Incretin-based drugs and the risk of gallbladder or biliary tract diseases among patients with type 2 diabetes across categories of body mass index: a nationwide cohort study

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Summary

Background Despite emerging evidence of gallbladder or biliary tract diseases (GBD) risk regarding incretin-based drugs, population-specific safety profile considering obesity is lacking. We aimed to assess whether stratification by body mass index (BMI) modifies the measures of association between incretin-based drugs and the risk of GBD.

Methods We conducted an active-comparator, new-user cohort study using a nationwide claims data (2013–2022) of Korea. We included type 2 diabetes (T2D) patients stratified by Asian BMI categories: Normal, 18.5 to <23 kg/m^2; Overweight, 23 to <25 kg/m^2; Obese, ≥25 kg/m^2. The primary outcome was a composite of GBD, including cholelithiasis, cholecystitis, obstruction of the gallbladder or bile duct, cholangitis, and cholecystectomy. We used 1:1 propensity score (PS) matching and estimated hazard ratios (HR) with 95% confidence intervals (CI) using Cox models.

Findings New users of DPP4i and SGLT2i were 1:1 PS matched (n = 251,420 pairs; 186,697 obese, 39,974 overweight, and 24,749 normal weight pairs). The overall HR for the risk of GBD with DPP4i vs. SGLT2i was 1.21 (95% CI 1.14–1.28), with no effect modification by BMI (p-value: 0.83). For the second cohort, new users of GLP1RA and SGLT2i were 1:1 PS matched (n = 45,443 pairs; 28,011 obese, 8948 overweight, and 8484 normal weight pairs). The overall HR for the risk of GBD with GLP1RA vs. SGLT2i was 1.27 (1.07–1.50), with no effect modification by BMI (p-value: 0.73).

Interpretation The increased risks of GBD were presented in both cohorts with no evidence of effect heterogeneity by BMI.

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Keywords: Gallbladder or biliary tract diseases; Body mass index; Diabetes mellitus; Dipeptidyl-peptidase 4 inhibitors; Glucagon-like peptide 1 receptor agonists; Sodium-glucose cotransporter 2 inhibitors; Cohort study

Introduction

Obesity and type 2 diabetes (T2D) are two of the most common chronic diseases caused by metabolic imbalances.[1] The insulin resistance and excessive cholesterol synthesis by the liver seen in patients with these conditions are known to lead to supersaturation of bile and decreased gallbladder contractility, leading to various gallbladder or biliary tract diseases (GBD).[2]

Incretin-based drugs, namely dipeptidyl peptidase 4 inhibitors (DPP4i) and glucagon-like peptide 1 receptor

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Research in context

Evidence before this study

Randomized clinical trials of glucagon-like peptide 1 receptor agonists (GLP1RA) for weight management or cardiovascular outcomes presented higher proportion of patients with acute gallstone diseases (e.g., cholelithiasis, cholecystitis) with liraglutide than with placebo. Meta-analyses of randomized clinical trials suggested increased risk of gallbladder or biliary tract diseases (GBD) after the use of GLP1RA or dipeptidyl peptidase 4 inhibitors (DPP4i). There has been no clinical trial specifically designed to evaluate the association between incretin-based drugs and risk of gallbladder or biliary tract diseases, and existing safety evidence has been generated based on populations with a majority of overweight and obese patients, and normal weight patients were often underrepresented.

Added value of this study

In this nationwide study of more than 1.8 million patients with type 2 diabetes, we assessed the comparative safety of incretin-based drugs vs. SGLT2i in large cohorts stratified by baseline body mass index (BMI) status. Use of either DPP4i or GLP1RA was significantly associated with an increased risk of gallbladder or biliary tract diseases compared to the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i), respectively, on both relative and absolute scales among obese patients in both cohorts.

Implications of all the available evidence

SGLT2i may be the preferred option over the incretin-based drugs for obese patients at risk of gallbladder or biliary tract diseases. Prescribers should be aware of the risks for of gallbladder or biliary tract diseases when using incretin-based drugs among T2D patients regardless of BMI status given the no effect modification by BMI.

agonists (GLP1RA), are widely used as glucose lowering regimen for T2D. However, randomized clinical trials of GLP1RA for weight management or cardiovascular outcomes presented higher proportion of patients with acute gallstone diseases (e.g., cholelithiasis, cholecystitis) with liraglutide (GLP1RA) than with placebo.[3,4] Additionally, meta-analyses of randomized clinical trials suggested increased risk of GBD after the use of GLP1RA or DPP4i.[4–7] Biological mechanisms underlying the association between the use of incretin-based drugs and the risk of GBD are not clear, but might be attributed to gallbladder motility inhibition or delayed gallbladder emptying.[8] However, there has been no clinical trial specifically designed to evaluate the association between incretin-based drugs and risk of GBD, and existing safety evidence regarding this clinical topic has been generated based on populations with a majority of overweight and obese patients, and normal weight patients were often underrepresented.[3–7,9] Despite the fact that obesity itself is an independent risk factor for GBD, there is a lack of safety studies evaluating the heterogeneity in the risk of GBD associated with incretin-based drugs across obesity status.

We hypothesized that stratification of patients with type 2 diabetes taking antidiabetic drugs (incretin-based drugs or comparator drug) by body mass index (BMI) would modify the measures of association between the drugs and the risk of GBD. Therefore, we conducted a active-comparator, new-user cohort study to emulate a target trial stratifying individuals into three categories: normal weight, overweight, and obesity. We aimed to evaluate the association between the use of DPP4i and GLP1RA and the risk of GBD compared to the use of comparator drug within each BMI subgroup in large population based cohorts.

Methods

Data source

We utilized health administrative claims data from January 1, 2013, to December 31, 2022, provided by the National Health Insurance Service (NHIS), the sole health insurance provider in South Korea. The NHIS database includes claims data for approximately 97% of the Korean population, which exceeds 50 million individuals. Sociodemographic variables such as age, sex, residence, income level, health insurance types are included. Additionally, healthcare utilization information, including diagnoses, prescriptions, medical procedures, and health examinations records, was also available. Diagnoses were coded according to the International Classification of Diseases, 10th Revision (ICD-10), and drugs were coded based on domestic chemical codes mapped to the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO). A range of clinical variables such as BMI (calculated as the ratio of weight [kg] and height squared [m^2]), waist circumference, fasting blood glucose, blood pressure, and cholesterol levels were verified through biennial records from the National Health Screening Program (NHSP) for the entire population (non-mandatory). This study was approved by the institutional review board of Sungkyunkwan University (SKKU 2024-03-020) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (Supplement 2).[10]

Study population and design

Pursuing the target trial emulation design framework,[11] we emulated the analysis of a hypothetical trial to enhance the robustness of causal inference using an

observational claims database. We conducted a cohort study based on pre-specified criteria, which included study participants eligibility, balance of baseline characteristics between treatment groups, start and end of follow-up, and assessment of outcome variables (eTable 1 in Supplement 1). Adult patients aged 18 years or older with type 2 diabetes were selected based on ICD-10 codes of E11 to E14 during the study period from January 1, 2013, to December 31, 2022. We constructed two distinct cohorts of new users for each type of incretin-based drug. The first cohort consist of new users of DPP4i (alogliptin, evogliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, and vildagliptin) compared to new users of sodium-glucose cotransporter 2 inhibitors (SGLT2i). The second cohort comprised new users of GLP1RA (albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide) in comparison with new users of SGLT2i. We identified all individuals who initiated these study drugs between September 1, 2014, and December 31, 2022, accounting for the first date of SGLT2i reimbursement in Korea. The index date (time zero) was defined as the date of the first prescription of the study drug (eFigure 1 in Supplement 1).

Then, we excluded individuals diagnosed with end-stage renal disease or who received dialysis within a year prior to the index date considering contraindication to SGLT2i. To ensure the identification of incident cases, patients with a prior diagnosis of gallbladder or biliary disease, or biliary cancer any time before the index date were also excluded. Additionally, patients who had undergone bariatric surgery within the year before the index date were excluded, as rapid weight loss is a known risk factor for gallstone formation.[12] Finally, we excluded patients who initiated both incretin-based drug and comparator SGLT2i on the same date to avoid exposure misclassification.

Eligible individuals were categorized into three groups based on BMI measured within 36 months prior to the index date: Normal weight, 18.5 to <23 kg/m^2; Overweight, 23 to <25 kg/m^2; Obesity, ≥25 kg/m^2 (eFigure 2 and 3 in Supplement 1). The cutoffs for BMI were based on the WHO recommendations for Asian population.[13] Those without BMI values within 36 months prior to the index date or with BMI <18.5 kg/m^2 were excluded. We excluded underweight patients from our study population, since we could not rule out the potential impact of their underweight status on drug prescribing, nor the presence of associated unmeasured confounders (e.g., frailty, low muscle mass, severe illness, nutritional deficiencies).

Exposures and follow-up

The drugs of interest were DPP4i and GLP1RA. We selected SGLT2i (dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin) as the active-comparator as it is not known to be associated with GBD and share the same line of therapy with incretin-based drugs in type 2 diabetes (i.e., second- or third-line antidiabetic drug). Patients were followed from the index date until the outcome occurrence, treatment change (either switching to or adding a comparator drug), treatment discontinuation, death, or end of the study period (December 31, 2022), whichever occurs earlier (eTables 2 and 3 in Supplement 1). We introduced a 90-day grace period to determine treatment discontinuation; therefore, patients were considered as exposed within 90 days after the most recent filled prescription days supply ran out.

Outcome definition

We considered a composite outcome of GBD comprised cholelithiasis (ICD-10: K80), cholecystitis (K81), obstruction of gallbladder or bile duct, cholangitis (K82–K83), major complications of gallstones (biliary acute pancreatitis [K85.1], disorders of gallbladder and biliary tract in diseases classfied elsewhere [K87.0], gallstone ileus [K56.3]) and cholecystectomy. All outcomes, except for cholecystectomy, were identified through diagnosis codes in the primary or secondary position in the inpatient setting. Cholecystectomy was identified through domestic procedural code (eTable 4 in Supplement 1). We also evaluated cholecystectomy as a separate outcome, considering that cholecystectomy is the preferred option for treatment of symptomatic cholelithiasis.[14]

Covariates

We assessed the calendar year and age at the index date, as well as the number of antidiabetic medications (other than incretin-based drugs and SGLT2i) prescribed in the year prior to the index date. We also defined three levels of diabetes treatment based on the number of antidiabetic medications (excluding the study drugs) prescribed in the year preceding the index date: level 1, taking none or only one class of antidiabetic medication other than insulin; level 2, taking ≥2 different classes of antidiabetic medications without insulin; and level 3, taking insulin with or without other classes of antidiabetic medications. Clinical characteristics, including the Charlson comorbidity index, comorbidities and comedications, were assessed within the year prior to the index date. Smoking (categorized as never, past, current, or unknown) and drinking behaviors (yes, no, or unknown) were also obtained from the NHSP survey results. Additionally, as proxies for health-seeking behavior, the number of outpatient visits, hospitalizations, visits to internal medicine specialists, endocrinologists, and cardiologists were evaluated within the year before the index date. The specialties of the physicians who prescribed the drugs of interest to each treatment group on the index date were also recorded. A complete list of covariates is provided in eTable 5 in Supplement 1.

Clinical variables from the NHSP were available for a subset of population, with missing rates ranging from 0.1% to 39.3% (eTables 6 and 7 in Supplement 1). We assessed waist circumference, blood pressure, and results from blood test conducted on venous samples after a fasting period of at least 8 h. These tests included fasting blood glucose, total cholesterol, low- and high-density cholesterol, triglycerides, hemoglobin, serum creatinine, estimated glomerular filtration rate calculated using the modification of diet in renal disease study equation, and liver enzymes levels (aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase). All clinical variables were assessed within three years prior to the index date and were only included in the propensity score model for sensitivity analysis.

Statistical analyses

Descriptive statistics were employed to compare patient's baseline characteristics in each cohort. Continuous variables were presented as means with standard deviations, while categorial variables were summarized as frequency and proportions. Propensity score (PS) matching (1:1) was utilized to control for potential confounders in each cohort (DPP4i vs. SGLT2i; GLP1RA vs. SGLT2i). We estimated the PS for each BMI stratum and then pooled the three matched BMI strata to create the total PS matched population for each cohort. Within each BMI stratum, patients from each treatement group were matched using the nearest neighbor method (without replacement) with a maximum caliper of 0.01 on the PS scale. This approach aimed to estimate the average treatment effect in the treated (ATT) for whom comparator matches could be found within the BMI strata. Multivariable logistic regression models were used to estimate the predicted probability of initiating incretin-based drugs (DPP4i or GLP1RA) vs. SGLT2i, given all the baseline covariates mentioned above. Absolute standardized differences greater than 0.1 were considered indicative of significant covariate imbalances between the treatment groups. Incidence rates (IRs) and incidence rate differences (RDs) per 1000 person-years with 95% confidence intervals (CIs) were estimated based on the Poisson distribution. Cumulative incidence curves for the primary outcome in each treatment group were plotted using the Kaplan–Meier method. Log-rank p-values were estimated to test differences between treatment groups. We also calculated the number needed to harm (NNH) over one and five years of follow-up for patients taking each incretin drug. Cox proportional hazard models (stratified by BMI strata) were employed to estimate hazard ratios (HRs) and 95% CIs for the risk of GBD associated with incretin-based drugs vs. SGLT2i. p-values for homogeneity were calculated on both the relative (HR) and absolute (RD) scales, and values less than 0.05 were considered indicative of treatment heterogeneity among BMI strata. To reconfirm the risk of GBD presented in stratified populations, we also modeled baseline BMI as a continuous variable using restricted cubic spline model with 5 knots placed on 5th, 27.5th, 50th, 72.5th, and 95th percentile.

