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Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease

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IMPORTANCE Several oral antidiabetic drug (OAD) classes can potentially improve patient outcomes in nonalcoholic fatty liver disease (NAFLD) to varying degrees, but clinical data on which class is favored are lacking.

OBJECTIVE To investigate which OAD is associated with the best patient outcomes in NAFLD and type 2 diabetes (T2D).

DESIGN, SETTING, AND PARTICIPANTS This retrospective nonrandomized interventional cohort study used the National Health Information Database, which provided population-level data for Korea. This study involved patients with T2D and concomitant NAFLD.

EXPOSURES Receiving either sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, or sulfonylureas, each combined with metformin for 80% or more of 90 consecutive days.

MAIN OUTCOMES AND MEASURES The main outcomes were NAFLD regression assessed by the fatty liver index and composite liver-related outcome (defined as liver-related hospitalization, liver-related mortality, liver transplant, and hepatocellular carcinoma) using the Fine-Gray model regarding competing risks.

RESULTS In total, 80 178 patients (mean [SD] age, 58.5 [11.9] years; 43 007 [53.6%] male) were followed up for 219 941 person-years, with 4102 patients experiencing NAFLD regression. When compared with sulfonylureas, SGLT2 inhibitors (adjusted subdistribution hazard ratio [ASHR], 1.99 [95% CI, 1.75-2.27]), thiazolidinediones (ASHR, 1.70 [95% CI, 1.41-2.05]), and DPP-4 inhibitors (ASHR, 1.45 [95% CI, 1.31-1.59]) were associated with NAFLD regression. SGLT2 inhibitors were associated with a higher likelihood of NAFLD regression when compared with thiazolidinediones (ASHR, 1.40 [95% CI, 1.12-1.75]) and DPP-4 inhibitors (ASHR, 1.45 [95% CI, 1.30-1.62]). Only SGLT2 inhibitors (ASHR, 0.37 [95% CI, 0.17-0.82]), not thiazolidinediones or DPP-4 inhibitors, were significantly associated with lower incidence rates of adverse liver-related outcomes when compared with sulfonylureas.

CONCLUSIONS AND RELEVANCE The results of this cohort study suggest that physicians may lean towards prescribing SGLT2 inhibitors as the preferred OAD for individuals with NAFLD and T2D, considering their potential benefits in NAFLD regression and lower incidences of adverse liver-related outcomes. This observational study should prompt future research to determine whether prescribing practices might merit reexamination.

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Supplemental content

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Nonalcoholic fatty liver disease (NAFLD) is the foremost cause of chronic liver disease and affects approximately 25% of the global population.[1] The NAFLD spectrum encompasses nonalcoholic fatty liver, nonalcoholic steatohepatitis (NASH), and liver cirrhosis, leading eventually to hepatocellular carcinoma (HCC).[1,2] Approximately 20% of patients with nonalcoholic fatty liver have their condition progress to NASH, and 20% of those with NASH have their condition progress to cirrhosis, though some patient conditions can be reversible.[2] Patients with NAFLD are at high risk of not only adverse liver-related outcomes, including HCC, but also extrahepatic outcomes, such as cancer and cardiometabolic disease.[2,3] Despite the indisputable NAFLD societal burden, there is currently no pharmacotherapy approved by either the US Food and Drug Administration or the European Medicines Agency.[2]

Type 2 diabetes (T2D) is bidirectionally related to NAFLD.[4,5] The prevalence of NAFLD is estimated at 55.5% in patients with T2D.[5] Furthermore, T2D adversely affects the prognosis of patients with NAFLD due to accelerated fibrosis progression and a higher risk of decompensation and HCC.[6] Patients with NAFLD and T2D are more likely to develop NASH, cirrhosis, HCC, extrahepatic malignant neoplasm, and cardiovascular disease.[3,6] Several studies have examined if drugs used to treat T2D also provide benefits, such as NAFLD regression. For instance, sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors are representative oral antidiabetic drugs (OADs) that may improve NAFLD.[7] Although patients with both NAFLD and T2D may benefit from OADs, large-scale data determining which drug class is favorable for NAFLD regression in a health care setting are sparse, hindering OAD selection in clinical care. This cohort study compared NAFLD regression and other liver-related parameters associated with various OADs in patients with T2D and concomitant NAFLD using nationwide claim data from Korea.

Key Points

Question Among sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and sulfonylureas, which class of oral antidiabetic drugs (OADs) is the preferred therapeutic option for patients with both nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D)?

Findings In this nationwide cohort study involving 80 178 patients diagnosed with T2D and concurrent NAFLD in Korea, spanning 219 941 person-years, SGLT2 inhibitors were associated with a higher likelihood of NAFLD regression and lower incidence of adverse liver-related outcome parameters when compared with other OADs.

