Sodium–glucose cotransporter 2 inhibitors do not increase the risk of fractures in real-world clinical practice in Korea: A national observational cohort study

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ABSTRACT

Aims/Introduction: This study aimed to determine whether sodium–glucose cotransporter 2 inhibitors (SGLT2i) were related to increased fracture risk in adults with type 2 diabetes compared with dipeptidyl peptidase-4 inhibitors (DPP-4i).

Materials and Methods: Between 1 May 2016 and 31 December 2018, we carried out a new-user cohort study using the Korean National Health Insurance Service database. Propensity score matching was carried out on 478,826 new users of an SGLT2i or DPP-4i. After propensity score matching on >80 covariates, 84,460 individuals were initiated on SGLT2i or DPP-4i, with 42,230 individuals in each treatment group. The time to first fracture event was compared between the SGLT2i and DPP-4i groups using Cox proportional hazards models, and the results are reported as hazard ratios with 95% confidence intervals for fracture occurrence. Subgroup analyses investigated fractures between treatment groups according to baseline characteristics.

Results: Individuals who were started on SGLT2i were not linked with increased fracture risk in both as-treated and intention-to-treat analyses (as-treated: hazard ratio 0.98, 95% confidence interval 0.92–1.04; intention-to-treat: hazard ratio 0.94, 95% confidence interval 0.89–1.00). We identified no significant interaction between the individuals’ age, sex, fracture history or thiazolidinedione use in any subgroup analyses, showing that none of these variables appeared to be impact modifiers in the connection between SGLT2i and fractures.

Conclusions: Our study found no increase in the risk of fracture among individuals treated with SGLT2i in a real-world clinical setting for type 2 diabetes.

INTRODUCTION

Osteoporosis and type 2 diabetes are some of the most prevalent diseases, particularly among the elderly. Several older individuals have both conditions and take medications for these diseases concurrently. Fragility fractures are more common in people with type 2 diabetes. Older adults with type 2 diabetes should be aware of their fracture risk. Antidiabetic medications might influence bone metabolism, although the increased fracture risk is probably a result of a combination of factors. Therefore, new antidiabetic agents with no adverse effects on bones are sought. There have been concerns that sodium–glucose cotransporter 2 inhibitors (SGLT2i), a recently developed type of antidiabetic medication, might cause bone loss due to changes in calcium and phosphate homeostasis as a result of secondary hyperparathyroidism caused by the induction of increased phosphate reabsorption.

Previous studies examined the association between SGLT2i monotherapy and fracture risk in people with type 2 diabetes, but yielded conflicting conclusions. The Data and Safety Monitoring Committee carried out a routine interim review of the CANagliflozin cardioVascular Assessment Study (CANVAS) in 2013 and discovered a greater fracture incidence in
the canagliflozin group than in the placebo group. However, the risks of canagliflozin on fracture were inconsistent between the CANVAS and CANVAS-Renal (CANVAS-R) trials. The difference between the proportion of Asian patients enrolled in CANVAS and CANVAS-R (18% vs 8%, respectively) has been suggested as one of the hypotheses for the discordant risks.

Asians typically have pancreatic β-cell dysfunction and less obesity, but more visceral obesity than white people. These pathophysiological differences might impact the bone metabolism effects of SGLT2i in Asians. In Korea, vitamin D insufficiency was more prevalent than in the USA and Canada. Lumbar spine bone density was also found to be lower than those for the femoral neck or hip of Koreans. Therefore, it is necessary to evaluate the impact of SGLT2i on fracture risk in a Korean population with type 2 diabetes.

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are frequently used in the same way as SGLT2i for patients with type 2 diabetes. DPP-4i are relatively new and widely used glucose-lowering drugs. The proportion of patients using DPP-4i as second-line drugs was 56% in 2016, and it is most commonly used in Korea. DPP-4i have been shown to be safe, with a neutral risk of cardiovascular complications and no risk of bone fracture. Additionally, a recent study reported that DPP-4i have no discernible effect on the risk of fractures in a Korean population. As a result, DPP-4i are suitable active comparators for assessing SGLT2i safety on fracture risk in people with type 2 diabetes in a clinical context.

The present study aimed to determine whether SGLT2i was related to increased fracture risk in people with type 2 diabetes compared with DPP-4i, using real-world data from a national claim database in Korea.