Several additional analyses were conducted. First, we stratified patients by age (18–65 years, >65 years), sex (male, female), history of gastrointestinal (GI) diseases (gastric disease, irritable bowel disease, inflammatory bowel disease, pancreatitis, liver disease, diverticular disease, appendicitis), and history of diabetic neuropathy, and repeated the main analysis to test for potential effect modifications. p-value for interaction <0.05 was used to denote significant heterogeneity amongst subgroups. Second, we conducted an intention-to-treat analysis, carrying forward the initial treatment for 365 days without accounting for drug switching or discontinuation to address potential informative censoring. Third, the main analysis was repeated by varying the grace period to 60 days to consider for potential exposure misclassification. Fourth, we applied the PS fine stratification weighting method to control for potential confounders within each cohort and measured the average treatment effect (ATE) in whole population. Fifth, clinical variables from health examination results were additionally included in the PS model. This analysis was conducted for a subset of population with the variables available. Sixth, we conducted multiple imputation analysis based on the 'multiple imputation by chained equations' algorithm to impute missing clinical variables. The 5 imputed datasets using SAS MI procedure were analyzed separately to estimate the HRs, and then combined using MIANALYZE procedure. Finally, the main analysis was repeated in a restricted population with BMI records available within a year prior to index date. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics 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 2024-03-020).

Role of the funding source

The funders had no role in the study design, collection, analysis, interpretation of data, writing of the report, and the decision to submit the article for publication.

Results

Characteristics of study cohorts

DPP4i vs. SGLT2i

A total of 1,619,901 and 252,037 new users of DPP4i and SGLT2i were identified, respectively, with a mean

age of 59.8 years (eTable 8 in Supplement 1). After 1:1 PS matching, we identified 251,420 pairs in total; 24,749 pairs (9.8%) for normal weight, 39,974 pairs (15.9%) for overweight, and 186,697 pairs (74.3%) for obese group (eFigure 1 in Supplement 1). As detailed in Table 1, patients in the higher BMI groups were younger and more likely to have a history of liver disease, hypertension, and alcohol consumption. They also exhibited higher blood pressure, total cholesterol, triglycerides, and liver enzyme levels. Patients in the lower BMI groups were more frequently treated with insulin and metformin and had higher level of diabetes treatment and CCI scores.

GLP1RA vs. SGLT2i

A total of 45,457 and 728,047 new users of GLP1RA and SGLT2i were identified, respectively, with a mean age of 57.4 years (eTable 9 in Supplement 1). After 1:1 PS matching, we identified 45,443 pairs in total; 8484 pairs (18.7%) for normal weight, 8948 pairs (19.7%) for overweight, and 28,011 pairs (61.6%) for obese group (eFigure 2 in Supplement 1). As presented in Table 2, patients in the higher BMI groups were younger and more likely to have a history of hypertension and alcohol consumption. They also presented higher blood pressure, triglycerides, and liver enzyme but lower fasting blood glucose levels.

All baseline characteristics, including clinical variables not included in the PS model, were balanced between treatment groups within each BMI group for both cohorts presenting ASD less than 0.1 (eTables 8 and 9 in Supplement 1). Also, PS distributions were overlapped between treatment groups after PS matching (eFigures. 4 and 5 in Supplement 1).

Comparative GBD safety for each cohort

DPP4i vs. SGLT2i

During a mean follow-up of 2.0 years, the risk of GBD increased with DPP4i vs. SGLT2i in total cohort (HR 1.21, 95% CI 1.14–1.28), overweight (1.26, 1.09–1.47) and obese (1.20, 1.13–1.29) groups, while the risk was not significant in the normal weight group (1.17, 0.97–1.42). The incidence rates of GBD per 1000 person-years were 5.00 (95% CI 4.81–5.19) for DPP4i and 4.14 (95% CI 3.96–4.33) for SGLT2i, corresponding to RD of 0.85 (95% CI 0.59–1.12). Increased risk of GBD was also observed on the absolute scale in the overweight (RD 0.96, 95% CI 0.32–1.61) and obese group (RD 0.86, 95% CI 0.55–1.17). The cubic spline analysis also presented a significant risk of GBD around BMI value of 22.5, with continued risk in the obese range (eFigure 6). However, no evidence of effect heterogeneity among the BMI strata was found on either the absolute (p for homogeneity = 0.866) or relative scales (p for homogeneity = 0.826) (Fig. 1). The NNH at 5 year was 247 for obese, 233 for overweight, and 310 for normal weight group. Kaplan–Meier curves for the cumulative incidence of GBD were consistent with these findings across all BMI strata (Fig. 2).

GLP1RA vs. SGLT2i

During a mean follow-up of 1.3 years, the risk of GBD increased with GLP1RA vs. SGLT2i in total cohort (1.27, 1.07–1.50) and obese (1.24, 1.01–1.54) group. The risk was not significant in the overweight (1.19, 0.82–1.73) and normal (1.46, 0.98–2.18) groups. The incidence rates of GBD per 1000 person-years were 5.66 (95% CI 5.00–6.41) for GLP1RA and 4.30 (95% CI 3.86–4.79) for SGLT2i, corresponding to RD of 1.36 (95% CI 0.52–2.20). Increased risk of GBD was also observed on the absolute scale in the obese (RD 1.17, 95% CI 0.15–2.20) and normal groups (2.22, 0.03–4.41). The cubic spline analysis presented the point estimate of HR higher than 1 across all BMI range but with a wide confidence interval (eFigure 6). There was no evidence for effect heterogeneity among the BMI strata on either the absolute (p for homogeneity = 0.690) or relative scales (p for homogeneity = 0.731) (Fig. 1). The NNH at 5 year was 198 for obese, 248 for overweight, and 141 for normal weight group. Kaplan–Meier curves for the cumulative incidence of GBD were consistent with these results across all BMI strata (Fig. 2).

Subgroup and sensitivity analyses

Subgroup analyses revealed no significant effect modification for the first cohort (DPP4i vs. SGLT2i), with a consistently increased risk remaining across all subgroups of the obese group. For the second cohort (GLP1RA vs. SGLT2i), an effect modification by GI history was presented in overweight group, with a higher risk observed in patients with a history of GI diseases (HR 1.40, 95% CI 0.91–2.13) than their counterpart (0.45, 0.19–1.05; p for interaction = 0.0125). In addition, an effect modification by age group was presented in obese group, with a higher risk observed in older patients (1.61, 1.13–2.29) than their counterpart (1.03, 0.79–1.34; p for interaction = 0.0185) (Fig. 3). Assessing cholecystectomy as a separate outcome yielded consistent results with the composite GBD outcome (eTable 10 in Supplement 1). A range of sensitivity analyses supported the main findings, with detailed descriptions provided in eTables 11–16 in Supplement 1.

Discussion

In this nationwide study of more than 1.8 million patients with diabetes, we assessed the comparative safety of incretin-based drugs vs. SGLT2i in large cohorts stratified by BMI status. Both DPP4i and GLP1RA were associated with an increased risk of GBD compared to SGLT2i. There was no evidence of effect heterogeneity by BMI status in either cohort. The increased risk of GBD remained significant on both relative and absolute scales among obese patients in both cohorts.

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m^2)			Overweight (23 ≤ BMI <25 kg/m^2)			Obese (BMI ≥25 kg/m^2)			Overall		
	DPP4i (n = 24,749)	SGLT2i (n = 24,749)	ASD	DPP4i (n = 39,974)	SGLT2i (n = 39,974)	ASD	DPP4i (n = 186,697)	SGLT2i (n = 186,697)	ASD	DPP4i (n = 251,420)	SGLT2i (n = 251,420)	ASD
Follow-up years; mean (SD)	2.25 (2.1)	1.59 (1.7)		2.27 (2.0)	1.76 (1.8)		2.02 (1.9)	1.88 (1.8)		2.08 (1.9)	1.84 (1.8)	
Body mass index; mean (SD), kg/m^2	21.6 (1.1)	21.6 (1.1)	0.001	24.03 (0.6)	24.03 (0.6)	0.003	29.38 (3.9)	29.42 (3.7)	0.009	27.77 (4.4)	27.79 (4.3)	0.006
Cohort entry year; n (%)			0.047			0.048			0.051			0.043
2014	707 (2.9)	729 (3.0)		925 (2.3)	935 (2.3)		3025 (1.6)	3005 (1.6)		4657 (1.9)	4669 (1.9)	
2015	1926 (7.8)	1792 (7.2)		2662 (6.7)	2557 (6.4)		10,174 (5.5)	10,354 (5.6)		14,762 (5.9)	14,703 (5.9)	
2016	2450 (9.9)	2473 (10.0)		3595 (9.0)	3586 (9.0)		15,211 (8.2)	15,655 (8.4)		21,256 (8.5)	21,714 (8.6)	
2017	2823 (11.4)	2872 (11.6)		4557 (11.4)	4588 (11.5)		19,614 (10.5)	19,735 (10.6)		26,994 (10.7)	27,195 (10.8)	
2018	2600 (10.5)	2606 (10.5)		4227 (10.6)	4361 (10.9)		20,381 (10.9)	20,453 (11.0)		27,208 (10.8)	27,420 (10.9)	
2019	3438 (13.9)	3469 (14.0)		5910 (14.8)	5991 (15.0)		28,195 (15.1)	27,872 (14.9)		37,543 (14.9)	37,332 (14.9)	
2020	3507 (14.2)	3489 (14.1)		5990 (15.0)	5960 (14.9)		29,724 (15.9)	29,452 (15.8)		39,221 (15.6)	38,901 (15.5)	
2021	4144 (16.7)	4181 (16.9)		6778 (17.0)	6762 (16.9)		33,864 (18.1)	33,682 (18.0)		44,786 (17.8)	44,625 (17.8)	
2022	3154 (12.7)	3138 (12.7)		5330 (13.3)	5234 (13.1)		26,509 (14.2)	26,489 (14.2)		34,993 (13.9)	34,861 (13.9)	
Age; mean (SD)	59.97 (11.8)	60.01 (11.5)	0.004	58.77 (11.2)	58.8 (10.9)	0.003	53.55 (12.5)	53.59 (12.1)	0.003	55.01 (12.5)	55.05 (12.1)	0.003
Age group; n (%)			0.001			0.002			0.005			0.004
18–65	17,041 (68.9)	17,032 (68.8)		29,348 (73.4)	29,310 (73.3)		155,837 (83.5)	155,474 (83.3)		202,226 (80.4)	201,816 (80.3)	
>65	7708 (31.1)	7717 (31.2)		10,626 (26.6)	10,664 (26.7)		30,860 (16.5)	31,223 (16.7)		49,194 (19.6)	49,604 (19.7)	
Sex; n (%)			0.001			0.010			0.004			0.002
Male	13,905 (56.2)	13,965 (56.4)		23,804 (59.6)	23,884 (59.8)		111,669 (59.8)	111,846 (59.9)		149,378 (59.4)	149,695 (59.5)	
Female	10,844 (43.8)	10,784 (43.6)		16,170 (40.5)	16,090 (40.3)		75,028 (40.2)	74,851 (40.1)		102,042 (40.6)	101,725 (40.5)	
Antihyperglycemic medications; n (%)												
Alpha-glucosidase inhibitors	1178 (4.8)	1176 (4.8)	0.001	1184 (3.0)	1157 (2.9)	0.004	2716 (1.5)	2745 (1.5)	0.001	5078 (2.0)	5078 (2.0)	0.001
GLP1 RAs	73 (0.3)	64 (0.3)	0.007	88 (0.2)	93 (0.2)	0.003	602 (0.3)	685 (0.4)	0.008	763 (0.3)	842 (0.3)	0.006
Insulin	2623 (10.6)	2621 (10.6)	0.001	3115 (7.8)	3202 (8.0)	0.008	11,651 (6.2)	11,697 (6.3)	0.001	17,389 (6.9)	17,520 (7.0)	0.002
Meglitinides	146 (0.6)	143 (0.6)	0.002	168 (0.4)	168 (0.4)	0.001	436 (0.2)	422 (0.2)	0.002	750 (0.3)	733 (0.3)	0.001
Metformin	13,786 (55.7)	13,720 (55.4)	0.005	21,384 (53.5)	21,428 (53.6)	0.002	88,395 (47.4)	88,759 (47.5)	0.004	123,565 (49.2)	123,907 (49.3)	0.003
Sulfonylureas	6792 (27.4)	6632 (26.8)	0.015	9108 (22.8)	9048 (22.6)	0.004	32,122 (17.2)	32,053 (17.2)	0.001	48,022 (19.1)	47,733 (19.0)	0.003
Thiazolidinediones	1474 (6.0)	1435 (5.8)	0.007	2142 (5.4)	2096 (5.2)	0.005	10,274 (5.5)	10,094 (5.4)	0.004	13,890 (5.5)	13,625 (5.4)	0.005
Number of antihyperglycemic medications being taken; n (%)			0.022			0.001			0.001			0.001
0–1	16,872 (68.2)	17,045 (68.9)		29,386 (73.5)	29,438 (73.6)		147,415 (79.0)	147,508 (79.0)		193,673 (77.0)	193,991 (77.2)	
2–3	7597 (30.7)	7427 (30.0)		10,333 (25.9)	10,281 (25.7)		38,431 (20.6)	38,319 (20.5)		56,361 (22.4)	56,027 (22.3)	
4+	280 (1.1)	277 (1.1)		255 (0.6)	255 (0.6)		851 (0.5)	870 (0.5)		1386 (0.6)	1402 (0.6)	
Level of diabetes treatment[a]; n (%)			0.037			0.001			0.001			0.001
1	16,255 (65.7)	16,416 (66.3)		28,736 (71.9)	28,783 (72.0)		145,047 (77.7)	145,097 (77.7)		190,038 (75.6)	190,296 (75.7)	
2	5871 (23.7)	5712 (23.1)		8123 (20.3)	7989 (20.0)		29,999 (16.1)	29,903 (16.0)		43,993 (17.5)	43,604 (17.3)	
3	2623 (10.6)	2621 (10.6)		3115 (7.8)	3202 (8.0)		11,651 (6.2)	11,697 (6.3)		17,389 (6.9)	17,520 (7.0)	
Diabetes related conditions; n (%)												
Diabetic nephropathy	908 (3.7)	881 (3.6)	0.006	1349 (3.4)	1355 (3.4)	0.001	5488 (2.9)	5477 (2.9)	0.001	7745 (3.1)	7713 (3.1)	0.001
Diabetic neuropathy	3339 (13.5)	3200 (12.9)	0.017	4402 (11.0)	4384 (11.0)	0.001	16,139 (8.6)	15,985 (8.6)	0.003	23,880 (9.5)	23,569 (9.4)	0.004
Diabetic retinopathy	4095 (16.6)	4124 (16.7)	0.003	5776 (14.5)	5682 (14.2)	0.007	19,990 (10.7)	20,151 (10.8)	0.003	29,861 (11.9)	29,957 (11.9)	0.001
Hypoglycaemia	89 (0.4)	96 (0.4)	0.005	87 (0.2)	100 (0.3)	0.007	288 (0.2)	303 (0.2)	0.002	464 (0.2)	499 (0.2)	0.003

