366 (7.8)	10 511 (9.0)	0.04	8525 (8.9)	8406 (8.8)	0.00
Nitrates	10 435 (5.7)	4401 (3.8)	0.09	3936 (4.1)	4005 (4.2)	0.00
Antidiabetic drugs use*						
Insulin	16 190 (8.8)	11 936 (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	131 146 (71.5)	96 152 (82.6)	0.27	77 600 (81.0)	77 293 (80.7)	0.01
Sulfonylureas	67 199 (36.6)	55 606 (47.8)	0.23	44 058 (46.0)	43 708 (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	93 614 (51.0)	79 927 (68.7)	0.37	63 427 (66.2)	62 978 (65.7)	0.01
Diabetic complications*						
Nephropathy	7407 (4.0)	5987 (5.1)	0.05	4619 (4.8)	4540 (4.7)	0.00
Neuropathy	18 812 (10.3)	15 687 (13.5)	0.10	11 976 (12.5)	12 000 (12.5)	0.00
Retinopathy	25 013 (13.6)	17 826 (15.3)	0.05	14 393 (15.0)	14 306 (14.9)	0.00
Level of antidiabetic treatments*			0.43			0.01
1	74 165 (40.4)	24 584 (21.1)		23 095 (24.1)	23 539 (24.6)	
2	93 130 (50.8)	79 876 (68.6)		63 212 (66.0)	62 814 (65.6)	
3	16 190 (8.8)	11 936 (10.3)		9507 (9.9)	9461 (9.9)	
CCI groups*			0.21			0.00
0	35 872 (19.6)	14 734 (12.7)		13 090 (13.7)	13 369 (14.0)	
1–2	84 028 (45.8)	53 535 (46.0)		44 784 (46.7)	44 767 (46.7)	
≥3	63 585 (34.7)	48 127 (41.3)		37 940 (39.6)	37 678 (39.3)	

**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.
†Assessed a year prior to the index date.
ASD, absolute standardised difference; CCB, calcium channel blocker; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; NSAID, non-steroidal anti-inflammatory drug; PS, propensity score; RAS, renin-angiotensin system; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

of the main analysis in both cohorts. In the analysis assessing ascites and oesophageal 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 to 0.93) groups. In patients with reduced renal function (eGFR≤60 mL/min/1.73 m^2), SGLT-2i was shown to have less favourable effects compared with GLP-1RA (HR 1.45, 95% CI 1.03 to 2.06) (online supplemental eTables 7–18).

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, oesophageal 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 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 with