MATERIALS AND METHODS

Data source
We carried out new-user cohort research using the Korean National Health Insurance Service database, which serves as a centralized repository for longitudinal data on 97% of the Korean population. The Korean National Health Insurance Service database contains information on sociodemographic characteristics; claims, such as diagnoses (International Classification of Diseases, tenth revision code); prescriptions for drugs (Anatomical Therapeutic Chemical code), clinical procedures and national health screening; and mortality (linked to the National Death Registry using unique resident registration numbers). Annual health insurance premiums, which are determined by income and assets, were used to indirectly measure socioeconomic status.

The institutional review board of Ajou University Hospital approved this study (AJIRB-MED-EXP-21-392), which waived the requirement for informed consent due to the de-identification of all patient data.

Study population
Between 1 May 2016 and 31 December 2018, the study included participants with type 2 diabetes who were recently started on SGLT2i or DPP-4i (as defined by the Anatomical Therapeutic Chemical codes indicated in Table S1). No past use of SGLT2i or DPP-4i within the 12-month period preceding the first prescription was considered new use (as initial or add-on therapy). The index date was defined as the date on which SGLT2i or DPP-4i was prescribed. Individuals were excluded if they: (i) had been diagnosed with end-stage renal disease or kidney transplantation (both of which are contraindications for SGLT2i treatment); (ii) had been diagnosed with type 1 diabetes; (iii) had been diagnosed with gestational diabetes within the past year before the index date; (iv) were under the age of 18 years on the index date; (v) had been diagnosed with a malignancy within the past 5 years before the index date; or (vi) had been diagnosed with HIV within the past year (Figure S1).

Follow up and outcome
The outcome was defined as the development of any fracture after the initiation of treatment. Fractures were found during any hospital visit, whether inpatient or outpatient, with a fracture diagnosis (defined using diagnosis codes as detailed in Table S1). Two time-at-risk periods were evaluated: (i) risk during the period of drug exposure as determined by an as-treated (AT) analysis; and (ii) risk after initiating the treatment as determined by an intention-to-treat (ITT) study. The AT method defined the follow-up period as the time between the index date and the date of the first fracture, withdrawal of the original treatment, switch to or addition of the comparator drug, date of death from any cause, or end of the research period (31 December 2018). In the ITT analysis, the follow-up period was defined as the time from the index date to the date of the first fracture, date of death from any cause or end of the study period (31 December 2018).

Statistical analysis
We used descriptive statistics to assess the baseline characteristics of people with type 2 diabetes who were started on SGLT2i or DPP-4i. Frequencies and percentages are used to represent categorical variables, whereas mean and standard deviation are used to represent continuous variables. To eliminate confounding variables, those initiating SGLT2i were matched 1:1 with those initiating DPP-4i based on their estimated propensity score. The probability of initiating treatment with SGLT2i versus DPP-4i was determined using a multivariable logistic regression model that included virtually all baseline factors associated with treatment assignment or outcome. A total of 12 months before cohort enrollment, baseline variables were examined (defined using diagnosis codes as detailed in Table S1). Matching was carried out using a nearest-neighbor caliper width of 0.25 multiplied by the standard deviation of the propensity score distribution. Standardized differences were used to balance covariates; a standard deviation of ≤10% showed appropriate group balance.

After propensity score matching, the time interval between drug initiation and fracture occurrence was visualized using...
Kaplan–Meier curves, and the incidence curves were compared using the log-rank test. Fracture rates were determined in the therapy group. In each category, the crude incidence rate was computed by dividing the number of incident occurrences by the total number of person-years at risk. The time to the first incident was compared between the SGLT2i and DPP-4i groups using Cox proportional hazards models and is reported as hazard ratios (HRs) for fracture occurrence with 95% confidence intervals (CIs). Subgroup studies compared the fracture rate between treatment groups according to their baseline characteristics.

The SAS Enterprise Guide 7.1 (SAS Institute, Inc., Cary, NC, USA) and R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria) software programs were used to analyze the data.

RESULTS

During the study period, we identified 478,826 patients who were initiated on SGLT2i or DPP-4i, of which 42,588 and 436,238 received SGLT2i and DPP-4i, respectively (Figure S1). The distribution of specific SGLT2i or DPP-4i compounds within each group is shown in Table S2. SGLT2i compounds included dapagliflozin (54.3%), em格化lipiflazin (39.2%) and ipragliflozin (6.5%; Table S2).