(Table 1 continues on next page)

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m^2)			Overweight (23 ≤ BMI <25 kg/m^2)			Obese (BMI ≥25 kg/m^2)			Overall		
	DPP4i (n = 24,749)	SGLT2i (n = 24,749)	ASD	DPP4i (n = 39,974)	SGLT2i (n = 39,974)	ASD	DPP4i (n = 186,697)	SGLT2i (n = 186,697)	ASD	DPP4i (n = 251,420)	SGLT2i (n = 251,420)	ASD
(Continued from previous page)												
Gastrointestinal diseases; n (%)												
Gastric disease	15,341 (62.0)	15,350 (62.0)	0.001	24,886 (62.3)	24,799 (62.0)	0.004	112,185 (60.1)	112,523 (60.3)	0.004	152,412 (60.6)	152,672 (60.7)	0.002
Irritable bowel disease	2337 (9.4)	2304 (9.3)	0.005	3622 (9.1)	3575 (8.9)	0.004	14,637 (7.8)	14,540 (7.8)	0.002	20,596 (8.2)	20,419 (8.1)	0.003
Inflammatory bowel disease	37 (0.2)	39 (0.2)	0.002	59 (0.2)	62 (0.2)	0.002	254 (0.1)	253 (0.1)	0.001	350 (0.1)	354 (0.1)	0.001
Pancreatitis	209 (0.8)	202 (0.8)	0.003	221 (0.6)	201 (0.5)	0.007	733 (0.4)	761 (0.4)	0.002	1163 (0.5)	1164 (0.5)	0.001
Liver disease	3249 (13.1)	3212 (13.0)	0.004	5752 (14.4)	5675 (14.2)	0.006	33,663 (18.0)	33,773 (18.1)	0.002	42,664 (17.0)	42,660 (17.0)	0.001
Diverticular disease	80 (0.3)	78 (0.3)	0.001	152 (0.4)	157 (0.4)	0.002	611 (0.3)	660 (0.4)	0.005	843 (0.3)	895 (0.4)	0.004
Appendicitis	53 (0.2)	48 (0.2)	0.004	87 (0.2)	97 (0.2)	0.005	389 (0.2)	389 (0.2)	0.001	529 (0.2)	534 (0.2)	0.001
Comorbidities; n (%)												
Acute kidney injury	34 (0.1)	39 (0.2)	0.005	83 (0.2)	71 (0.2)	0.007	280 (0.2)	291 (0.2)	0.002	397 (0.2)	401 (0.2)	0.001
Anxiety	1262 (5.1)	1268 (5.1)	0.001	1939 (4.9)	1977 (5.0)	0.004	7931 (4.3)	7993 (4.3)	0.002	11,132 (4.4)	11,238 (4.5)	0.002
Asthma	1229 (5.0)	1286 (5.2)	0.010	2048 (5.1)	2015 (5.0)	0.004	9994 (5.4)	9895 (5.3)	0.002	13,271 (5.3)	13,196 (5.3)	0.001
Atrial fibrillation	577 (2.3)	575 (2.3)	0.001	752 (1.9)	741 (1.9)	0.002	2698 (1.5)	2782 (1.5)	0.004	4027 (1.6)	4098 (1.6)	0.002
Cancer	1123 (4.5)	1164 (4.7)	0.008	1717 (4.3)	1718 (4.3)	0.001	6634 (3.6)	6725 (3.6)	0.003	9474 (3.8)	9607 (3.8)	0.003
Cardiomyopathy	166 (0.7)	162 (0.7)	0.002	192 (0.5)	199 (0.5)	0.003	691 (0.4)	720 (0.4)	0.003	1049 (0.4)	1081 (0.4)	0.002
Chronic kidney disease	284 (1.2)	302 (1.2)	0.007	366 (0.9)	358 (0.9)	0.002	1407 (0.8)	1407 (0.8)	0.001	2057 (0.8)	2067 (0.8)	0.001
Chronic obstructive pulmonary disease	1366 (5.5)	1324 (5.4)	0.007	1856 (4.6)	1819 (4.6)	0.004	6929 (3.7)	6899 (3.7)	0.001	10,151 (4.0)	10,042 (4.0)	0.002
Congestive heart failure	985 (4.0)	925 (3.7)	0.013	1149 (2.9)	1194 (3.0)	0.007	5329 (2.9)	5434 (2.9)	0.003	7463 (3.0)	7553 (3.0)	0.002
Dementia	664 (2.7)	671 (2.7)	0.002	775 (1.9)	789 (2.0)	0.003	2129 (1.1)	2199 (1.2)	0.004	3568 (1.4)	3659 (1.5)	0.003
Depression	1108 (4.5)	1110 (4.5)	0.001	1602 (4.0)	1605 (4.0)	0.001	7252 (3.9)	7212 (3.9)	0.001	9962 (4.0)	9927 (4.0)	0.001
Epilepsy	142 (0.6)	144 (0.6)	0.001	201 (0.5)	207 (0.5)	0.002	890 (0.5)	880 (0.5)	0.001	1233 (0.5)	1231 (0.5)	0.001
Hyperlipidemia	9664 (39.1)	9667 (39.1)	0.001	16,849 (42.2)	16,859 (42.2)	0.001	79,227 (42.4)	79,394 (42.5)	0.002	105,740 (42.1)	105,920 (42.1)	0.001
Hypertension	8915 (36.0)	8849 (35.8)	0.006	16,274 (40.7)	16,487 (41.2)	0.011	91,712 (49.1)	91,852 (49.2)	0.001	116,901 (46.5)	117,188 (46.6)	0.002
Inflammatory arthritis	5451 (22.0)	5401 (21.8)	0.005	8795 (22.0)	8773 (22.0)	0.001	41,685 (22.3)	41,599 (22.3)	0.001	55,931 (22.3)	55,773 (22.2)	0.002
Ischemic heart disease	2841 (11.5)	2825 (11.4)	0.002	4468 (11.2)	4478 (11.2)	0.001	15,782 (8.5)	15,905 (8.5)	0.002	23,091 (9.2)	23,208 (9.2)	0.002
Obstructive sleep apnea	57 (0.2)	47 (0.2)	0.009	113 (0.3)	103 (0.3)	0.005	1199 (0.6)	1205 (0.7)	0.001	1369 (0.5)	1355 (0.5)	0.001
Osteoarthritis	5254 (21.2)	5151 (20.8)	0.010	8409 (21.0)	8355 (20.9)	0.003	37,657 (20.2)	37,661 (20.2)	0.001	51,320 (20.4)	51,167 (20.4)	0.002
Osteoporosis	1647 (6.7)	1636 (6.6)	0.002	2043 (5.1)	2047 (5.1)	0.001	6305 (3.4)	6291 (3.4)	0.001	9995 (4.0)	9974 (4.0)	0.001
Parkinson's disease	55 (0.2)	69 (0.3)	0.011	116 (0.3)	103 (0.3)	0.006	303 (0.2)	286 (0.2)	0.002	474 (0.2)	458 (0.2)	0.001
Pneumonia	1321 (5.3)	1300 (5.3)	0.004	2073 (5.2)	2017 (5.1)	0.006	9233 (5.0)	9245 (5.0)	0.001	12,627 (5.0)	12,562 (5.0)	0.001
Psychosis	54 (0.2)	46 (0.2)	0.007	95 (0.2)	83 (0.2)	0.006	533 (0.3)	545 (0.3)	0.001	682 (0.3)	674 (0.3)	0.001
Renal dysfunction	158 (0.6)	155 (0.6)	0.002	200 (0.5)	215 (0.5)	0.005	992 (0.5)	1008 (0.5)	0.001	1350 (0.5)	1378 (0.6)	0.002
Stroke	893 (3.6)	927 (3.8)	0.007	1217 (3.0)	1251 (3.1)	0.005	4230 (2.3)	4177 (2.2)	0.002	6340 (2.5)	6355 (2.5)	0.001
Thyroid disease	1750 (7.1)	1752 (7.1)	0.001	2700 (6.8)	2763 (6.9)	0.006	12,591 (6.7)	12,664 (6.8)	0.002	17,041 (6.8)	17,179 (6.8)	0.002
Comedications; n (%)												
ACE inhibitors or ARBs	8336 (33.7)	8367 (33.8)	0.003	15,602 (39.0)	15,792 (39.5)	0.010	90,311 (48.4)	90,552 (48.5)	0.003	114,249 (45.4)	114,711 (45.6)	0.004
Anticoagulants	1473 (6.0)	1482 (6.0)	0.002	2121 (5.3)	2103 (5.3)	0.002	6889 (3.7)	6999 (3.8)	0.003	10,483 (4.2)	10,584 (4.2)	0.002
Anticonvulsants	2611 (10.6)	2562 (10.4)	0.006	3797 (9.5)	3743 (9.4)	0.005	16,340 (8.8)	16,187 (8.7)	0.003	22,748 (9.1)	22,492 (9.0)	0.004
Antidepressants	1387 (5.6)	1399 (5.7)	0.002	2060 (5.2)	2100 (5.3)	0.005	9563 (5.1)	9488 (5.1)	0.002	13,010 (5.2)	12,987 (5.2)	0.001
Antipsychotics	4922 (19.9)	4913 (19.9)	0.001	7610 (19.0)	7564 (18.9)	0.003	33,767 (18.1)	33,454 (17.9)	0.004	46,299 (18.4)	45,931 (18.3)	0.004
Benzodiazepines	7694 (31.1)	7689 (31.1)	0.001	12,203 (30.5)	12,083 (30.2)	0.007	49,503 (26.5)	49,802 (26.7)	0.004	69,400 (27.6)	69,574 (27.7)	0.002

(Table 1 continues on next page)