	Exposure		Comparator		RD per 1000 PYs (95% CI)	Adjusted HR (95% CI)
	Events	IR per 1000 PYs (95% CI)	Events	IR per 1000 PYs (95% CI)		
(A) SGLT-2i vs GLP-1RA						
Primary outcome						
Hepatic decompensation events	237	10.61 (9.34 to 12.05)	173	14.21 (12.24 to 16.50)	-3.60 (-6.12 to -1.09)	0.93 (0.76 to 1.14)
Secondary outcome						
Ascites	180	8.03 (6.94 to 9.30)	108	8.84 (7.32 to 10.68)	-0.81 (-2.85 to 1.23)	1.12 (0.88 to 1.43)
Oesophageal varices with bleeding	14	0.62 (0.37 to 1.05)	10	0.82 (0.44 to 1.52)	-0.20 (-0.80 to 0.41)	0.80 (0.35 to 1.83)
Hepatic failure	68	3.02 (2.38 to 3.83)	64	5.24 (4.10 to 6.69)	-2.21 (-3.69 to -0.74)	0.71 (0.50 to 1.00)
Liver transplant	5	0.22 (0.09 to 0.53)	17	1.39 (0.86 to 2.23)	-1.17 (-1.85 to -0.48)	0.25 (0.09 to 0.70)
Liver-cause death	6	0.27 (0.12 to 0.59)	8	0.65 (0.33 to 1.30)	-0.39 (-0.89 to 0.11)	0.45 (0.15 to 1.32)
All-cause death	114	5.05 (4.20 to 6.07)	56	4.57 (3.51 to 5.93)	0.48 (-1.03 to 2.00)	1.24 (0.90 to 1.72)
(B) SGLT-2i vs TZD						
Primary outcome						
Hepatic decompensation events	1666	7.64 (7.28 to 8.02)	1954	10.18 (9.73 to 10.64)	-2.53 (-3.12 to -1.95)	0.77 (0.72 to 0.82)
Secondary outcome						
Ascites	1150	5.25 (4.96 to 5.57)	1380	7.16 (6.79 to 7.54)	-1.90 (-2.39 to -1.42)	0.75 (0.70 to 0.82)
Oesophageal varices with bleeding	120	0.55 (0.46 to 0.65)	138	0.71 (0.60 to 0.84)	-0.17 (-0.32 to -0.01)	0.77 (0.60 to 0.98)
Hepatic failure	579	2.64 (2.43 to 2.86)	676	3.50 (3.24 to 3.77)	-0.86 (-1.20 to -0.52)	0.77 (0.69 to 0.87)
Liver transplant	29	0.13 (0.09 to 0.19)	35	0.18 (0.13 to 0.25)	-0.05 (-0.13 to 0.03)	0.79 (0.48 to 1.29)
Liver-cause death	68	0.31 (0.24 to 0.39)	98	0.51 (0.41 to 0.62)	-0.20 (-0.32 to -0.07)	0.61 (0.45 to 0.84)
All-cause death	948	4.31 (4.04 to 4.59)	1155	5.95 (5.62 to 6.31)	-1.65 (-2.09 to -1.21)	0.73 (0.67 to 0.79)

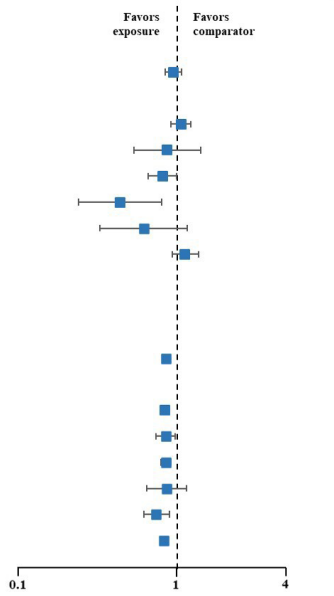

Figure 1 Hepatic decompensation events in 1:1 propensity score-matched initiators of (A) SGLT-2i versus GLP-1RA and (B) SGLT-2i versus TZD. GLP-1RA, glucagon-like peptide-1 receptor agonist; IR, incidence rate; PY, person-year; RD, rate difference; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

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 2237 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 using health insurance claims data from the USA, 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 to 1.28).[19] Similarly, a study using the Clinical Practice Research Datalink (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 to 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 unfavourable 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 with 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 with 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 stimulates 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, where SGLT-2i directly or indirectly encourages 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 normalising nutrient signalling 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.[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