Meaning The results from this study suggest that SGLT2 inhibitors may be the preferred choice among OADs for individuals with both NAFLD and T2D, highlighting the need for additional research to determine whether a shift in prescribing practices is warranted.

Methods

Data Source

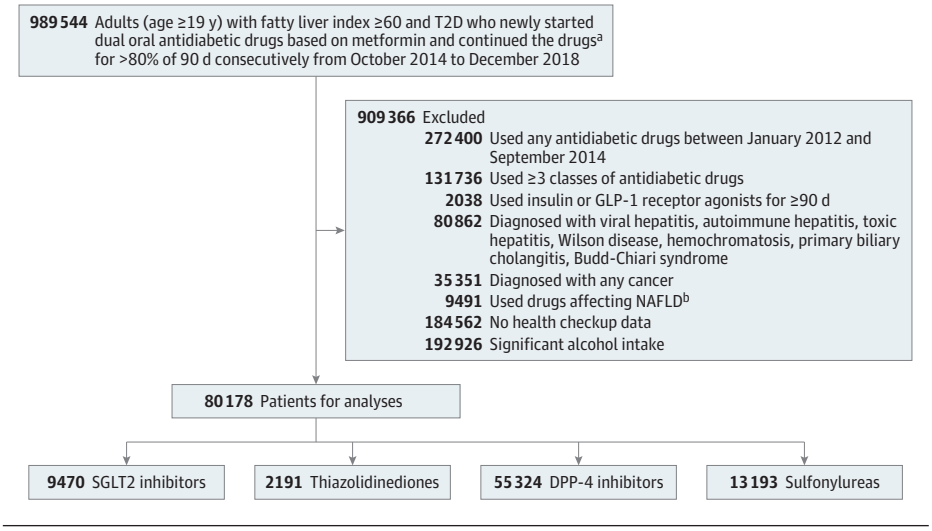
The results of this study were based on a nationwide database derived from the National Health Insurance Service (NHIS) in South Korea. Public health insurance administered by NHIS is mandatory for all South Korean citizens. All employees of any age and nonemployees older than 40 years are provided with a biennial health checkup as part of NHIS benefits. The NHIS operates the National Health Insurance Database (NHID) that contains health information, including diagnoses, pharmacotherapies, procedures, and operations; health checkups, including height, weight, weekly alcohol consumption, smoking behavior, and blood test results (total cholesterol, triglycerides, fasting glucose, aspartate transaminase, alanine transaminase, γ-glutamyltransferase, and creatinine); and the date and cause of death information as compiled by data from Statistics Korea. NHIS-administered health screenings use a questionnaire based on the Alcohol Use Disorders Identification Test.[8] The NHID has been extensively used and validated in different cohort studies.[9] Informed consent was not required because NHID operates under strict confidentiality guidelines, and all data are anonymized. This study was approved by the institutional review board of Seoul Metropolitan Government Seoul National University Boramae Medical Center.

Study Population

Participants were included in the study if the following criteria were met: (1) 19 years of age or older; (2) hepatic steatosis at baseline, defined as a fatty liver index (FLI) score of 60 or more[10]; (3) T2D diagnosis; and (4) newly starting SGLT2 inhibitors, thiazolidinediones, DPP-4 inhibitors, or sulfonylureas as supplementary medications to metformin, and consistently adhering to the prescribed regimen for 80% or more of 90 consecutive days spanning from October 1, 2014 to December 31, 2018.[11,12] Because the aforementioned 90-day period might result in immortal time bias, the index date was set at 90 days from the initiation of additional OADs besides metformin.[13] Study participants who had used OADs between January 2012 and September 2014 were excluded from the observed cohort to ensure that all participants were using OADs for the first time.[11] To ensure comparability, patients who had not yet initiated any OADs before the introduction of SGLT2 inhibitors were excluded from the cohort, considering that SGLT2 inhibitors were the most recently approved class among the others.[12]

Participants were also excluded based on the following criteria: (1) receiving 3 or more OAD classes before the index date; (2) history of use of injectable antidiabetic drugs, such as insulin or glucagonlike peptide-1 receptor agonists, for 90 days or more prior to the index date; (3) other competing liver diseases that may change the liver-related parameters observed in this study before the index date (eg, viral hepatitis, autoimmune hepatitis, toxic hepatitis, Wilson disease, hemochromatosis, primary biliary cholangitis, and Budd-Chiari syndrome); (4) any cancer before the index date; (5) history of using drugs that are associated with NAFLD before the index date (eg, amiodarone, corticosteroids, methotrexate, tamoxifen,

Figure 1. Study Participant Inclusion and Attrition Flow Diagram



GLP-1 indicates glucagonlike peptide-1; NAFLD, nonalcoholic fatty liver disease; and T2D, type 2 diabetes.

[a] The 4 classes of oral antidiabetic drugs assessed were sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas.