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m²)			Overweight (23 ≤ BMI <25 kg/m²)			Obese (BMI ≥25 kg/m²)			Overall		
	DPP4i (n = 24,749)	SGLT2i (n = 24,749)	ASD	DPP4i (n = 39,974)	SGLT2i (n = 39,974)	ASD	DPP4i (n = 186,697)	SGLT2i (n = 186,697)	ASD	DPP4i (n = 251,420)	SGLT2i (n = 251,420)	ASD
(Continued from previous page)												
Beta-blockers	983 (4.0)	1003 (4.1)	0.004	1515 (3.8)	1486 (3.7)	0.004	6673 (3.6)	6625 (3.6)	0.001	9171 (3.7)	9114 (3.6)	0.001
Bisphosphonates	869 (3.5)	913 (3.7)	0.010	1101 (2.8)	1126 (2.8)	0.004	3305 (1.8)	3388 (1.8)	0.003	5275 (2.1)	5427 (2.2)	0.004
Calcium channel blockers	6733 (27.2)	6654 (26.9)	0.007	12,097 (30.3)	12,096 (30.3)	0.001	70,205 (37.6)	70,312 (37.7)	0.001	89,035 (35.4)	89,062 (35.4)	0.001
Corticosteroids	8574 (34.6)	8517 (34.4)	0.005	14,035 (35.1)	13,899 (34.8)	0.007	65,025 (34.8)	65,433 (35.1)	0.005	87,634 (34.9)	87,849 (34.9)	0.002
Diuretics	3482 (14.1)	3432 (13.9)	0.006	5808 (14.5)	5934 (14.8)	0.009	36,110 (19.3)	36,019 (19.3)	0.001	45,400 (18.1)	45,385 (18.1)	0.001
Nitrates	518 (2.1)	500 (2.0)	0.005	667 (1.7)	670 (1.7)	0.001	2182 (1.2)	2203 (1.2)	0.001	3367 (1.3)	3373 (1.3)	0.001
NSAIDs	14,315 (57.8)	14,217 (57.4)	0.008	23,397 (58.5)	23,344 (58.4)	0.003	109,926 (58.9)	109,870 (58.9)	0.001	147,638 (58.7)	147,431 (58.6)	0.002
Opioids	2368 (9.6)	2360 (9.5)	0.001	3597 (9.0)	3707 (9.3)	0.010	15,602 (8.4)	15,719 (8.4)	0.002	21,567 (8.6)	21,786 (8.7)	0.003
Platelet inhibitors	12,914 (52.2)	13,030 (52.7)	0.009	20,711 (51.8)	20,858 (52.2)	0.007	91,656 (49.1)	91,718 (49.1)	0.001	125,281 (49.8)	125,606 (50.0)	0.003
Sedative hypnotics	2119 (8.6)	2143 (8.7)	0.003	3100 (7.8)	3141 (7.9)	0.004	11,670 (6.3)	11,691 (6.3)	0.001	16,889 (6.7)	16,975 (6.8)	0.001
Tricyclic antidepressant	1311 (5.3)	1305 (5.3)	0.001	1863 (4.7)	1882 (4.7)	0.002	7682 (4.1)	7662 (4.1)	0.001	10,856 (4.3)	10,849 (4.3)	0.001
Proton-pump inhibitors	9692 (39.2)	9796 (39.6)	0.009	15,526 (38.8)	15,519 (38.8)	0.001	69,466 (37.2)	69,561 (37.3)	0.001	94,684 (37.7)	94,876 (37.7)	0.002
Histamine type 2 receptor antagonists	13,766 (55.6)	13,668 (55.2)	0.008	21,533 (53.9)	21,574 (54.0)	0.002	97,274 (52.1)	97,348 (52.1)	0.001	132,573 (52.7)	132,590 (52.7)	0.001
Bile and liver medications	2260 (9.1)	2275 (9.2)	0.002	4142 (10.4)	4107 (10.3)	0.003	31,371 (16.8)	31,379 (16.8)	0.001	37,773 (15.0)	37,761 (15.0)	0.001
Fibrates	1350 (5.5)	1360 (5.5)	0.002	2885 (7.2)	2865 (7.2)	0.002	16,396 (8.8)	16,401 (8.8)	0.001	20,631 (8.2)	20,626 (8.2)	0.001
Statins	11,902 (48.1)	11,909 (48.1)	0.001	20,729 (51.9)	20,804 (52.0)	0.004	93,498 (50.1)	93,609 (50.1)	0.001	126,129 (50.2)	126,322 (50.2)	0.002
Other lipid modifying drugs	2724 (11.0)	2714 (11.0)	0.001	5141 (12.9)	5088 (12.7)	0.004	24,727 (13.2)	24,574 (13.2)	0.002	32,592 (13.0)	32,376 (12.9)	0.003
Charlson Comorbidity Index; n (%)			0.037			0.001			0.001			0.001
0	13,321 (53.8)	13,526 (54.7)		23,033 (57.6)	23,019 (57.6)		110,430 (59.2)	110,371 (59.1)		146,784 (58.4)	146,916 (58.4)	
1	5998 (24.2)	5840 (23.6)		8625 (21.6)	8600 (21.5)		35,407 (19.0)	35,072 (18.8)		50,030 (19.9)	49,512 (19.7)	
2	3279 (13.3)	3252 (13.1)		5368 (13.4)	5392 (13.5)		28,586 (15.3)	28,818 (15.4)		37,233 (14.8)	37,462 (14.9)	
≥3	2151 (8.7)	2131 (8.6)		2948 (7.4)	2963 (7.4)		12,274 (6.6)	12,436 (6.7)		17,373 (6.9)	17,530 (7.0)	
Number of outpatients visits; n (%)			0.001			0.001			0.001			0.001
0–2	1625 (6.6)	1614 (6.5)		2424 (6.1)	2372 (5.9)		11,713 (6.3)	11,461 (6.1)		15,762 (6.3)	15,447 (6.1)	
3–5	2093 (8.5)	2080 (8.4)		3595 (9.0)	3513 (8.8)		17,796 (9.5)	17,837 (9.6)		23,484 (9.3)	23,430 (9.3)	
6+	21,031 (85.0)	21,055 (85.1)		33,955 (84.9)	34,089 (85.3)		157,188 (84.2)	157,399 (84.3)		212,174 (84.4)	212,543 (84.5)	
Number of hospitalizations; n (%)			0.001			0.001			0.082			0.001
0	19,566 (79.1)	19,609 (79.2)		32,437 (81.2)	32,354 (80.9)		154,050 (82.5)	153,786 (82.4)		206,053 (82.0)	205,749 (81.8)	
1–2	4676 (18.9)	4631 (18.7)		6896 (17.3)	6955 (17.4)		30,166 (16.2)	30,385 (16.3)		41,738 (16.6)	41,971 (16.7)	
3+	507 (2.1)	509 (2.1)		641 (1.6)	665 (1.7)		2481 (1.3)	2526 (1.4)		3629 (1.4)	3700 (1.5)	
Number of internal medicine visits; mean (SD)	1.02 (3.3)	1.03 (3.6)	0.002	0.95 (3.7)	0.96 (3.7)	0.002	0.86 (3.2)	0.86 (3.4)	0.001	0.89 (3.3)	0.89 (3.4)	0.001
Number of gastroenterologist visits; mean (SD)	0.25 (1.3)	0.26 (1.3)	0.005	0.24 (1.1)	0.23 (1.2)	0.003	0.22 (1.1)	0.23 (1.1)	0.009	0.23 (1.1)	0.23 (1.1)	0.007
Number of cardiologist visits; mean (SD)	0.57 (1.9)	0.56 (1.7)	0.005	0.53 (1.7)	0.53 (1.6)	0.002	0.45 (1.6)	0.46 (1.5)	0.004	0.48 (1.6)	0.48 (1.5)	0.003
Number of endocrinologist visits; mean (SD)	0.51 (1.7)	0.51 (1.6)	0.001	0.5 (1.7)	0.5 (1.6)	0.003	0.48 (1.6)	0.5 (1.6)	0.011	0.48 (1.6)	0.5 (1.6)	0.009
Prescriber specialty; n (%)												
Internal medicine	2720 (11.0)	2708 (10.9)	0.002	4170 (10.4)	4199 (10.5)	0.002	18,769 (10.1)	18,691 (10.0)	0.001	25,659 (10.2)	25,598 (10.2)	0.001
Gastroenterologist	393 (1.6)	410 (1.7)	0.005	700 (1.8)	682 (1.7)	0.003	3830 (2.1)	3963 (2.1)	0.005	4923 (2.0)	5055 (2.0)	0.004
Endocrinologist	2999 (12.1)	3020 (12.2)	0.003	5554 (13.9)	5590 (14.0)	0.003	28,745 (15.4)	29,787 (16.0)	0.015	37,298 (14.8)	38,397 (15.3)	0.012
Others	18,798 (76.0)	18,772 (75.9)	0.002	29,885 (74.8)	29,857 (74.7)	0.002	137,780 (73.8)	136,800 (73.3)	0.012	186,463 (74.2)	185,429 (73.8)	0.009
Smoking; n (%)			0.031			0.001			0.001			0.001
Never	14,363 (58.0)	14,254 (57.6)		22,665 (56.7)	22,597 (56.5)		104,279 (55.9)	104,123 (55.8)		141,307 (56.2)	140,974 (56.1)	

(Table 1 continues on next page)

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m^2)			Overweight (23 ≤ BMI <25 kg/m^2)			Obese (BMI ≥25 kg/m^2)			Overall		
	DPP4i (n = 24,749)	SGLT2i (n = 24,749)	ASD	DPP4i (n = 39,974)	SGLT2i (n = 39,974)	ASD	DPP4i (n = 186,697)	SGLT2i (n = 186,697)	ASD	DPP4i (n = 251,420)	SGLT2i (n = 251,420)	ASD
(Continued from previous page)												
Past smoker	4747 (19.2)	4840 (19.6)		9016 (22.6)	9071 (22.7)		42,176 (22.6)	42,179 (22.6)		55,939 (22.3)	56,090 (22.3)	
Current smoker	5635 (22.8)	5650 (22.8)		8283 (20.7)	8298 (20.8)		40,212 (21.5)	40,359 (21.6)		54,130 (21.5)	54,307 (21.6)	
Unknown	4 (0.0)	5 (0.0)		10 (0.0)	8 (0.0)		30 (0.0)	36 (0.0)		44 (0.0)	49 (0.0)	
Drinking; n (%)			0.022			0.001			0.001			0.001
Yes	7724 (31.2)	7822 (31.6)		13,640 (34.1)	13,680 (34.2)		69,090 (37.0)	69,376 (37.2)		90,454 (36.0)	90,878 (36.2)	
No	17,015 (68.8)	16,918 (68.4)		26,320 (65.8)	26,283 (65.8)		117,559 (63.0)	117,264 (62.8)		160,894 (64.0)	160,465 (63.8)	
Unknown	10 (0.0)	9 (0.0)		14 (0.0)	11 (0.0)		48 (0.0)	57 (0.0)		72 (0.0)	77 (0.0)	
Clinical variables[b]; mean (SD)												
Waist circumference [cm]	78.1 (5.8)	78.2 (5.9)	0.009	83.3 (5.4)	83.43 (7.1)	0.021	93.93 (9.5)	94.14 (10.7)	0.021	90.69 (10.4)	90.87 (11.3)	0.017
Fasting blood glucose [mg/dL]	160.2 (66.9)	157.6 (64.8)	0.040	155.83 (59.1)	153.38 (57.2)	0.042	153.61 (55.8)	150.52 (53.3)	0.057	154.61 (57.5)	151.67 (55.2)	0.052
Systolic blood pressure [mmHg]	125.5 (15.7)	125.4 (15.5)	0.007	127.67 (15.0)	127.38 (15.0)	0.020	131.39 (15.4)	131.27 (15.3)	0.008	130.22 (15.5)	130.07 (15.4)	0.009
Diastolic blood pressure [mmHg]	76.4 (10.1)	76.4 (10.2)	0.007	78.12 (10.0)	77.89 (10.0)	0.023	81.44 (10.9)	81.4 (10.8)	0.004	80.42 (10.8)	80.35 (10.8)	0.007
Total cholesterol. [mg/dL]	193.9 (49.5)	193.7 (50.7)	0.005	197.34 (50.8)	197.22 (52.4)	0.002	200.96 (50.9)	200.39 (51.9)	0.011	199.63 (50.8)	199.17 (51.9)	0.009
Low density lipoprotein cholesterol [mg/dL]	109.7 (44.7)	109.7 (43.6)	0.001	112.14 (65.7)	111.34 (43.3)	0.014	113.04 (53.1)	112.68 (45.6)	0.007	112.53 (54.6)	112.14 (45.0)	0.008
High density lipoprotein cholesterol [mg/dL]	54.5 (50.4)	54.0 (16.1)	0.012	51.42 (16.1)	51.38 (13.6)	0.002	49.29 (15.1)	49.36 (13.5)	0.005	50.17 (21.8)	50.17 (13.9)	0.001
Triglycerides [mg/dL]	161.4 (158.3)	158.5 (167.9)	0.018	182.89 (163.2)	184 (169.0)	0.007	212.02 (189.8)	209.78 (193.0)	0.012	201.98 (183.4)	200.2 (187.6)	0.010
Serum creatinine [mg/dL]	0.9 (0.3)	0.9 (0.8)	0.002	0.88 (0.7)	0.87 (0.6)	0.009	0.87 (0.4)	0.87 (0.4)	0.017	0.87 (0.5)	0.87 (0.5)	0.013
eGFR [mL/min/1.73 m^2]	91.2 (27.9)	91.2 (27.1)	0.001	90.35 (25.8)	90.09 (24.4)	0.010	91.94 (26.2)	92.05 (25.6)	0.004	91.61 (26.3)	91.66 (25.6)	0.002
Hemoglobin [g/dL]	14.2 (1.7)	14.2 (1.6)	0.016	14.51 (1.6)	14.54 (1.6)	0.019	14.8 (1.6)	14.82 (1.6)	0.014	14.69 (1.6)	14.72 (1.6)	0.015
AST (SGOT) [IU/L]	28.4 (25.8)	28.6 (27.2)	0.010	29.73 (23.2)	29.94 (31.2)	0.008	37.23 (40.4)	37.44 (33.9)	0.006	35.16 (37.1)	35.38 (33.1)	0.006
ALT (SGPT) [IU/L]	27.6 (25.1)	27.9 (24.2)	0.013	32.3 (26.9)	32.7 (27.4)	0.015	47.04 (43.2)	47.53 (43.5)	0.012	42.79 (40.2)	43.25 (40.4)	0.012
GGT [IU/L]	55.3 (100.9)	54.4 (115.7)	0.008	55.94 (79.8)	54.56 (74.7)	0.018	65.94 (75.3)	64.89 (68.9)	0.014	63.3 (79.0)	62.22 (75.8)	0.014

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; ASD, absolute standardized difference; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DPP4i, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transferase; GLP1RA, glucagon like peptide 1 receptor agonists; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SGLT2i, sodium glucose cotransporter 2 inhibitors; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvate transaminase. [a]Defined depending on the number of antidiabetic medication (excluding the study drugs of interest), prescribed in the year preceding the index date: level 1, as taking none or only one class of antidiabetic medication other than insulin, level 2, as taking ≥2 different classes of antidiabetic medication without insulin, and level 3, as taking insulin with or without other classes of antidiabetic medication. [b]Clinical variables were not included in the multivariable logistic regression model for propensity score estimation. Presented descriptive statistics (mean [SD]) here were based on patients with information on these variables available.