Before propensity score matching, the two groups had different baseline characteristics. Individuals initiated on SGLT2i were younger, and had higher proportions of hyperlipidemia and heart disease, but lower proportions of stroke, peripheral vascular disease, chronic kidney disease, osteoporosis and fracture (Table 1). After propensity score matching on >80 covariates, 84,460 individuals were initiated on SGLT2i or DPP-4i, with 42,230 individuals in each treatment group (Figure S1). Furthermore, baseline characteristics were well balanced between groups, with a standardized difference of 4% for all variables (Table 1).

In both the AT and ITT analyses, people started on SGLT2i did not have an increased fracture risk compared with those started on DPP-4i (AT: HR 0.98, 95% CI 0.92–1.04; ITT: HR 0.94, 95% CI 0.89–1.00) (Figures 1 and 2). Similar results were observed for the fracture sites (Figure S2).

Major risk factor variables were included in the Korean National Health Insurance Service claims database, but vital status information was missing. Therefore, we carried out a sensitivity analysis using a cohort consisting solely of individuals who had a national health screening within the 12-month period preceding cohort entry. Table S3 summarizes the baseline characteristics of participants who underwent national health screening. Although there were slight differences in the magnitude and significance of association, including vital status variables, it had no significant effect on the identified connections (AT: HR 0.95, 95% CI 0.86–1.06; ITT: HR 0.94, 95% CI 0.86–1.03, Figure S3).

We identified no significant interactions between the people’s age, sex, fracture history or use of thiazolidinedione in any of the subgroup analyses, implying that none of these variables were effect modifiers of the link between SGLT2i and fractures (Figure 3).

DISCUSSION

We have shown that initiating SGLT2i did not enhance fracture risk when compared with initiating DPP-4i in this cohort trial of >85,000 persons with type 2 diabetes based on nationwide real-world data from Korea. Furthermore, the results were consistent, regardless of the risk factors for fracture, such as old age or previous fractures.

SGLT2i are a new class of glucose-lowering medications that enhance renal glucose excretion. SGLT2i have been proven to have protective effects against cardiovascular disease in cardiovascular outcome clinical trials and in real-world settings. Conversely, SGLT2i increased parathyroid hormone levels and decreased 1,25-dihydroxy vitamin D levels, thereby impairing bone metabolism. SGLT2i might indirectly promote bone turnover by encouraging weight reduction and improve bone metabolism impairment associated with diabetes by lowering blood glucose levels. Canagliflozin might have a deleterious effect on bone microarchitecture in animal studies, which could be explained by the diabetes-related decrease in bone structural strength and toughness. Additionally, canagliflozin resulted in a decrease in total hip bone mineral density in a randomized controlled trial. Conversely, ertugliflozin and dapagliflozin showed no negative effect on bone mineral density loss.

The CANVAS study, a large cardiovascular outcome trial of SGLT2i, found that canagliflozin was associated with a greater fracture rate than the placebo (HR 1.51, 95% CI 1.04–2.19). The CANVAS Program, which combined data from the CANVAS and CANVAS-R trials (a second canagliflozin trial carried out concurrently with CANVAS), showed an elevated fracture risk (HR 1.26, 95% CI 1.04–1.52); however, the risk was modestly decreased. The fracture risk was raised in the canagliflozin group in the CANVAS trial (HR 1.55, 95% CI 1.21–1.97), but not in the CANVAS-R trial (HR 0.86, 95% CI 0.62–1.19). However, the discordant risk between CANVAS and CANVAS-R was not clearly explained. Furthermore, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDiDEN) trial recently showed no significant difference in fracture risk between the canagliflozin and placebo groups.

Other SGLT2i cardiovascular outcome trials, including the EMPA-REG OUTCOME, SGLT2i empagliflozin and Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 trials, found no evidence of increased fracture risk. Recent meta-analyses of randomized controlled trials have shown that SGLT2i are not related to increased fracture risk.