[b] These drugs included amiodarone, corticosteroids, methotrexate, tamoxifen, synthetic estrogen, valproic acid, and intravenous tetracycline.

synthetic estrogen, valproic acid, or intravenous tetracycline)[14]; (6) no health checkup information before the index date; and (7) clinically significant alcohol intake (≥210 g/wk for male patients and ≥140 g/wk for female patients).[15] Patients who used an α-glucosidase inhibitor or meglitinide were also excluded. Finally, 4 different groups of patients were determined according to the OAD class most commonly used for 90 consecutive days: SGLT2 inhibitors, thiazolidinediones, DPP-4 inhibitors, and sulfonylureas. The patient inclusion and exclusion procedures are outlined in **Figure 1**. In Supplement 1, see eFigure 1 for the study design and eTable 1 for operational definitions related to inclusion and exclusion criteria.

Outcomes

The primary outcome was NAFLD regression, defined as a reduction in FLI score to less than 30 at follow-up from a baseline of more than 60.[10] SGLT2 inhibitors were recently introduced and clinical outcomes (eg, HCC) require long-term observation in patients with NAFLD; therefore, we primarily focused on comparing the different classes of OADs for providing benefits such as NAFLD regression using the FLI, a simple and readily available index adopted in numerous studies. We considered composite liver-related outcome as the secondary end point,[1,16] incorporating incidences of liver-related hospitalization, liver-related mortality, liver transplant, and/or HCC development. Liver-related hospitalization was defined as a case of discharge with the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes corresponding to cirrhosis, decompensated cirrhosis, HCC, other liver diseases, or a case of paracentesis or varix ligation performed during hospitalization. Liver-related mortality was defined as death caused by cirrhosis, decompensated cirrhosis, HCC, or other liver diseases based on the *ICD-10* code. Liver transplant was defined as surgical procedure codes representing liver transplant or *ICD-10* codes Z94.4 or T86.4. HCC development was defined as the concurrent presence of *ICD-10* code C22 and special claim code V193. A cancer claim code was also introduced in mid-2005 and was highly accurate for a cancer diagnosis using the *ICD-10* code.[9]

Statistical Analysis

Baseline characteristic differences across the 4 OAD classes were balanced using inverse probability of treatment weighting (IPTW).[17] We also considered inverse probability of censoring weighting (IPCW) to reflect differences in loss to follow-up across classes.[18] To calculate the treatment and censoring weights, we considered the following baseline variables: continuous (age, total cholesterol, triglycerides, glucose, aspartate transaminase, alanine transaminase, γ-glutamyltransferase, creatinine, and calendar days until entry), and categorical (sex, weekly alcohol intake [no intake vs light intake, the latter defined as consumption of <210 g/wk for male patients and <140 g/wk for female patients], hypertension, body mass index [BMI, <25, 25-29.9, 30-34.9, and ≥35, calculated as weight in kilograms divided by height in meters squared], and smoking behavior [nonsmoker, former smoker, and current smoker]). For IPTW, we applied multinomial logistic regression in multigroup analyses, and we used logistic regression models conditional on baseline covariates for pairwise analyses. For IPCW, we used the Cox proportional hazards model conditional on the same baseline covariates as IPTW, additionally including the class of OADs. We used the product of the IPTW and IPCW for weighting in the data analysis. We truncated weights at the 99.9 percentile. We conducted a Gray test to compare the cumulative incidences among the OAD classes and applied the Fine-Gray model to estimate the subdistribution hazard ratios for NAFLD regression and adverse liver-related outcomes.[19] For the Gray test and Fine-Gray model, all-cause mortality and liver transplant were treated as competing events for NAFLD regression, and mortality unrelated to the liver was the competing event for the composite liver-related outcomes. We presented subdistribution hazard ratios adjusted for several covariates (ASHRs), along