Table 1: **Baseline characteristics of patients received DPP4 inhibitors or SGLT2 inhibitors after propensity score matching.**

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m^2)			Overweight (23 ≤ BMI<25 kg/m^2)			Obese (BMI≥25 kg/m^2)			Overall		
	GLP1RA (n = 8484)	SGLT2i (n = 8484)	ASD	GLP1RA (n = 8948)	SGLT2i (n = 8948)	ASD	GLP1RA (n = 28,011)	SGLT2i (n = 28,011)	ASD	GLP1RA (n = 45,443)	SGLT2i (n = 45,443)	ASD
Follow-up years; mean (SD)	0.87 (1.0)	1.38 (1.4)		0.95 (1.1)	1.59 (1.5)		1 (1.1)	1.83 (1.6)		0.97 (1.1)	1.7 (1.6)	
Body mass index; mean (SD), kg/m^2	21.4 (1.2)	21.4 (1.1)	0.001	23.98 (0.6)	23.99 (0.6)	0.016	29.18 (3.8)	29.19 (3.7)	0.002	26.7 (4.4)	26.71 (4.4)	0.002
Cohort entry year; n (%)			0.036			0.034			0.036			0.036
2014	0 (0.0)	0 (0.0)		5 (0.1)	1 (0.0)		53 (0.2)	54 (0.2)		58 (0.1)	55 (0.1)	
2015	33 (0.4)	21 (0.3)		27 (0.3)	22 (0.3)		241 (0.9)	220 (0.8)		301 (0.7)	263 (0.6)	
2016	350 (4.1)	342 (4.0)		442 (4.9)	458 (5.1)		1598 (5.7)	1658 (5.9)		2390 (5.3)	2458 (5.4)	
2017	1137 (13.4)	1226 (14.5)		1242 (13.9)	1249 (14.0)		4158 (14.8)	4262 (15.2)		6537 (14.4)	6737 (14.8)	
2018	1503 (17.7)	1441 (17.0)		1516 (16.9)	1465 (16.4)		4670 (16.7)	4628 (16.5)		7689 (16.9)	7534 (16.6)	
2019	1504 (17.7)	1485 (17.5)		1558 (17.4)	1603 (17.9)		4912 (17.5)	4858 (17.3)		7974 (17.6)	7946 (17.5)	
2020	1120 (13.2)	1141 (13.5)		1203 (13.4)	1174 (13.1)		3767 (13.5)	3802 (13.6)		6090 (13.4)	6117 (13.5)	
2021	1459 (17.2)	1455 (17.2)		1532 (17.1)	1537 (17.2)		4553 (16.3)	4556 (16.3)		7544 (16.6)	7548 (16.6)	
2022	1378 (16.2)	1373 (16.2)		1423 (15.9)	1439 (16.1)		4059 (14.5)	3973 (14.2)		6860 (15.1)	6785 (14.9)	
Age; mean (SD)	62.17 (11.2)	62.21 (11.2)	0.003	61.69 (11.1)	61.75 (11.1)	0.006	56.35 (12.8)	56.26 (12.5)	0.007	58.49 (12.5)	58.45 (12.3)	0.003
Age group; n (%)			0.001			0.001			0.004			0.003
18–65	5170 (60.9)	5175 (61.0)		5602 (62.6)	5608 (62.7)		20,981 (74.9)	21,025 (75.1)		31,753 (69.9)	31,808 (70.0)	
>65	3314 (39.1)	3309 (39.0)		3346 (37.4)	3340 (37.3)		7030 (25.1)	6986 (24.9)		13,690 (30.1)	13,635 (30.0)	
Sex; n (%)			0.032			0.025			0.034			0.032
Male	4572 (53.9)	4625 (54.5)		5114 (57.2)	5110 (57.1)		15,102 (53.9)	15,144 (54.1)		24,788 (54.6)	24,879 (54.8)	
Female	3912 (46.1)	3859 (45.5)		3834 (42.9)	3838 (42.9)		12,909 (46.1)	12,867 (45.9)		20,655 (45.5)	20,564 (45.3)	
Antihyperglycemic medications; n (%)												
Alpha-glucosidase inhibitors	348 (4.1)	344 (4.1)	0.002	255 (2.9)	279 (3.1)	0.016	587 (2.1)	587 (2.1)	0.001	1190 (2.6)	1210 (2.7)	0.003
DPP4 inhibitors	7000 (82.5)	6971 (82.2)	0.009	7307 (81.7)	7292 (81.5)	0.004	21,877 (78.1)	22,054 (78.7)	0.015	36,184 (79.6)	36,317 (79.9)	0.007
Insulin	4543 (53.6)	4603 (54.3)	0.014	4586 (51.3)	4652 (52.0)	0.015	12,465 (44.5)	12,383 (44.2)	0.006	21,594 (47.5)	21,638 (47.6)	0.002
Meglitinides	113 (1.3)	113 (1.3)	0.001	124 (1.4)	120 (1.3)	0.004	252 (0.9)	224 (0.8)	0.011	489 (1.1)	457 (1.0)	0.007
Metformin	7389 (87.1)	7359 (86.7)	0.010	7850 (87.7)	7856 (87.8)	0.002	23,801 (85.0)	24,066 (85.9)	0.027	39,040 (85.9)	39,281 (86.4)	0.015
Sulfonylureas	5603 (66.0)	5652 (66.6)	0.012	5999 (67.0)	6079 (67.9)	0.019	17,206 (61.4)	17,528 (62.6)	0.024	28,808 (63.4)	29,259 (64.4)	0.021
Thiazolidinediones	1914 (22.6)	1963 (23.1)	0.014	1893 (21.2)	1928 (21.6)	0.010	5791 (20.7)	5831 (20.8)	0.004	9598 (21.1)	9722 (21.4)	0.007
Number of antihyperglycemic medications being taken; n (%)			0.001			0.044			0.036			0.039
0–1	484 (5.7)	487 (5.7)		473 (5.3)	473 (5.3)		2462 (8.8)	2240 (8.0)		3419 (7.5)	3200 (7.0)	
2–3	5216 (61.5)	5188 (61.2)		5774 (64.5)	5681 (63.5)		18,759 (67.0)	18,929 (67.6)		29,749 (65.5)	29,798 (65.6)	
4+	2784 (32.8)	2809 (33.1)		2701 (30.2)	2794 (31.2)		6790 (24.2)	6842 (24.4)		12,275 (27.0)	12,445 (27.4)	
Level of diabetes treatment; n (%)[a]			0.001			0.020			0.042			0.021
1	256 (3.0)	242 (2.9)		264 (3.0)	247 (2.8)		1856 (6.6)	1615 (5.8)		2376 (5.2)	2104 (4.6)	
2	3685 (43.4)	3639 (42.9)		4098 (45.8)	4049 (45.3)		13,690 (48.9)	14,013 (50.0)		21,473 (47.3)	21,701 (47.8)	
3	4543 (53.6)	4603 (54.3)		4586 (51.3)	4652 (52.0)		12,465 (44.5)	12,383 (44.2)		21,594 (47.5)	21,638 (47.6)	
Diabetes related conditions; n (%)												
Diabetic nephropathy	1010 (11.9)	1002 (11.8)	0.003	1138 (12.7)	1117 (12.5)	0.007	3433 (12.3)	3340 (11.9)	0.010	5581 (12.3)	5459 (12.0)	0.008
Diabetic neuropathy	2785 (32.8)	2770 (32.7)	0.004	2753 (30.8)	2792 (31.2)	0.009	7171 (25.6)	7156 (25.6)	0.001	12,709 (28.0)	12,718 (28.0)	0.000
Diabetic retinopathy	3356 (39.6)	3310 (39.0)	0.011	3500 (39.1)	3505 (39.2)	0.001	8823 (31.5)	8764 (31.3)	0.005	15,679 (34.5)	15,579 (34.3)	0.005
Hypoglycaemia	113 (1.3)	119 (1.4)	0.006	72 (0.8)	84 (0.9)	0.014	127 (0.5)	127 (0.5)	0.001	312 (0.7)	330 (0.7)	0.005

(Table 2 continues on next page)