SGLT2i did not increase the risk of fractures in a recent real-world clinical practice setting. In a longitudinal cohort study carried out in the USA using a commercial insurance claims database, newly prescribed canagliflozin was not associated with increased fracture risk in middle-aged people with type 2 diabetes.
## Table 1 | Baseline characteristics of people with type 2 diabetes before and after propensity score matching

|                         | Before PSM | After PSM | Standardized difference |
|-------------------------|------------|-----------|-------------------------|
|                         | SGLT2i (n = 42,588) | DPP-4i (n = 436,238) | SGLT2i (n = 42,230) | DPP-4i (n = 42,230) | Standardized difference |
| Mean age, years (SD)    | 54.6 (12.4) | 62.0 (12.8) | 58.6 | 54.8 (12.3) | 54.8 (12.3) | 0.0 |
| Women                   | 17,595 (41.3) | 188,317 (43.2) | 3.8 | 17,409 (41.2) | 17,409 (41.2) | 0.0 |
| Index year              | 2016       | 9,084 (21.3) | 127,485 (29.2) | 21.7 | 9,047 (21.4) | 12,190 (29.0) | 0.0 |
|                         | 2017       | 18,288 (42.9) | 185,176 (42.4) | 18.1 | 18,167 (43.0) | 18,190 (43.1) | 0.0 |
|                         | 2018       | 15,216 (35.7) | 123,577 (28.3) | 15.0 | 15,016 (35.6) | 15,189 (36.0) | 0.0 |
| Household income        | Low        | 9,917 (23.3) | 102,806 (23.6) | 3.1 | 9,823 (23.3) | 9,885 (23.4) | 0.9 |
|                         | Intermediate | 14,892 (35.0) | 143,867 (33.0) | 14.7 | 14,763 (35.0) | 14,782 (35.0) | 0.3 |
|                         | High       | 16,033 (37.6) | 164,803 (37.8) | 15.4 | 15,904 (37.7) | 15,783 (37.4) | 0.8 |
|                         | Missing    | 1,746 (4.1) | 24,762 (5.7) | 1,740 (4.1) | 1,780 (4.2) | 1.1 |
| Drugs                   | Metformin  | 29,911 (70.2) | 228,203 (52.3) | 37.4 | 29,599 (70.1) | 29,996 (71.0) | 2.1 |
|                         | Sulfonylureas | 11,534 (27.1) | 141,412 (32.4) | 11.7 | 11,501 (27.2) | 11,639 (27.6) | 0.7 |
|                         | GLP-1 RA   | 13.0 (0.0) | 42.0 (0.0) | 1.5 | 11.0 (0.0) | 13.0 (0.0) | 0.3 |
|                         | Thiazolidinediones | 1,816 (4.3) | 22,364 (5.1) | 4.1 | 1,809 (4.3) | 1,790 (4.2) | 0.8 |
|                         | Meglitinides | 119 (0.3) | 1,851 (0.4) | 2.4 | 118 (0.3) | 136 (0.3) | 0.8 |
|                         | Insulin    | 3,217 (7.6) | 38,543 (8.8) | 4.7 | 3,141 (7.4) | 3,024 (7.2) | 1.1 |
|                         | Alpha-glucosidase inhibitors | 608 (1.4) | 10,396 (2.4) | 7.0 | 608 (1.4) | 667 (1.6) | 1.1 |
| Other drugs             | ACE inhibitor | 1,082 (2.5) | 9,640 (2.2) | 2.2 | 1,061 (2.5) | 1,016 (2.4) | 0.7 |
|                         | ARB        | 18,369 (43.1) | 183,813 (42.1) | 2.0 | 18,186 (43.1) | 18,255 (43.2) | 0.3 |
|                         | Beta-blocker | 6,213 (14.6) | 60,537 (13.9) | 2.0 | 6,104 (14.5) | 5,927 (14.0) | 1.2 |
|                         | Calcium channel blocker | 6,848 (16.1) | 86,299 (19.8) | 9.6 | 6,792 (16.1) | 6,714 (15.9) | 0.5 |
|                         | Thiazides  | 3,319 (7.8) | 37,873 (8.7) | 3.2 | 3,281 (7.8) | 3,176 (7.5) | 0.9 |
|                         | Loop diuretics | 2,128 (5.0) | 33,856 (7.8) | 11.3 | 2,097 (5.0) | 2,002 (4.7) | 1.0 |
|                         | Other diuretics | 1,157 (2.7) | 13,378 (3.1) | 2.1 | 1,123 (2.7) | 1,049 (2.5) | 1.1 |
|                         | Nitrates   | 2,665 (6.3) | 23,785 (5.5) | 3.4 | 2,614 (6.2) | 2,507 (5.9) | 1.1 |
|                         | Digoxin    | 369 (0.9) | 6,409 (1.5) | 5.6 | 364 (0.9) | 353 (0.8) | 0.3 |
|                         | Antiarhythmic drugs | 300 (0.7) | 3,266 (0.7) | 0.5 | 295 (0.7) | 272 (0.6) | 0.7 |
|                         | COPD drugs | 10,169 (23.9) | 108,136 (24.8) | 2.1 | 10,074 (23.9) | 10,047 (23.8) | 0.2 |
|                         | Statin     | 28,778 (67.6) | 265,351 (60.8) | 14.1 | 28,497 (67.5) | 28,533 (67.6) | 0.2 |
|                         | Antiplaquelet | 14,371 (33.7) | 160,900 (36.9) | 6.6 | 14,258 (33.8) | 14,055 (33.3) | 1.0 |
|                         | Anticoagulants | 727 (1.7) | 8,896 (2.0) | 2.5 | 711 (1.7) | 675 (1.6) | 0.7 |
|                         | NSAIDs    | 32,458 (76.2) | 337,345 (77.3) | 2.6 | 32,192 (76.2) | 32,198 (76.2) | 0.0 |
|                         | Oral corticosteroids | 14,727 (34.6) | 148,535 (34.0) | 1.1 | 14,598 (34.6) | 14,454 (34.2) | 0.7 |
|                         | Bisphosphonates | 1,144 (2.7) | 25,087 (5.8) | 15.3 | 1,144 (2.7) | 1,076 (2.5) | 1.0 |
|                         | Opioids   | 20,287 (47.6) | 228,408 (52.4) | 9.5 | 20,150 (47.7) | 20,046 (47.5) | 0.5 |
|                         | Antidepressants | 4,697 (11.0) | 60,093 (13.8) | 8.3 | 4,656 (11.0) | 4,591 (10.9) | 0.5 |