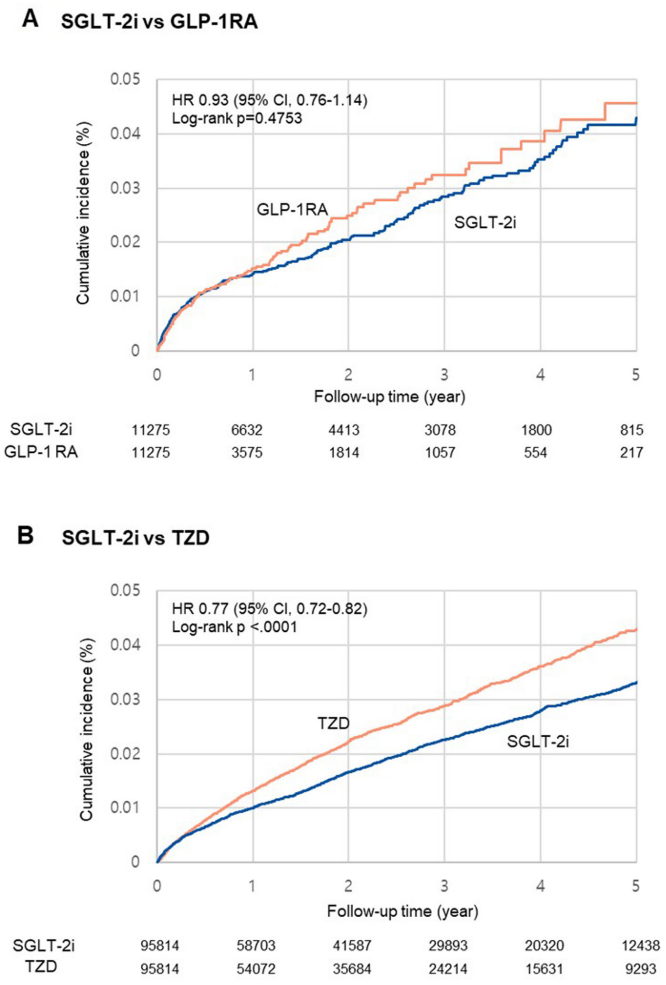

Figure 2 Cumulative incidence of hepatic decompensation events in 1:1 propensity score-matched initiators of (A) SGLT-2i versus GLP-1RA and (B) SGLT-2i versus TZD. GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

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, haemoglobin 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 utilisation 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 (MRI) 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-1RA 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,[9] 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

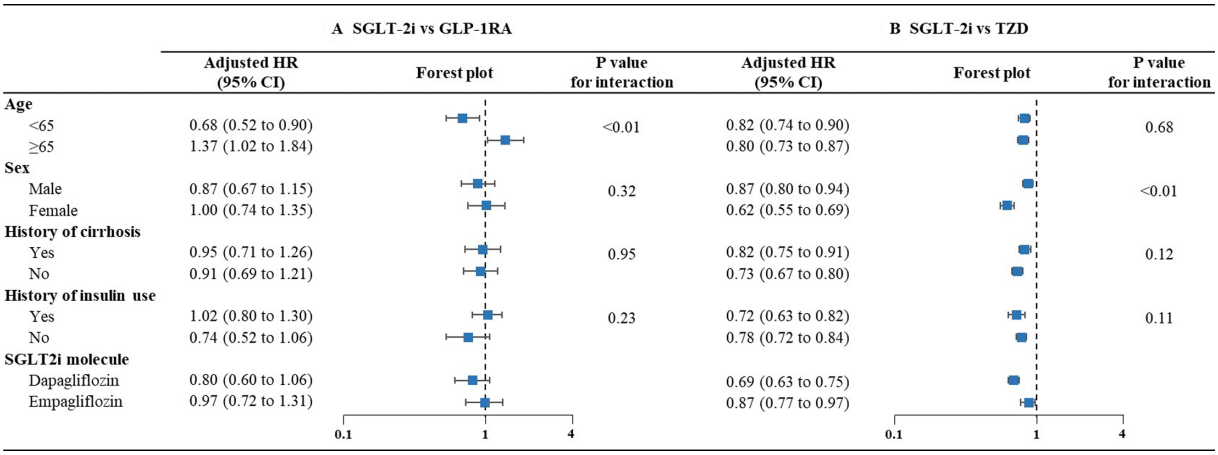

Figure 3 Results of subgroup analyses for hepatic decompensation events in 1:1 propensity score-matched initiators of (A) SGLT-2i versus GLP-1RA and (B) SGLT-2i versus TZD. GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

of GLP-1RA and glucose-dependent insulinotropic polypeptide 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 with 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.

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