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m^2)			Overweight (23 ≤ BMI<25 kg/m^2)			Obese (BMI≥25 kg/m^2)			Overall		
	GLP1RA (n = 8484)	SGLT2i (n = 8484)	ASD	GLP1RA (n = 8948)	SGLT2i (n = 8948)	ASD	GLP1RA (n = 28,011)	SGLT2i (n = 28,011)	ASD	GLP1RA (n = 45,443)	SGLT2i (n = 45,443)	ASD
(Continued from previous page)												
Gastrointestinal diseases; n (%)												
Gastric disease	5429 (64.0)	5485 (64.7)	0.014	5745 (64.2)	5756 (64.3)	0.003	17,310 (61.8)	17,261 (61.6)	0.004	28,484 (62.7)	28,502 (62.7)	0.001
Irritable bowel disease	788 (9.3)	830 (9.8)	0.017	784 (8.8)	782 (8.7)	0.001	2202 (7.9)	2207 (7.9)	0.001	3774 (8.3)	3819 (8.4)	0.004
Inflammatory bowel disease	10 (0.1)	7 (0.1)	0.011	14 (0.2)	17 (0.2)	0.008	43 (0.2)	52 (0.2)	0.008	67 (0.2)	76 (0.2)	0.005
Pancreatitis	120 (1.4)	129 (1.5)	0.009	70 (0.8)	78 (0.9)	0.010	145 (0.5)	152 (0.5)	0.003	335 (0.7)	359 (0.8)	0.006
Liver disease	1027 (12.1)	976 (11.5)	0.019	1105 (12.4)	1115 (12.5)	0.003	4542 (16.2)	4604 (16.4)	0.006	6674 (14.7)	6695 (14.7)	0.001
Diverticular disease	21 (0.3)	20 (0.2)	0.002	27 (0.3)	31 (0.4)	0.008	61 (0.2)	69 (0.3)	0.006	109 (0.2)	120 (0.3)	0.005
Appendicitis	13 (0.2)	12 (0.1)	0.003	10 (0.1)	6 (0.1)	0.015	53 (0.2)	50 (0.2)	0.003	76 (0.2)	68 (0.2)	0.004
Comorbidities; n (%)												
Acute kidney injury	61 (0.7)	68 (0.8)	0.009	66 (0.7)	74 (0.8)	0.010	188 (0.7)	180 (0.6)	0.004	315 (0.7)	322 (0.7)	0.002
Anxiety	499 (5.9)	506 (6.0)	0.003	485 (5.4)	502 (5.6)	0.008	1429 (5.1)	1459 (5.2)	0.005	2413 (5.3)	2467 (5.4)	0.005
Asthma	411 (4.8)	429 (5.1)	0.010	500 (5.6)	510 (5.7)	0.005	1737 (6.2)	1772 (6.3)	0.005	2648 (5.8)	2711 (6.0)	0.006
Atrial fibrillation	144 (1.7)	135 (1.6)	0.008	137 (1.5)	120 (1.3)	0.016	437 (1.6)	451 (1.6)	0.004	718 (1.6)	706 (1.6)	0.002
Cancer	545 (6.4)	523 (6.2)	0.011	564 (6.3)	590 (6.6)	0.012	1638 (5.9)	1692 (6.0)	0.008	2747 (6.0)	2805 (6.2)	0.005
Cardiomyopathy	26 (0.3)	35 (0.4)	0.018	26 (0.3)	35 (0.4)	0.017	104 (0.4)	98 (0.4)	0.004	156 (0.3)	168 (0.4)	0.004
Chronic kidney disease	415 (4.9)	413 (4.9)	0.001	482 (5.4)	427 (4.8)	0.028	1365 (4.9)	1291 (4.6)	0.012	2262 (5.0)	2131 (4.7)	0.013
Chronic obstructive pulmonary disease	476 (5.6)	495 (5.8)	0.010	481 (5.4)	497 (5.6)	0.008	1370 (4.9)	1448 (5.2)	0.013	2327 (5.1)	2440 (5.4)	0.011
Congestive heart failure	247 (2.9)	268 (3.2)	0.014	284 (3.2)	289 (3.2)	0.003	984 (3.5)	988 (3.5)	0.001	1515 (3.3)	1545 (3.4)	0.004
Dementia	389 (4.6)	391 (4.6)	0.001	385 (4.3)	398 (4.5)	0.007	708 (2.5)	706 (2.5)	0.001	1482 (3.3)	1495 (3.3)	0.002
Depression	504 (5.9)	498 (5.9)	0.003	465 (5.2)	493 (5.5)	0.014	1520 (5.4)	1502 (5.4)	0.003	2489 (5.5)	2493 (5.5)	0.000
Epilepsy	79 (0.9)	90 (1.1)	0.013	72 (0.8)	77 (0.9)	0.006	196 (0.7)	196 (0.7)	0.001	347 (0.8)	363 (0.8)	0.004
Hyperlipidemia	4429 (52.2)	4441 (52.4)	0.003	4649 (52.0)	4571 (51.1)	0.017	14,048 (50.2)	14,000 (50.0)	0.003	23,126 (50.9)	23,012 (50.6)	0.005
Hypertension	3243 (38.2)	3251 (38.3)	0.002	3925 (43.9)	4014 (44.9)	0.020	13,980 (49.9)	14,027 (50.1)	0.003	21,148 (46.5)	21,292 (46.9)	0.006
Inflammatory arthritis	2071 (24.4)	2120 (25.0)	0.013	2289 (25.6)	2351 (26.3)	0.016	7071 (25.2)	7147 (25.5)	0.006	11,431 (25.2)	11,618 (25.6)	0.009
Ischemic heart disease	935 (11.0)	950 (11.2)	0.006	1170 (13.1)	1208 (13.5)	0.013	2992 (10.7)	3062 (10.9)	0.008	5097 (11.2)	5220 (11.5)	0.009
Obstructive sleep apnea	5 (0.1)	4 (0.1)	0.005	26 (0.3)	27 (0.3)	0.002	178 (0.6)	186 (0.7)	0.004	209 (0.5)	217 (0.5)	0.003
Osteoarthritis	2050 (24.2)	2136 (25.2)	0.024	2307 (25.8)	2371 (26.5)	0.016	6966 (24.9)	7050 (25.2)	0.007	11,323 (24.9)	11,557 (25.4)	0.012
Osteoporosis	591 (7.0)	614 (7.2)	0.011	505 (5.6)	502 (5.6)	0.001	1162 (4.2)	1182 (4.2)	0.004	2258 (5.0)	2298 (5.1)	0.004
Parkinson's disease	66 (0.8)	56 (0.7)	0.014	66 (0.7)	60 (0.7)	0.008	108 (0.4)	100 (0.4)	0.005	240 (0.5)	216 (0.5)	0.007
Pneumonia	539 (6.4)	566 (6.7)	0.013	517 (5.8)	533 (6.0)	0.008	1658 (5.9)	1719 (6.1)	0.009	2714 (6.0)	2818 (6.2)	0.010
Psychosis	21 (0.3)	22 (0.3)	0.002	28 (0.3)	32 (0.4)	0.008	111 (0.4)	115 (0.4)	0.002	160 (0.4)	169 (0.4)	0.003
Renal dysfunction	65 (0.8)	69 (0.8)	0.005	66 (0.7)	77 (0.9)	0.014	224 (0.8)	209 (0.8)	0.006	355 (0.8)	355 (0.8)	0.000
Stroke	474 (5.6)	507 (6.0)	0.017	524 (5.9)	523 (5.8)	0.001	1203 (4.3)	1185 (4.2)	0.003	2201 (4.8)	2215 (4.9)	0.001
Thyroid disease	699 (8.2)	679 (8.0)	0.009	696 (7.8)	679 (7.6)	0.007	2246 (8.0)	2230 (8.0)	0.002	3641 (8.0)	3588 (7.9)	0.004
Comedications; n (%)												
ACE inhibitors or ARBs	3603 (42.5)	3637 (42.9)	0.008	4668 (52.2)	4715 (52.7)	0.011	17,118 (61.1)	17,059 (60.9)	0.004	25,389 (55.9)	25,411 (55.9)	0.001
Anticoagulants	542 (6.4)	559 (6.6)	0.008	556 (6.2)	608 (6.8)	0.024	1502 (5.4)	1584 (5.7)	0.013	2600 (5.7)	2751 (6.1)	0.014
Anticonvulsants	1915 (22.6)	2016 (23.8)	0.028	1934 (21.6)	1944 (21.7)	0.003	5544 (19.8)	5614 (20.0)	0.006	9393 (20.7)	9574 (21.1)	0.010
Antidepressants	679 (8.0)	671 (7.9)	0.003	766 (8.6)	770 (8.6)	0.002	2308 (8.2)	2324 (8.3)	0.002	3753 (8.3)	3765 (8.3)	0.001
Antipsychotics	1741 (20.5)	1767 (20.8)	0.008	1866 (20.9)	1901 (21.2)	0.010	5659 (20.2)	5685 (20.3)	0.002	9266 (20.4)	9353 (20.6)	0.005
Benzodiazepines	2936 (34.6)	3042 (35.9)	0.026	3023 (33.8)	3050 (34.1)	0.006	8692 (31.0)	8705 (31.1)	0.001	14,651 (32.2)	14,797 (32.6)	0.007
Beta-blockers	353 (4.2)	365 (4.3)	0.007	340 (3.8)	345 (3.9)	0.003	1188 (4.2)	1178 (4.2)	0.002	1881 (4.1)	1888 (4.2)	0.001

(Table 2 continues on next page)

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m^2)			Overweight (23 ≤ BMI<25 kg/m^2)			Obese (BMI≥25 kg/m^2)			Overall		
	GLP1RA (n = 8484)	SGLT2i (n = 8484)	ASD	GLP1RA (n = 8948)	SGLT2i (n = 8948)	ASD	GLP1RA (n = 28,011)	SGLT2i (n = 28,011)	ASD	GLP1RA (n = 45,443)	SGLT2i (n = 45,443)	ASD
(Continued from previous page)												
Bisphosphonates	367 (4.3)	378 (4.5)	0.006	323 (3.6)	355 (4.0)	0.019	682 (2.4)	719 (2.6)	0.008	1372 (3.0)	1452 (3.2)	0.010
Calcium channel blockers	2423 (28.6)	2444 (28.8)	0.005	3069 (34.3)	3064 (34.2)	0.001	11,759 (42.0)	11,761 (42.0)	0.001	17,251 (38.0)	17,269 (38.0)	0.001
Corticosteroids	2652 (31.3)	2691 (31.7)	0.010	2876 (32.1)	2894 (32.3)	0.004	9014 (32.2)	9076 (32.4)	0.005	14,542 (32.0)	14,661 (32.3)	0.006
Diuretics	1154 (13.6)	1174 (13.8)	0.007	1504 (16.8)	1554 (17.4)	0.015	6162 (22.0)	6084 (21.7)	0.007	8820 (19.4)	8812 (19.4)	0.000
Nitrates	148 (1.7)	165 (1.9)	0.015	188 (2.1)	196 (2.2)	0.006	486 (1.7)	511 (1.8)	0.007	822 (1.8)	872 (1.9)	0.008
NSAIDs	5276 (62.2)	5300 (62.5)	0.006	5687 (63.6)	5700 (63.7)	0.003	17,844 (63.7)	18,030 (64.4)	0.014	28,807 (63.4)	29,030 (63.9)	0.010
Opioids	1062 (12.5)	1099 (13.0)	0.013	1129 (12.6)	1206 (13.5)	0.026	3360 (12.0)	3603 (12.9)	0.026	5551 (12.2)	5908 (13.0)	0.024
Platelet inhibitors	5407 (63.7)	5419 (63.9)	0.003	5867 (65.6)	5902 (66.0)	0.008	17,377 (62.0)	17,593 (62.8)	0.016	28,651 (63.1)	28,914 (63.6)	0.012
Sedative hypnotics	953 (11.2)	938 (11.1)	0.006	973 (10.9)	993 (11.1)	0.007	2531 (9.0)	2499 (8.9)	0.004	4457 (9.8)	4430 (9.8)	0.002
Tricyclic antidepressant	761 (9.0)	771 (9.1)	0.004	714 (8.0)	742 (8.3)	0.011	2044 (7.3)	2026 (7.2)	0.002	3519 (7.7)	3539 (7.8)	0.002
Proton-pump inhibitors	3910 (46.1)	3970 (46.8)	0.014	4070 (45.5)	4130 (46.2)	0.013	12,129 (43.3)	12,155 (43.4)	0.002	20,109 (44.3)	20,255 (44.6)	0.006
Histamine type 2 receptor antagonists	5137 (60.6)	5159 (60.8)	0.005	5346 (59.8)	5411 (60.5)	0.015	16,337 (58.3)	16,383 (58.5)	0.003	26,820 (59.0)	26,953 (59.3)	0.006
Bile and liver medications	869 (10.2)	838 (9.9)	0.012	1003 (11.2)	1057 (11.8)	0.019	5440 (19.4)	5546 (19.8)	0.010	7312 (16.1)	7441 (16.4)	0.008
Fibrates	614 (7.2)	586 (6.9)	0.013	958 (10.7)	976 (10.9)	0.006	3852 (13.8)	3881 (13.9)	0.003	5424 (11.9)	5443 (12.0)	0.001
Statins	6281 (74.0)	6245 (73.6)	0.010	7063 (78.9)	7012 (78.4)	0.014	21,374 (76.3)	21,375 (76.3)	0.001	34,718 (76.4)	34,632 (76.2)	0.004
Other lipid modifying drugs	1589 (18.7)	1588 (18.7)	0.001	1816 (20.3)	1800 (20.1)	0.004	5907 (21.1)	5879 (21.0)	0.002	9312 (20.5)	9267 (20.4)	0.002
Charlson Comorbidity Index; n (%)			0.001			0.046			0.041			0.031
0	2716 (32.0)	2688 (31.7)		2822 (31.5)	2705 (30.2)		10,166 (36.3)	10,139 (36.2)		15,704 (34.6)	15,532 (34.2)	
1	3786 (44.6)	3809 (44.9)		4027 (45.0)	4113 (46.0)		10,982 (39.2)	10,929 (39.0)		18,795 (41.4)	18,851 (41.5)	
2	694 (8.2)	717 (8.5)		743 (8.3)	742 (8.3)		2947 (10.5)	2934 (10.5)		4384 (9.7)	4393 (9.7)	
≥3	1288 (15.2)	1270 (15.0)		1356 (15.2)	1388 (15.5)		3916 (14.0)	4009 (14.3)		6560 (14.4)	6667 (14.7)	
Number of outpatients visits; n (%)			0.001			0.001			0.001			0.001
0–2	74 (0.9)	68 (0.8)		62 (0.7)	60 (0.7)		254 (0.9)	237 (0.9)		390 (0.9)	365 (0.8)	
3–5	181 (2.1)	191 (2.3)		196 (2.2)	181 (2.0)		769 (2.8)	780 (2.8)		1146 (2.5)	1152 (2.5)	
6+	8229 (97.0)	8225 (97.0)		8690 (97.1)	8707 (97.3)		26,988 (96.4)	26,994 (96.4)		43,907 (96.6)	43,926 (96.7)	
Number of hospitalizations; n (%)			0.053			0.023			0.062			0.062
0	5781 (68.1)	5629 (66.4)		6194 (69.2)	6046 (67.6)		20,073 (71.7)	19,732 (70.4)		32,048 (70.5)	31,407 (69.1)	
1–2	2268 (26.7)	2386 (28.1)		2376 (26.6)	2509 (28.0)		7001 (25.0)	7309 (26.1)		11,645 (25.6)	12,204 (26.9)	
3+	435 (5.1)	469 (5.5)		378 (4.2)	393 (4.4)		937 (3.4)	970 (3.5)		1750 (3.9)	1832 (4.0)	
Number of internal medicine visits; mean (SD)	1.76 (5.1)	1.8 (4.9)	0.009	1.81 (6.1)	1.72 (5.3)	0.016	1.56 (5.3)	1.59 (4.9)	0.006	1.64 (5.4)	1.65 (5.0)	0.002
Number of gastroenterologist visits; mean (SD)	0.4 (1.6)	0.42 (1.7)	0.015	0.39 (1.6)	0.43 (1.9)	0.022	0.41 (1.6)	0.42 (1.7)	0.006	0.4 (1.6)	0.42 (1.7)	0.011
Number of cardiologist visits; mean (SD)	0.45 (1.5)	0.46 (1.5)	0.012	0.53 (1.6)	0.56 (1.6)	0.020	0.52 (1.6)	0.53 (1.6)	0.011	0.51 (1.6)	0.53 (1.6)	0.013
Number of endocrinologist visits; mean (SD)	2.04 (3.1)	1.99 (3.1)	0.016	2.12 (3.1)	2.04 (3.1)	0.025	2.14 (3.2)	2.08 (3.1)	0.017	2.11 (3.2)	2.06 (3.1)	0.018
Prescriber specialty; n (%)												
Internal medicine	939 (11.1)	959 (11.3)	0.007	897 (10.0)	923 (10.3)	0.010	2699 (9.6)	2777 (9.9)	0.009	4535 (10.0)	4659 (10.3)	0.009
Gastroenterologist	167 (2.0)	182 (2.2)	0.012	190 (2.1)	202 (2.3)	0.009	697 (2.5)	693 (2.5)	0.001	1054 (2.3)	1077 (2.4)	0.003
Endocrinologist	3108 (36.6)	3049 (35.9)	0.014	3582 (40.0)	3491 (39.0)	0.021	12,079 (43.1)	12,030 (43.0)	0.004	18,769 (41.3)	18,570 (40.9)	0.009
Others	4365 (51.5)	4400 (51.9)	0.008	4407 (49.3)	4459 (49.8)	0.012	13,084 (46.7)	13,083 (46.7)	0.001	21,856 (48.1)	21,942 (48.3)	0.004
Smoking			0.001			0.001			0.001			0.001
Never	5159 (60.8)	5176 (61.0)		5378 (60.1)	5344 (59.7)		17,065 (60.9)	17,022 (60.8)		27,602 (60.7)	27,542 (60.6)	
Past smoker	1521 (17.9)	1521 (17.9)		1868 (20.9)	1891 (21.1)		5662 (20.2)	5680 (20.3)		9051 (19.9)	9092 (20.0)	