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Table 1. (Continued)

| Category                               | Before PSM |                      | Before PSM |                      |
|----------------------------------------|------------|----------------------|------------|----------------------|
|                                        | SGlt2 (n = 42,588) | DPP-4i (n = 436,238) | Standardized difference | SGlt2 (n = 42,230) | DPP-4i (n = 42,230) | Standardized difference |
| Antipsychotics                         | 1,128 (2.6) | 17,077 (3.9)          | 7.1        | 1,113 (2.6)         | 10,888 (2.6)          | 0.4                     |
| Anticonvulsants                        | 4,236 (9.9) | 56,199 (12.9)         | 9.2        | 4,203 (10.0)        | 41,222 (9.8)          | 0.6                     |
| Lithium                                | 152 (0.4)   | 951 (0.2)             | 2.6        | 143 (0.3)           | 145 (0.3)              | 0.1                     |
| Benzo diazepines                       | 11,208 (26.3)| 138,232 (31.7)       | 11.9       | 11,138 (26.4)       | 109,939 (26.0)         | 0.8                     |
| Agents for dementia                    | 2,327 (5.5) | 42,957 (9.8)          | 16.5       | 2,321 (5.5)         | 2,303 (5.5)            | 0.2                     |
| Antiparkinson agents                   | 647 (1.5)   | 10,541 (2.4)          | 6.5        | 644 (1.5)           | 615 (1.5)              | 0.6                     |
| Teniparatide                           | 6 (0.0)     | 113 (0.0)             | 1.4        | 6 (0.0)             | 5 (0.0)                | 0.2                     |
| SERMs in women                         | 185 (1.1)   | 2,993 (1.6)           | 4.7        | 185 (1.1)           | 130 (0.7)              | 3.3                     |
| Comorbidities                          |             |                      |            |                     |                      |                         |
| Diabetic retinopathy                   | 6,469 (15.2)| 71,076 (16.3)        | 3.0        | 6,398 (15.2)        | 6,293 (14.9)           | 0.7                     |
| Diabetes with other                    | 10,401 (24.4)| 115,465 (26.5)       | 4.7        | 10,322 (24.4)       | 10,131 (24.0)          | 1.1                     |
| Retinal detachment, vitreous           | 913 (2.1)   | 9,978 (2.3)           | 1.0        | 903 (2.1)           | 848 (2.0)              | 0.9                     |
| Retinal laser coagulation therapy      | 604 (1.4)   | 6,159 (1.4)           | 0.1        | 595 (1.4)           | 574 (1.4)              | 0.4                     |
| Diabetic neuropathy                    | 6,257 (14.7)| 76,254 (17.5)        | 7.6        | 6,206 (14.7)        | 6,214 (14.7)           | 0.1                     |
| Diabetic nephropathy                   | 4,288 (10.1)| 40,222 (9.2)         | 2.9        | 4,219 (10.0)        | 4,109 (9.7)            | 0.9                     |
| Hypoglycemia                           | 408 (1.0)   | 6,998 (1.6)           | 5.7        | 406 (1.0)           | 372 (0.9)              | 0.8                     |
| Diabetic ketoacidosis                  | 187 (0.4)   | 1,639 (0.4)           | 1.0        | 182 (0.4)           | 185 (0.4)              | 0.1                     |