Table 1. Unadjusted Baseline Characteristics

Characteristic	Median (IQR)			
	SGLT2 inhibitors (n = 9470)	Thiazolidinediones (n = 2191)	DPP-4 inhibitors (n = 55 324)	Sulfonylureas (n = 13 193)
Age, y	54 (46-61)	59 (50-67)	59 (50-67)	60 (52-69)
Sex, No. (%)				
Female	4748 (50.1)	987 (45.0)	25 258 (45.7)	6178 (46.8)
Male	4722 (49.9)	1204 (55.0)	30 066 (54.3)	7015 (53.2)
Waist circumference, cm	96 (91-102)	95 (90-100)	94 (89-99)	94 (89-99)
Body mass index, No. (%)[a]				
<25.0	265 (2.8)	158 (7.2)	4288 (7.8)	1069 (8.1)
25.0-29.9	4025 (42.5)	1190 (54.3)	30 483 (55.1)	7282 (55.2)
30.0-34.9	3845 (40.6)	690 (31.5)	16 874 (30.5)	3958 (30.0)
≥35.0	1335 (14.1)	153 (7.0)	3679 (6.6)	884 (6.7)
Alcohol intake, No. (%)				
No intake	7870 (83.1)	1854 (84.6)	46 417 (83.9)	11 240 (85.2)
Light intake[b]	1600 (16.9)	337 (15.4)	8907 (16.1)	1953 (14.8)
Smoking status, No. (%)				
Nonsmoker	5900 (62.3)	1319 (60.2)	33 582 (60.7)	8147 (61.8)
Former smoker	1638 (17.2)	418 (19.1)	10 124 (18.3)	2203 (16.7)
Current smoker	1932 (20.4)	454 (20.7)	11 618 (21)	2843 (21.6)
Hypertension, No. (%)	5332 (56.3)	1380 (63.0)	35 241 (63.7)	7850 (59.5)
Comorbidity index	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Laboratory examination results				
Total cholesterol, mg/dL	209 (179-240)	206 (175-239)	210 (181-242)	212 (183-244)
Triglycerides, mg/dL	195 (141-279)	203 (149-294)	208 (151-297)	211 (153-302)
Glucose, mg/dL	134 (116-165)	133 (115-159)	137 (118-168)	139 (118-177)
AST, U/L	33 (24-49)	31 (24-43)	31 (24-45)	31 (23-44)
ALT, U/L	44 (29-69)	38 (26-60)	40 (27-62)	39 (27-59)
γGT, U/L	52 (36-79)	50 (34-78)	53 (36-81)	53 (36-82)
Creatinine, mg/dL	0.8 (0.7-1.0)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	0.9 (0.7-1.0)
Calendar days until entry[c]	1197 (848-1550)	862 (402-1232)	983 (560-1373)	794 (401-1232)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DPP-4, dipeptidyl peptidase-4; γGT, γ-glutamyltransferase; SGLT2, sodium-glucose cotransporter 2. SI conversion factors: To convert total cholesterol from mg/dL to mmol/L, multiply by 0.0259; to convert triglycerides from mg/dL to mmol/L, multiply by 0.0113; to convert glucose from mg/dL to mmol/L, multiply by 0.0556; to convert AST, ALT, and γGT from U/L to μkat/L, multiply by 0.0113; to convert creatinine from mg/dL to mmol/L, multiply by 0.0884.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Light alcohol intake indicated consumption of less than 210 g/wk for male patients and less than 140 g/wk for female patients.

[c] This variable indicates the number of days since October 1, 2014, the first day data were collected for the cohort. Individual patients had varying times of entry.

with 95% CIs based on robust standard errors. A comorbidity index was calculated based on the Charlson Comorbidity Index using the *ICD-10* code.[20] Gramsch and Therneau tests confirmed the proportional hazard assumption.[21] We conducted sensitivity analyses on various drug use periods to confirm the robustness of the main findings at 30, 180, and 365 days. We further explored ASHRs, *P* values for interactions, and *P* values for trends among subgroups based on sex, BMI, alcohol intake, smoking, and hypertension.

Recent research suggests that the clinical characteristics and course of NAFLD vary by sex and menopausal status especially for female patients.[22] In this context, patients were grouped further according to age, with 50 years as a surrogate cutoff for menopause.[22] To assess the mediationlike effect of OAD-induced changes on BMI and serum glucose level, we conducted causal mediation analyses using Aalen additive hazards models with BMI and fasting serum glucose treated as time-varying mediators.[23]

Analyses were performed on a 2-sided basis, considering *P* values <.05 as significant. Data collection and analysis used SAS statistical software, version 9.4 (SAS Institute) and R statistical software, version 4.0.3 (R Project for Statistical Computing).

Results

Study Population Baseline Characteristics

In total, 989 544 adults started a new OAD in addition to metformin monotherapy between October 2014 and December 2018 (**Table 1**). By applying exclusion criteria, we included 80 178 patients with T2D and NAFLD for analyses (Figure 1). The study population was followed for a median of 967 (IQR, 638-1340) days and a total of 219 941 person-years. Patients who used an SGLT2 inhibitor, thiazolidinedione, DPP-4 inhibitor, or sulfonylurea were numbered 9470, 2191, 55 324, and 13 193, respectively. After IPTW adjustment, the baseline characteristics among patients using the 4 distinct classes of OADs exhibited well-balanced differences (Table 1; eTable 2 and eFigure 2 in Supplement 1). The distribution of weights used in IPTW, IPCW, inverse probability weighting (the product of IPTW and IPCW), and inverse probability weighting with truncation at 99.9% are presented in eFigure 3 in Supplement 1.