(Table 2 continues on next page)

Baseline characteristics	Normal (18.5 ≤ BMI<23 kg/m^2)			Overweight (23 ≤ BMI<25 kg/m^2)			Obese (BMI≥25 kg/m^2)			Overall		
	GLP1RA (n = 8484)	SGLT2i (n = 8484)	ASD	GLP1RA (n = 8948)	SGLT2i (n = 8948)	ASD	GLP1RA (n = 28,011)	SGLT2i (n = 28,011)	ASD	GLP1RA (n = 45,443)	SGLT2i (n = 45,443)	ASD
(Continued from previous page)												
Current smoker	1800 (21.2)	1782 (21.0)		1701 (19.0)	1712 (19.1)		5276 (18.8)	5300 (18.9)		8777 (19.3)	8794 (19.4)	
Unknown	4 (0.1)	5 (0.1)		1 (0.0)	1 (0.0)		8 (0.0)	9 (0.0)		13 (0.0)	15 (0.0)	
Drinking			0.024			0.023			0.001			0.001
Yes	1902 (22.4)	1965 (23.2)		2204 (24.6)	2170 (24.3)		8084 (28.9)	8207 (29.3)		12,190 (26.8)	12,342 (27.2)	
No	6576 (77.5)	6514 (76.8)		6740 (75.3)	6774 (75.7)		19,920 (71.1)	19,798 (70.7)		33,236 (73.1)	33,086 (72.8)	
Unknown	6 (0.1)	5 (0.1)		4 (0.0)	4 (0.0)		7 (0.0)	6 (0.0)		17 (0.0)	15 (0.0)	
Clinical variables[b]; mean (SD)												
Waist circumference [cm]	78.2 (6.0)	78.1 (6.0)	0.030	84.19 (5.5)	84.03 (5.5)	0.028	94.58 (10.9)	94.28 (9.3)	0.029	89.48 (11.4)	89.23 (10.5)	0.023
Fasting blood glucose [mg/dL]	174.1 (73.8)	169.5 (71.1)	0.063	168.42 (66.1)	163.48 (63.4)	0.076	166.61 (62.8)	161.2 (59.3)	0.088	168.36 (65.7)	163.2 (62.5)	0.081
Systolic blood pressure [mmHg]	123.3 (15.6)	124.1 (15.6)	0.047	126.03 (15.0)	126.84 (15.0)	0.055	129.69 (14.8)	130.15 (14.9)	0.031	127.78 (15.2)	128.37 (15.3)	0.038
Diastolic blood pressure [mmHg]	73.4 (9.7)	73.9 (9.8)	0.044	74.83 (9.6)	75.63 (9.7)	0.083	78.41 (10.3)	78.91 (10.2)	0.048	76.78 (10.2)	77.32 (10.3)	0.053
Total cholesterol. [mg/dL]	170.3 (60.1)	171.9 (49.1)	0.029	167.49 (44.1)	172.03 (47.0)	0.100	173.91 (46.3)	178.05 (50.0)	0.086	171.95 (48.8)	175.71 (49.3)	0.077
Low density lipoprotein cholesterol [mg/dL]	90.9 (54.0)	92.3 (43.3)	0.028	87.89 (36.6)	91.28 (38.6)	0.090	91.2 (40.8)	94.72 (85.8)	0.052	90.48 (42.9)	93.58 (71.9)	0.052
High density lipoprotein cholesterol [mg/dL]	52.4 (15.6)	52.9 (16.0)	0.037	49.21 (13.3)	49.4 (12.6)	0.015	47.63 (13.1)	48.37 (15.2)	0.052	48.83 (13.8)	49.42 (15.0)	0.041
Triglycerides [mg/dL]	137.8 (107.2)	138.2 (118.6)	0.003	158.39 (122.5)	162.97 (133.7)	0.036	188.57 (161.8)	189.82 (165.0)	0.008	173.03 (147.0)	174.96 (152.8)	0.013
Serum creatinine [mg/dL]	0.9 (0.4)	0.9 (0.3)	0.061	0.94 (0.4)	0.92 (0.3)	0.042	0.93 (0.4)	0.9 (0.4)	0.063	0.93 (0.4)	0.91 (0.4)	0.059
eGFR [mL/min/1.73 m^2]	86.9 (30.3)	87.8 (28.2)	0.032	84.58 (27.8)	85.3 (28.7)	0.025	87.2 (29.4)	88.21 (29.3)	0.034	86.63 (29.3)	87.57 (29.0)	0.032
Hemoglobin [g/dL]	13.7 (1.7)	13.7 (1.7)	0.033	13.92 (1.7)	14 (1.6)	0.045	14.23 (1.7)	14.3 (1.7)	0.040	14.06 (1.7)	14.13 (1.7)	0.039
AST (SGOT) [IU/L]	26.6 (26.0)	26.9 (25.1)	0.012	27.48 (19.9)	28.94 (67.9)	0.029	33.69 (26.7)	33.82 (27.1)	0.005	31.14 (25.6)	31.57 (38.6)	0.013
ALT (SGPT) [IU/L]	25.7 (28.4)	25.7 (23.9)	0.001	28.47 (28.6)	29.09 (28.1)	0.022	38.8 (34.2)	39.48 (36.7)	0.019	34.32 (32.7)	34.87 (33.6)	0.016
GGT [IU/L]	37.6 (67.7)	41.8 (82.2)	0.056	41.58 (81.0)	44.87 (71.6)	0.043	52.5 (61.6)	54.23 (63.4)	0.028	47.57 (67.3)	50.08 (69.1)	0.037

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; ASD, absolute standardized difference; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DPP4i, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transferase; GLP1RA, glucagon like peptide 1 receptor agonists; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SGLT2i, sodium glucose cotransporter 2 inhibitors; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvate transaminase. [a]Defined depending on the number of antidiabetic medication (excluding the study drugs of interest), prescribed in the year preceding the index date: level 1, as taking none or only one class of antidiabetic medication other than insulin, level 2, as taking ≥2 different classes of antidiabetic medication without insulin, and level 3, as taking insulin with or without other classes of antidiabetic medication. [b]Clinical variables were not included in the multivariable logistic regression model for propensity score estimation. Presented descriptive statistics (mean [SD]) here were based on patients with information on these variables available.

Table 2: **Baseline characteristics of patients received GLP-1 receptor agonists or SGLT2 inhibitors after propensity score matching.**

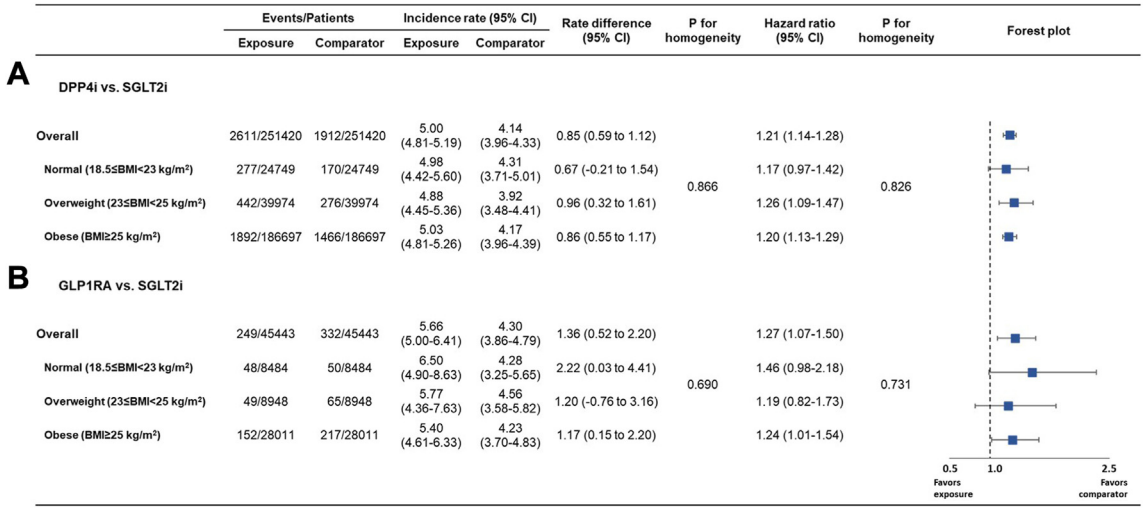

Fig. 1: Association between the use of DPP4i vs. SGLT2i (A) and the use of GLP1RA vs. SGLT2i (B) and the risk of gallbladder and biliary tract diseases compared with the use of SGLT2i across categories of body mass index. Abbreviations: CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitors; GLP1RA, glucagon like peptide 1 receptor agonists; HR, hazard ratio; IR, incidence rate; SGLT2i, sodium glucose cotransporter 2 inhibitors.

The increased risk of GBD has been raised in randomized clinical trials of GLP1RA (HR 1.60, 95% CI 1.23–2.09)[4] and subsequent safety evidence has been presented for GLP1RA and DPP4i, another incretin-based drug that inhibits degradation of naturally occurring GLP1. A meta-analysis of 76 randomized clinical trials of GLP1RA presented an increased risk of GBD (RR, 1.37, 95% CI 1.23–1.52),[5] and two meta-analyses of clinical trials of DPP4i presented an increased risk of GBD in terms of relative risk (RR 1.20, 95% CI 1.01–1.42)[7] and odds ratio (1.22, 95% CI 1.04–1.43).[6] However, results from observational studies were inconclusive. An observational cohort study using the United Kingdom Clinical Practice Research Datalink assessed each incretin-based drug compared to other oral antidiabetic drugs and found a significant risk of GBD for GLP1RA (HR 2.08, 95% CI 1.08–4.02), but not for DPP4i (HR 0.99, 95% CI 0.75–1.32).[9] Another cohort study using nationwide claims data from Taiwan compared GLP1RA vs. SGLT2i presented a non-significant risk of GBD for GLP1RA (HR 1.20, 95% CI 0.93–1.56).[15] Contrary to uncertainty presented in previous observational studies, we observed increased risk with both incretin-based drugs, with sufficient statistical power using large population cohorts. It is worth to note that the increased risk of GBD associated with DPP4i, which has been signaled until recently,[16,17] has also been confirmed in our large cohort, with a range of subgroup and sensitivity analyses demonstrating its robustness. Furthermore, results from clinical trials involving Asians are often presented in subgroups with insufficient sample sizes or through the findings of multiple conflicting meta-analyses. Given the low prevalence of GBD and underrepresentation of Asians in both relevant clinical trials and observational studies, the significance of our study lies in utilizing a large Asian real-world data to generate more precise estimates and to complement current body of evidence, which lacks ethnic diversity.

In addition, we specifically assessed the risk of GBD among stratified populations across categories BMI. Obesity is widely recognized as a predisposing factor for the formation and growth of cholesterol gallstones, increasing the likelihood of symptomatic gallstones through mechanisms such as gallbladder stasis, dyslipidemia, bile supersaturation with cholesterol, impaired gallbladder emptying, or insulin resistance.[14] Furthermore, it is well established that type 2 diabetes is strongly associated with cholesterol gallstones regardless of obesity.[18] Although we hypothesized that the risk of GBD associated with incretin-based drugs would vary across BMI status, our findings did not support this hypothesis. We also found that incidence rates of GBD were comparable across BMI strata, even in the normal weight group, which lacks a predisposing factor for obesity. Notably, patients in the lower BMI group exhibited higher fasting blood glucose levels, higher levels of diabetes treatment, and a greater prevalence of diabetic complications in our study. This suggests that individuals maintaining normal weight but suffering from type 2 diabetes may already be sufficiently predisposed to GBD risk.[19] The heightened severity of diabetes in normal weight individuals suggests the possibility of an opposing influence on the effect modification by BMI.