| Lower extremity amputation             | 14 (0.0)    | 365 (0.1)             | 2.1        | 14 (0.0)            | 13 (0.0)               | 0.1                     |
| Hypertension                           | 25,067 (58.9)| 262,318 (60.1)       | 2.6        | 24,830 (58.8)       | 24,872 (58.9)          | 0.2                     |
| Hyperlipidemia                         | 36,384 (85.4)| 352,391 (80.8)       | 12.4       | 36,052 (85.4)       | 36,072 (85.4)          | 0.0                     |
| Ischemic heart disease                 | 8,022 (18.8)| 74,888 (17.2)        | 4.3        | 7,911 (18.7)        | 7,778 (18.4)           | 0.8                     |
| Acute MI                               | 1,111 (2.6) | 8,058 (1.8)           | 5.2        | 1,081 (2.6)         | 10,20 (2.4)            | 0.9                     |
| Acute coronary syndrome/unstable angina| 1,810 (4.3) | 15,311 (3.5)         | 3.8        | 1,781 (4.2)         | 1,733 (4.1)            | 0.6                     |
| Stable angina                          | 1,892 (4.4) | 18,362 (4.2)          | 1.1        | 1,868 (4.4)         | 1,793 (4.2)            | 0.9                     |
| Cardiac procedure                      | 917 (2.2)   | 5,371 (1.2)           | 7.2        | 891 (2.1)           | 838 (2.0)              | 0.9                     |
| Any stroke                             | 2,204 (5.2) | 37,057 (8.5)          | 13.2       | 2,193 (5.2)         | 2,241 (5.3)            | 0.5                     |
| Ischemic stroke                        | 1,913 (4.5) | 32,935 (7.5)          | 12.9       | 1,904 (4.5)         | 1,952 (4.6)            | 0.5                     |
| Hemorrhagic stroke                     | 238 (0.6)   | 3,649 (0.8)           | 3.3        | 236 (0.6)           | 231 (0.5)              | 0.2                     |
| Transient ischemic attack              | 761 (1.8)   | 10,805 (2.5)          | 4.8        | 758 (1.8)           | 785 (1.9)              | 0.5                     |
| Other cerebrovascular disease          | 2,398 (5.6) | 33,142 (7.6)          | 7.9        | 2,383 (5.6)         | 2,427 (5.7)            | 0.4                     |
| Congestive heart failure               | 2,705 (6.4) | 27,059 (6.2)          | 0.6        | 2,648 (6.3)         | 2,537 (6.0)            | 1.1                     |
| Peripheral vascular disease            | 8,631 (20.3)| 101,101 (23.2)       | 7.1        | 8,573 (20.3)        | 8,479 (20.1)           | 0.6                     |
| Atrial fibrillation                    | 1,110 (2.6) | 12,212 (2.8)          | 1.2        | 1,088 (2.6)         | 1,043 (2.5)            | 0.7                     |
| Cardiac conduction disorders           | 171 (0.4)   | 2,041 (0.5)           | 1.0        | 170 (0.4)           | 154 (0.4)              | 0.6                     |
| COPD                                   | 5901 (13.9) | 71,021 (16.3)         | 6.8        | 5,857 (13.9)        | 5,735 (13.6)           | 0.8                     |
| Asthma                                 | 9,404 (22.1)| 94,471 (21.7)        | 6.0        | 9,308 (22.0)        | 9,174 (21.7)           | 0.8                     |
| Obstructive sleep apnea                | 291 (0.7)   | 1,237 (0.3)           | 5.8        | 275 (0.7)           | 239 (0.6)              | 1.1                     |
Table 1. (Continued)