NAFLD Regression

NAFLD regression was observed in 4102 patients. Among them, patients who used an SGLT2 inhibitor, thiazolidinedione, DPP-4

Table 2. Nonalcoholic Fatty Liver Disease Regression According to Oral Antidiabetic Drug Class

Variable	SGLT2 inhibitors	Thiazolidinediones	DPP-4 inhibitors	Sulfonylureas
Crude incidence				
Patients, No. (%)	9470 (11.8)	2191 (2.7)	55 324 (69.0)	13 193 (16.5)
Events, No. (%)	499 (12.2)	143 (3.5)	2947 (71.8)	513 (12.5)
PYs	22 220	6440	150 927	40 354
Incidence per 100 000 PYs	2246	2220	1953	1271
Adjusted subdistribution hazard ratio (95% CI)[a]				
Vs sulfonylureas	1.99 (1.75-2.27)	1.70 (1.41-2.05)	1.45 (1.31-1.59)	NA
Vs DPP-4 inhibitors	1.45 (1.30-1.62)	1.14 (0.96-1.36)	NA	NA
Vs thiazolidinediones	1.40 (1.12-1.75)	NA	NA	NA

Abbreviations: DPP-4, dipeptidyl peptidase-4; NA, not applicable; PY, person-year; SGLT2, sodium-glucose cotransporter 2.

[a] The subdistribution hazard ratio was calculated using the Fine-Gray competing risk model, treating all-cause mortality and liver transplant as competing risks and using the product of inverse probability of treatment weighting and inverse probability of censoring weighting as the final weight. Inverse probability of treatment weighting was calculated using multinomial logistic regression in the multigroup analyses, and logistic regression models in pairwise analyses conditional on the baseline covariates: age, sex, body mass index, alcohol consumption, smoking status, hypertension, comorbidity index, total cholesterol, triglycerides, glucose, liver enzymes, creatinine, and calendar days until entry. Inverse probability of censoring weighting was calculated using the Cox proportional hazards model conditional on the same baseline covariates, and further including the class of oral antidiabetic drugs.

inhibitor, and sulfonylurea and experienced NAFLD regression numbered 499, 143, 2947, and 513, respectively. The number of events per 100 000 person-years was 2246, 2220, 1953, and 1271, respectively. The information on censored patients is provided in eTable 3 in Supplement 1. The incidence of NAFLD regression was higher for the SGLT2 inhibitor (ASHR, 1.99 [95% CI, 1.75-2.27]), thiazolidinedione (ASHR, 1.70 [95% CI, 1.41-2.05]), and DPP-4 inhibitor (ASHR, 1.45 [95% CI, 1.31-1.59]) groups when compared with a sulfonylurea reference group (**Table 2** and **Figure 2**A). SGLT2 inhibitors produced the most favorable outcomes among the 4 OAD classes, showing higher NAFLD regression rates in pairwise comparisons: SGLT2 inhibitors vs thiazolidinediones (ASHR, 1.40 [95% CI, 1.12-1.75]) and SGLT2 inhibitors vs DPP-4 inhibitors (ASHR, 1.45 [95% CI, 1.30-1.62]) (Table 2 and eFigure 4 in Supplement 1).

Liver-Related Outcomes

Across the study population, 276 patients presented with adverse liver-related outcomes: 12 for SGLT2 inhibitors, 8 for thiazolidinediones, 191 for DPP-4 inhibitors, and 65 for sulfonylureas. The number of events per 100 000 person-years was 52, 118, 122, and 157 for patients using an SGLT2 inhibitor, thiazolidinedione, DPP-4 inhibitor, or sulfonylurea, respectively. The information on censored patients is documented in eTable 3 in Supplement 1. Only SGLT2 inhibitors (ASHR, 0.37 [95% CI, 0.17-0.82]) but neither thiazolidinediones (ASHR, 0.77 [95% CI, 0.36-1.64]) nor DPP-4 inhibitors (ASHR, 0.86 [95% CI, 0.65-1.15]) were significantly associated with a lower incidence of adverse liver-related outcomes when compared with sulfonylureas (**Table 3** and Figure 2B). However, SGLT2 inhibitors made no significant difference in liver-related outcomes when compared with DPP-4 inhibitors (ASHR, 0.67 [95% CI, 0.33-1.35]) or thiazolidinediones (ASHR, 0.70 [95% CI, 0.27-1.84]) (Table 3 and eFigure 5 in Supplement 1).

Sensitivity and Subgroup Analyses

Overall, the results were consistent regardless of the treatment duration of additional OADs when combined with metformin: (1) throughout 90 consecutive days; (2) 80% of 30 consecutive days; (3) throughout 30 consecutive days; (4) 80% of 180 consecutive days; (5) throughout 180 consecutive days; (6) 80% of 365 consecutive days; and (7) throughout 365 consecutive days (eTables 4 to 17 and eFigures 6 and 7 in Supplement 1). In addition, the results were generally replicated in various subgroups based on sex, BMI, alcohol intake, smoking, and hypertension (eFigures 8 and 9 in Supplement 1).