Furthermore, the high prevalence of comorbidities that are known to be risk factors for gallstone formation in both cohorts of obese patients underscores the

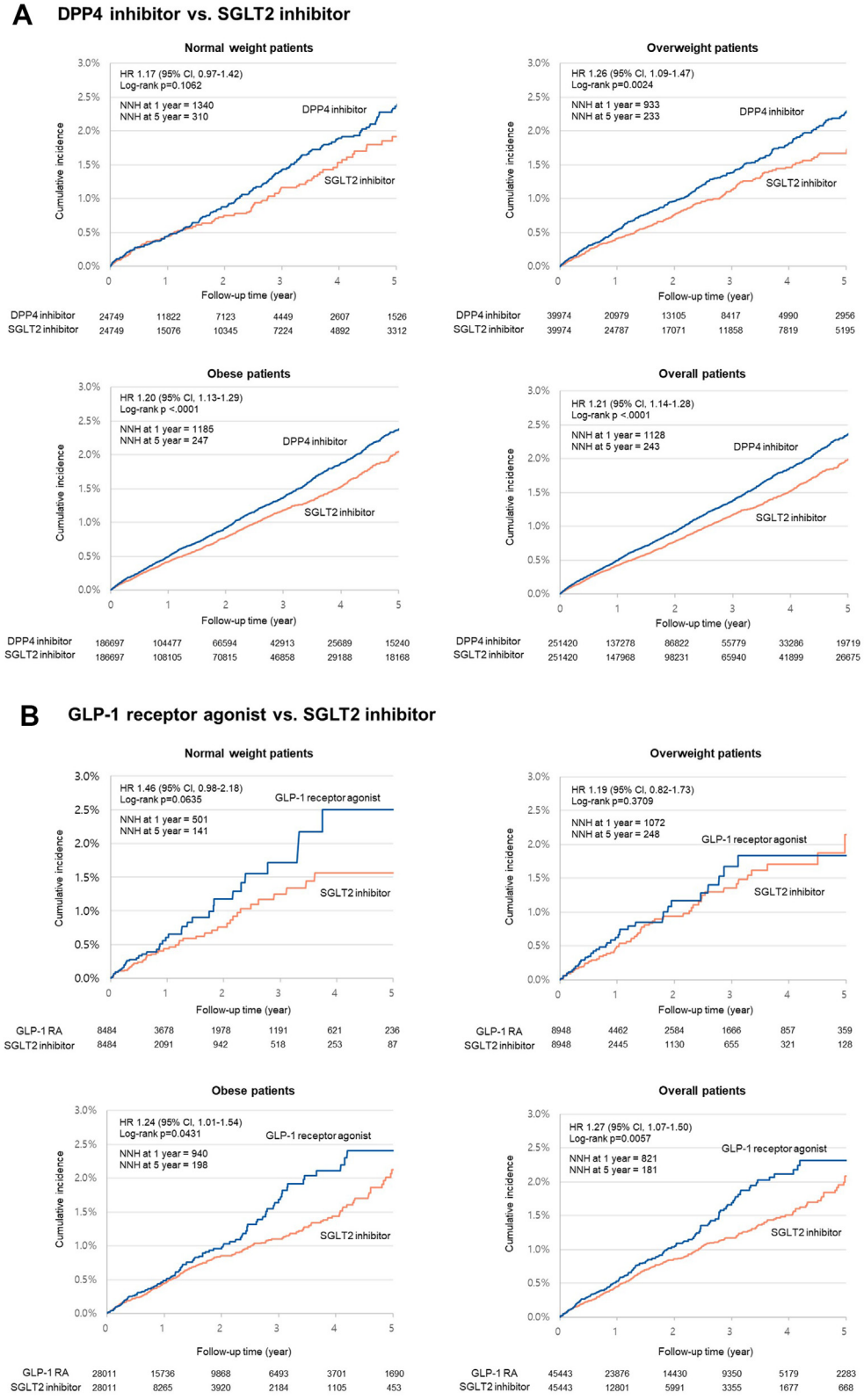

Fig. 2: Cumulative incidence of gallbladder and biliary tract diseases among PS matched populations for the (A) DPP4 inhibitor vs. SGLT2 inhibitor, and (B) GLP-1 receptor agonist vs. SGLT2 inhibitor. Abbreviations: CI, confidence interval; DPP4, dipeptidyl peptidase 4; GLP, glucagon like peptide; HR, hazard ratio; NNH, number needed to harm; SGLT2, sodium glucose cotransporter 2.

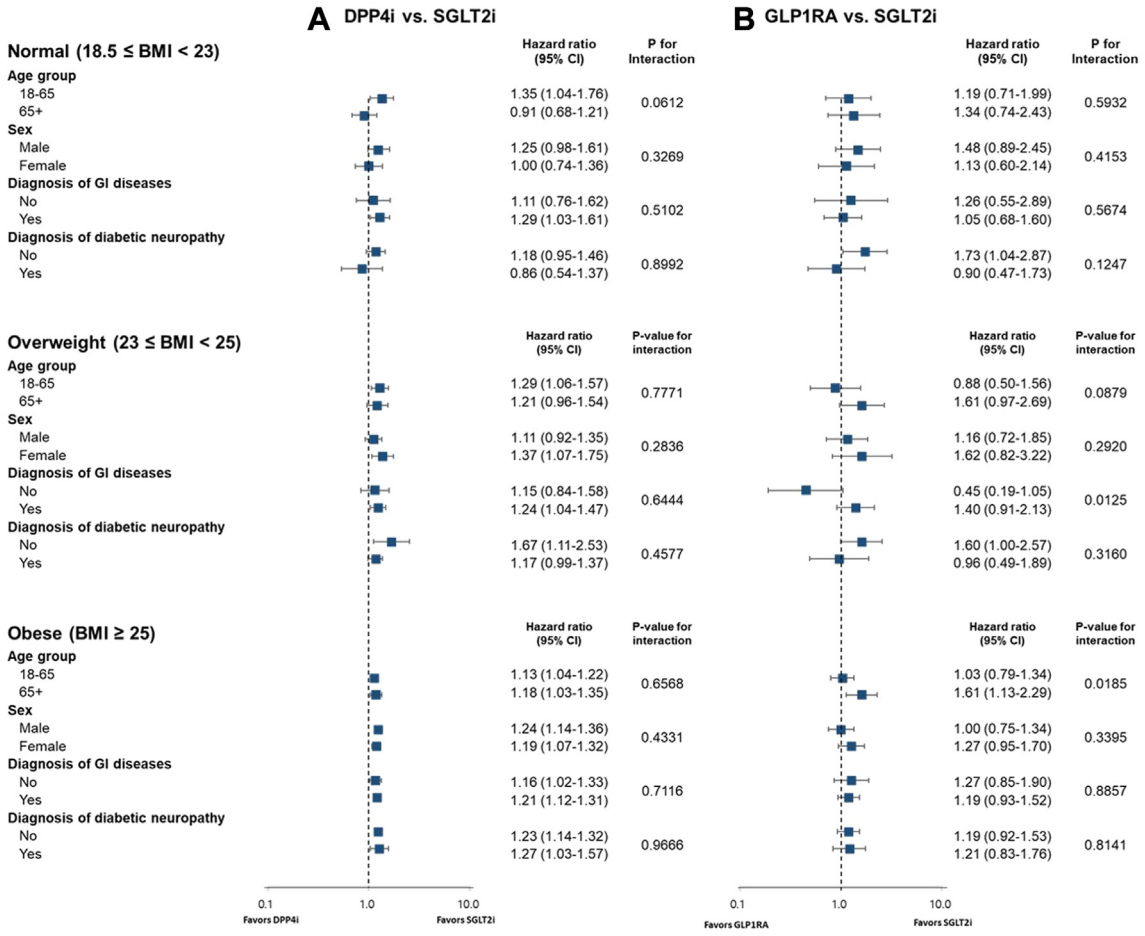

Fig. 3: Results of subgroup analyses with hazard ratios and 95% CIs for the association between the use of DPP4i vs. SGLT2i (A) and the use of GLP1RA vs. SGLT2i (B) and the risk of gallbladder and biliary tract diseases Abbreviations: BMI, body mass index; CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitors; GI, gastrointestinal; GLP1RA, glucagon like peptide 1 receptor agonists; HR, hazard ratio; IR, incidence rate; SGLT2i, sodium glucose cotransporter 2 inhibitors.

importance of considering comorbid risk factors when prescribing incretin-based drugs. We found a higher prevalence of hypertension[20] and liver disease,[21] correspondingly higher blood pressure and liver enzyme levels among patients in higher BMI groups. Although our findings presented no effect modification by obesity for the association between GBD risk and incretin-based drugs, obese patients with these higher prevalence of risk factors might be vulnerable to progression from asymptomatic to symptomatic GBD.[22] Further caution should be taken to ensure that the use of incretin-based drugs in these patients does not induce progression to symptomatic GBD.

There are several potential biological mechanisms that suggest an association between incretin-based drugs and an increased risk of GBD; however, these are still under investigation. The gut-derived incretin hormone GLP1 functions as an enterogastrone, eliciting a wide range of GI responses.[23] Both GLP1RA and DPP4i have been shown to alter the composition and function of the gut microbiota, potentially influencing endogenous GLP1 signaling and bile acid metabolism through crosstalk with gut microbiota metabolites.[24,25] Some gut microbiota metabolites promote the secretion of GLP1, which in turn suppresses the secretion of cholecystokinin, delaying gallbladder emptying,[26] refilling,[27] and decreasing gallbladder motility.[8] In addition, the activation of GLP1 receptors expressed in cholangiocytes is known to enhance proliferative reaction to cholestasis.[28] Biologic response of cholangiocytes to cholestasis could lead to proinflammatory secretions, subsequently developing gallbladder inflammation. Nevertheless, it remains uncertain whether incretin-based drugs elicit a sufficiently robust activation to induce inflammation, necessitating further research.[29]

Strengths and limitations of this study

Notably, our study presents a novel finding in assessing the impact of obesity among heterogeneous diabetic patients. Through stratification, we controlled for the confounding by obesity, a major risk factor for GBD. No effect modification by BMI was observed. Additionally, we reassessed the risk of GBD associated with incretin-based drugs in a large-scale cohort, employing a methodology that emulates randomized controlled trials by utilizing an active-comparator, new-user design and adjusting for a range of confounders.

This study has several limitations that should be considered. First, residual confounding due to unmeasured covariates cannot be ruled out. However, we adjusted for a wide range of covariates in the PS model, including comorbidities, comedications, and smoking/drinking behaviors. Sensitivity analysis that added clinical variables such as fasting blood glucose and cholesterol levels to the PS model presented consistent results. Second, there exists potential for outcome misclassification. Diagnosing GBD can be challenging due to mild or non-specific symptoms, often leading to misdiagnoses. Furthermore, identifying the nuanced gradation of severity and implications of GBD through ICD-10 codes in the claims database lacks validation and cannot be equated with the algorithmic categorization employed to assess GBD events in clinical trials.[4] Also, we cannot rule out the possibility of ascertainment bias induced by more intense surveillance among GLP1RA users after the publication of the RCTs[4] suggesting the risk of GBD for GLP1RA users. However, the significant increase in HRs and RDs observed as a separate outcome of cholecystectomy warrants attention, as this procedure is the preferred treatment of symptomatic GBD, which does not require intense surveillance. Lastly, the study population was not large enough in the second cohort (GLP1RA vs. SGLT2i) to stratify by BMI due to the limited number of GLP1RA users in Korea. Moreover, all GLP1RA drugs are currently indicated only for T2D. Given the emerging safety issues around semaglutide[30] or tirzepatide,[31] it is also crucial to ascertain the risks of GBD in high-dose GLP1RA indicated for obesity. If a larger study population using GLP1RA and reimbursement for obesity become available, conducting a follow-up safety study on GBD focusing on these agents would be beneficial.

Conclusion

In this nationwide cohort study emulating a target trial, the use of incretin-based drugs was significantly associated with an increased risk of GBD compared to the use of SGLT2i among patients with T2D. The increased risk remained significant in obese patients in both cohorts, although there was no evidence of effect heterogeneity by BMI status. Prescribers should be aware of the risk of GBD when using incretin-based drugs in patients with T2D regardless of BMI status. Given the increasing usage of incretin-based drugs in routine clinical practice, further studies, including randomized controlled trials that consider the heterogenous nature of individuals with T2D, on the association between the risk of GBD and drugs, would be beneficial.

Contributors

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.

Concept and design: HYK, SB, DY, BH, JYS.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: HYK, SB, DY, BH.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: HYK.

Administrative, technical, or material support: All authors.

Supervision: JYS, YMC, JHB.

Data sharing statement

No additional data are available to the public.

Declaration of interests

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, Pfizer, Celltrion, and SK Bioscience, outside the submitted work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101242.

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