| Condition                  | Before PSM | DPP-4i (n = 436,238) | Standardized difference | After PSM | DPP-4i (n = 42,230) | Standardized difference |
|----------------------------|------------|----------------------|-------------------------|-----------|---------------------|-------------------------|
|                            | SGLT2i (n = 42,588) |          |                          |           |                     |                          |
| Pneumonia                  | 3,477 (8.2) | 40,744 (9.3)         | 4.2                     | 3,445 (8.2) | 3,465 (8.2)         | 0.2                     |
| Chronic kidney disease     | 539 (1.3)  | 11,819 (2.7)         | 10.4                    | 539 (1.3)  | 533 (1.3)           | 0.1                     |
| Liver disease              | 24,594 (57.7) | 23,926 (53.4)         | 88                      | 24,359 (57.7) | 24,250 (57.4)         | 0.5                     |
| Osteoarthritis             | 15,914 (37.4) | 188,782 (43.5)         | 12.5                    | 15,816 (37.5) | 15,614 (37.0)         | 1.0                     |
| Dorsopathies               | 24,655 (57.9) | 265,856 (60.9)         | 6.2                     | 24,455 (57.9) | 24,375 (57.7)         | 0.4                     |
| Fractures                  | 3,674 (8.6)  | 48,834 (11.2)         | 8.6                     | 3,649 (8.6)  | 3,660 (8.7)          | 0.1                     |
| Osteoporosis               | 4,429 (10.4) | 73,326 (16.8)         | 18.8                    | 4,422 (10.5) | 4,220 (10.0)         | 1.6                     |
| Hyperthyroidism            | 1,407 (3.3)  | 13,565 (3.1)          | 1.1                     | 1,387 (3.3)  | 1,426 (3.4)          | 0.5                     |
| Hypothyroidism             | 3,658 (8.6)  | 33,638 (7.7)          | 3.2                     | 3,618 (8.6)  | 3,368 (8.0)          | 2.1                     |
| Depression                 | 4,827 (11.3) | 61,203 (14.0)         | 8.1                     | 4,781 (11.3) | 4,690 (11.1)         | 0.7                     |
| Anxiety                    | 7,532 (17.7) | 90,889 (20.8)         | 8.0                     | 7,468 (17.7) | 7,361 (17.4)         | 0.7                     |
| Sleep disorder             | 6,413 (15.1) | 78,865 (18.1)         | 8.1                     | 6,366 (15.1) | 6,421 (15.2)         | 0.4                     |
| Dementia                   | 824 (1.9)   | 24,349 (5.6)          | 19.3                    | 820 (1.9)   | 778 (1.8)           | 0.7                     |
| Delirium                   | 58 (0.1)    | 1,792 (0.4)           | 5.3                     | 57 (0.1)    | 49 (0.1)            | 0.5                     |
| Psychosis                  | 675 (1.6)   | 7,821 (1.8)           | 16                     | 663 (1.6)   | 673 (1.6)           | 0.2                     |
| Combined comorbidity score | 0.3 (0.9)   | 0.3 (1.0)             | 3.4                     | 0.3 (0.9)   | 0.2 (1.0)           | 1.2                     |

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; PSM, propensity score matching; SD, standard deviation; SERMs, selective estrogen receptor modulators; SGLT2i, sodium–glucose cotransporter 2 inhibitor.
Figure 1 | Cumulative risk curve of incident fracture treated with sodium–glucose cotransporter 2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP-4i) in (a) as-treated (AT) and (b) in intention-to-treat (ITT) analysis.