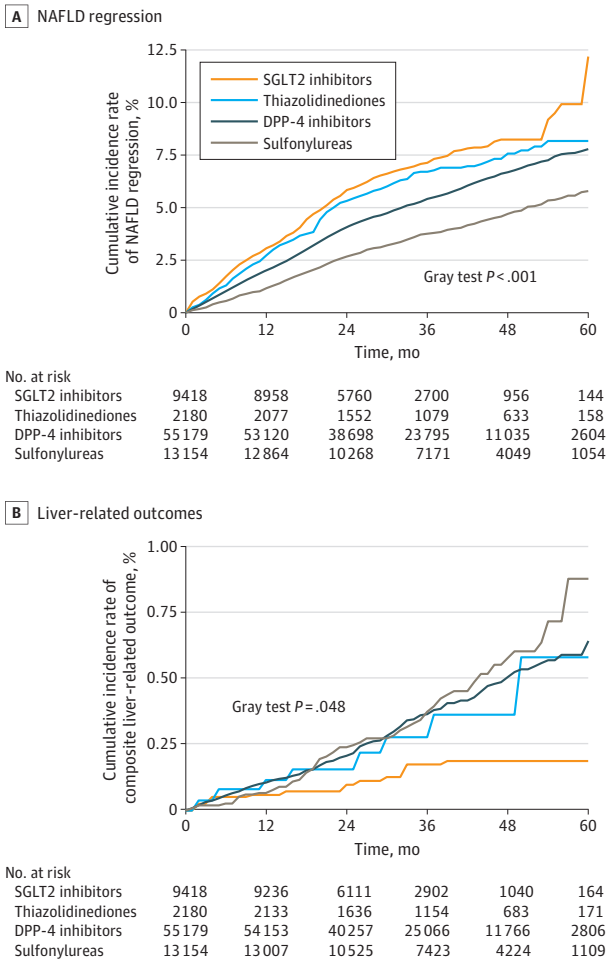
Sex Differences

The study population consisted of 43 007 male patients (53.6%) and 37 171 female patients (46.4%); among the female patients, 5862 were younger than 50 years, and 31 309 were 50 years and older. The results for NAFLD regression and composite liver-related outcomes were consistently replicated across subgroups of male patients, female patients younger than 50 years, and female patients 50 years and older (eTables 18 and 19; eFigures 10 and 11 in Supplement 1). Among female patients, menopausal status, using a surrogate age cutoff of 50 years, revealed a statistically significant interaction solely in the case of comparing SGLT2 inhibitors with DPP-4 inhibitors when NAFLD regression was examined (ASHR for female patients younger than 50 years vs older than 50 years, 1.05 [95% CI, 0.80-1.39] vs 1.46 [95% CI, 1.25-1.71]; *P* for interaction = .04).

Mediation Analyses

When evaluating SGLT2 inhibitors and sulfonylureas for clinical benefit on NAFLD regression, BMI change was associated with NAFLD regression by 7.6%, and the association of serum glucose level change with NAFLD regression was minimal (eTable 20 in Supplement 1). Comparing SGLT2 inhibitors with thiazolidinediones for NAFLD regression, BMI changes were associated with NAFLD regression by 22.1%, and serum glucose level changes was associated with minimal change (eTable 20 in Supplement 1). In the mediation analysis, BMI was significantly associated with NAFLD regression in all 4 groups. However, the mediation by BMI accounted for less than

Figure 2. Weighted Cumulative Incidence Function According to Oral Antidiabetic Drug Class



Sodium-glucose cotransporter 2 (SGLT2) inhibitors were associated with greater rates of nonalcoholic fatty liver disease (NAFLD) regression compared with other oral antidiabetic drug classes. Less adverse liver-related outcomes (defined as liver-related hospitalization, liver-related mortality, liver transplant, and hepatocellular carcinoma) were also observed for the SGLT2 inhibitor class. DPP-4 indicates dipeptidyl peptidase-4.

half of the total change, while the majority could be explained directly by OADs (eTable 20 in Supplement 1). The cumulative mediationlike associations of BMI with NAFLD regression over time in the observed OAD classes are visually depicted in eFigure 12 in Supplement 1.

Discussion

The results of this cohort study demonstrated that SGLT2 inhibitors might be preferred over other OADs (thiazolidinediones, DPP-4 inhibitors, and sulfonylureas) with respect to NAFLD regression and composite liver-related outcomes using a well-established Korean nationwide cohort. These findings demonstrated more favorable outcomes associated with the use of SGLT2 inhibitors, including NAFLD improvement, compared with thiazolidinediones. This observation is consistent with a randomized clinical trial published in 2017, which assessed patients with T2D.[24] SGLT2 inhibitors may offer advantages to patients with diabetic NAFLD due to their known ability to induce weight loss and lower glucose.[25,26] SGLT2 inhibitors redistribute visceral, subcutaneous, and ectopic fat (eg, liver fat) depots.[27] SGLT2 inhibitors facilitate glucose loss through the kidney, which provokes a fastinglike state and activates catabolic pathways in the liver and visceral adipose tissues.[28] SGLT2 inhibitors also reduce hepatic diacylglycerols that are associated with insulin resistance and the mammalian target of rapamycin signaling. They also ameliorate NAFLD independent of weight change.[28] Additionally, a preclinical pair-fed mouse model confirmed that SGLT2 inhibitors increase lipolysis and suppress systemic inflammation.[29] Increased ketogenesis associated with SGLT2 inhibition was also suggested as an underlying mechanism where SGLT2 inhibitors provided a protective mechanism against lipotoxicity.[30] SGLT2 inhibitors may also improve NAFLD by increasing adiponectin levels and lowering leptin levels in patients with T2D.[25]

Thiazolidinediones are also beneficial in terms of improvements in NASH viewed on histologic examination, regardless of the presence of T2D.[31] Thiazolidinediones, especially pioglitazones, restore lowered plasma adiponectin levels in patients with NASH, which is associated with improved hepatic steatosis and necroinflammation.[31,32] Moreover, thiazolidinediones also exhibit anti-inflammatory benefits in the liver and reduce HCC risks in Asian patients with T2D.[33] Although thiazolidinediones increase body weight, they decrease visceral to subcutaneous fat ratios and contribute to NAFLD improvement, rather than exacerbating the condition.[26,32] They also improve insulin resistance and redistribute abdominal fat depots from visceral adipose tissue to subcutaneous adipose tissue.[32]

Contrasting with SGLT2 inhibitors and thiazolidinediones, the association between NAFLD regression and DPP-4 inhibitors remains unclear.[34,35] DPP-4 inhibitors are not significantly associated with weight change.[26] Indeed, SGLT2 inhibitors exhibit glucose-lowering capabilities comparable to DPP-4 inhibitors and more favorable pleiotropic outcomes, such as improvements in body weight and liver enzymes. This distinction suggests that SGLT2 inhibitors have more favorable hepatoprotective benefits when compared with DPP-4 inhibitors.[36]

Strengths and Limitations

A major advantage of the present study is that the data were mined from the entire South Korean population, comprising approximately 50 million people. We performed head-to-head comparisons of several OAD classes that are associated with NAFLD regression, and the results demonstrated that SGLT2 inhibitors provided the most benefit in reversing NAFLD and improving liver-related outcomes. We applied several sophisticated statistical methodologies (IPTW, ICTW, and competing risk analyses) to minimize potential biases that may have been inadvertently introduced by the innate nature of a nonrandomized study. We also performed extensive sensitivity and subgroup analyses to ensure consistency in the results of the study.

Table 3. Liver-Related Outcomes According to Oral Antidiabetic Drug Class

Variable	SGLT2 inhibitors	Thiazolidinediones	DPP-4 inhibitors	Sulfonylureas
Crude incidence				
Patients, No. (%)	9470 (11.8)	2191 (2.7)	55 324 (69.0)	13 193 (16.5)
Events, No. (%)	12 (4.3)	8 (2.9)	191 (69.2)	65 (23.6)
PYs	23 082	6782	156 698	41 362
Incidence per 100 000 PYs	52	118	122	157
Adjusted subdistribution hazard ratio (95% CI)[a]				
Vs sulfonylureas	0.37 (0.17-0.82)	0.77 (0.36-1.64)	0.86 (0.65-1.15)	NA
Vs DPP-4 inhibitors	0.67 (0.33-1.35)	1.05 (0.51-2.14)	NA	NA
Vs thiazolidinediones	0.70 (0.27-1.84)	NA	NA	NA

Abbreviations: DPP-4, dipeptidyl peptidase-4; NA, not applicable; PY, person-year; SGLT2, sodium-glucose cotransporter 2.

[a] The subdistribution hazard ratio was calculated using the Fine-Gray competing risk model, treating mortality unrelated to liver disease as a competing risk and using the product of inverse probability of treatment weighting and inverse probability of censoring weighting as the final weight. Inverse probability of treatment weighting was calculated using multinomial logistic regression in the multigroup analyses, and logistic regression models in pairwise analyses conditional on the baseline covariates: age, sex, body mass index, alcohol consumption, smoking status, hypertension, comorbidity index, total cholesterol, triglycerides, glucose, liver enzymes, creatinine, and calendar days until entry. Inverse probability of censoring weighting was calculated using the Cox proportional hazards model conditional on the same baseline covariates and further including the class of oral antidiabetic drugs.

We also addressed important differences associated with sex and menstrual status in the measures of NAFLD outcomes.

Nonetheless, several limitations presented themselves. First, we included only patients with T2D receiving metformin-based dual therapy to represent individuals with poor glucose control. However, comparing the clinical benefits of OADs used alone proved challenging, as OADs other than metformin (eg, SGLT2 inhibitors, thiazolidinediones, DPP-4 inhibitors, and sulfonylureas) are seldom prescribed as monotherapy in accordance with clinical practice guidelines. The cost of these 4 classes of OADs is also not covered by the NHIS in the form of monotherapy.[37] The NHIS covers the cost of combination therapy only for patients with hemoglobin A_{1c} levels of 7% or higher, and more than 70% of Korean patients with T2D treated with OADs receive combination therapy.[37] Therefore, this study population may represent patients with T2D receiving OADs. Second, it was not possible to confirm NAFLD regression using radiological or histological diagnostic methods due to limited information available from the NHID. We sought to determine NAFLD incidence and regression using validated FLI values, rather than *ICD-10* codes that were prone to underdiagnosis.[10] The FLI might be a weak proxy for NAFLD, but extensive epidemiological data on the diagnostic and prognostic performance of the FLI supports its utility as an acceptable surrogate marker for hepatic steatosis.[38] Many studies concur that a decline in FLI over time indicates NAFLD regression.[39,40] Despite the broad adoption of this definition, there are concerns that decreases in its components (eg, BMI) may lead to decreases in the FLI, without implying NAFLD regression. However, decreases in BMI, waist circumference, and triglycerides may eventually lead to the amelioration of hepatic steatosis.[41] Furthermore, a pronounced association has been identified between changes in the FLI over time and alterations in liver fat as captured by magnetic resonance imaging–derived proton density fat fraction and ultrasound.[42,43] A number of previous studies have used a single cutoff for evaluating NAFLD regression, which could lead to an overestimation of NAFLD regression because even subtle changes in the components of the FLI may be incorrectly interpreted as NAFLD regression.[40,44] Therefore, we defined NAFLD regression with a dual cutoff criterion to take a more conservative approach to determining NAFLD regression using the FLI, which requires a minimum 30-point reduction from the baseline score—for example, the baseline FLI score is 60 or more and the follow-up FLI score is less than 30. Although the FLI has certain limitations in evaluating the presence and absence of NAFLD compared with more rigorous diagnostic methods, such as imaging and liver biopsy, the FLI holds significant clinical implications because it can be easily calculated, even in primary care settings or diabetes clinics lacking imaging equipment (eg, ultrasonography, transient elastography, and magnetic resonance imaging machines).[16,45-47] Third, the present study found through mediation analyses that NAFLD regression should be interpreted with caution because OADs may change BMI, which is used in calculating the FLI.[10] Further studies evaluating NAFLD regression using diagnostic methods other than the FLI will elucidate the direct and indirect effects of OADs on NAFLD regression.

Fourth, glycated hemoglobin values were not available from the NHID. Alternatively, we substituted fasting glucose for adjustment of IPTW and IPCW. Fifth, although IPTW was used to address the baseline differences among the OAD classes, the possibility of unmeasured confounding should not be ignored. Sixth, due to the small number of events and relatively insufficient follow-up duration, it was difficult to detect statistical significance across the different OAD classes regarding composite liver-related outcomes. HCC occurs rarely in patients with NAFLD, ranging from 10 to 130 cases per 100 000 person-years.[1] Therefore, we analyzed liver-related events as a composite outcome, which included liver-related hospitalization, liver-related death, liver transplant, and HCC. Nevertheless, given the recent introduction of SGLT2 inhibitors in South Korea, a sufficient number of events might not have been observed during the follow-up periods. Considering the low incidence of liver-related outcomes, only 52 to 157 cases per 100 000 person-years, further lengthy observational studies are required as high NAFLD prevalence may ultimately result in more cases with

liver-related outcomes, increasing the public burden of disease. Seventh, information about alcohol consumption and smoking behavior was sourced from self-reported surveys, which opens these data points to potential recall bias.[8]

Conclusions

Although the international clinical practice guidelines for patients with T2D recommended routine NAFLD screening,[15,48] no recommendations were provided regarding which OADs are preferred for patients with T2D and concomitant NAFLD. The results of this cohort study demonstrated that SGLT2 inhibitors might have potential benefits for patients with both NAFLD and T2D, compared with other OAD classes. However, these findings should be interpreted with caution due to the observational nature of this study. Further research on the clinical outcomes of different classes of OADs on NAFLD would provide a foundation for creating guidance for determining which OADs are preferred. Furthermore, because patients with T2D at risk of cardiovascular disease are advised to take SGLT2 inhibitors,[48] comprehensive research in this patient group is warranted to confirm the potential advantages of SGLT2 inhibitors for preventing cardiovascular disease over other OADs.

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