| Total follow-up (years) | No. of events | Event rate (100 PY) | HR (95% CI) | P-value |
|-------------------------|---------------|---------------------|-------------|---------|
| AT                      |               |                     |             |         |
| SGLT2i                  | 41,771        | 1,923               | 4.60        | 0.98 (0.92–1.04) | 0.522 |
| DPP-4i                  | 38,980        | 1,851               | 4.75        |         |
| ITT                     |               |                     |             |         |
| SGLT2i                  | 52,902        | 2,377               | 4.49        | 0.94 (0.89–1.00) | 0.042 |
| DPP-4i                  | 52,419        | 2,500               | 4.77        |         |

Figure 2 | Hazard ratio (HR) for fracture in people who were started on sodium–glucose cotransporter 2 inhibitor (SGLT2i) compared with that of individuals who were started on dipeptidyl peptidase-4 inhibitor (DPP-4i). AT, as-treated; CI, confidence interval; ITT, intention-to-treat; PY, person-years.
diabetes when compared with those who were newly prescribed glucagon-like peptide-1 receptor agonist\textsuperscript{10}. Compared with that of glucagon-like peptide-1 receptor agonist, the use of SGLT2i had a neutral correlation with fractures in nationwide health and administrative registries in Sweden and Denmark\textsuperscript{36}. Additionally, when compared with those taking DPP-4i, those prescribed SGLT2i were not at increased risk of fracture, and when stratified by SGLT2 compound (canagliflozin, dapagliflozin or empagliflozin), no type of SGLT2i was associated with increased fracture risk. Indeed, canagliflozin users had a decreased fracture risk (HR 0.47, 95% CI 0.25–0.88)\textsuperscript{37}. In the present nationwide cohort research, we observed no statistically significant link between SGLT2i and fracture risk. Canagliflozin is not accessible in Korea, which might have contributed to the SGLT2i group’s increased incidence of neutral fracture.

A higher proportion of Asian patients in CANVAS than in CANVAS-R has been suggested as one of the hypotheses for the discordant risks\textsuperscript{10}. However, in the ITT analysis, individuals treated with SGLT2i had a considerably lower fracture risk than those treated with DPP-4i; this difference was especially obvious.

**Table 3** Subgroup analysis of hazard ratio (HR) for fracture in people who were started on sodium–glucose cotransporter 2 inhibitor (SGLT2i) compared with that of individuals who were started on dipeptidyl peptidase-4 inhibitor (DPP-4i) in (a) as-treated (AT) and (b) intention-to-treat (ITT) analysis. PY, person-years; T2D, type 2 diabetes.

| Age groups | SGLT2i | DPP-4i | HR (95% CI) | P-value | P for interaction |
|------------|--------|--------|-------------|---------|------------------|
| **(a) AT** |        |        |             |         |                  |
|           | Event rate (100 PY) |        |             |         |                  |
| < 65 years | 3.89   | 3.96   | 0.99 (0.91–1.07) | 0.738   | 0.804            |
| 65 years   | 7.37   | 7.60   | 0.97 (0.86–1.08) | 0.533   |                   |
| Sex        |        |        |             |         |                  |
| Men        | 3.72   | 3.89   | 0.96 (0.87–1.05) | 0.380   | 0.632            |
| Women      | 5.83   | 5.94   | 0.99 (0.91–1.08) | 0.797   |                   |
| History of fracture |        |        |             |         |                  |
| Yes        | 22.18  | 24.18  | 0.94 (0.84–1.05) | 0.283   | 0.274            |
| No         | 3.38   | 3.40   | 0.99 (0.92–1.07) | 0.802   |                   |
| Use of TZD |        |        |             |         |                  |
| Yes        | 5.23   | 5.89   | 0.91 (0.75–1.10) | 0.345   | 0.333            |
| No         | 4.53   | 4.64   | 0.99 (0.92–1.05) | 0.636   |                   |
| **(b) ITT**|        |        |             |         |                  |
|           | Event rate (100 PY) |        |             |         |                  |
| < 65 years | 3.78   | 4.00   | 0.94 (0.88–1.01) | 0.070   | 0.863            |
| 65 years   | 7.33   | 7.72   | 0.95 (0.86–1.04) | 0.285   |                   |
| Sex        |        |        |             |         |                  |
| Men        | 3.59   | 3.98   | 0.90 (0.83–0.97) | 0.010   | 0.151            |
| Women      | 5.76   | 5.91   | 0.98 (0.90–1.05) | 0.522   |                   |
| History of fracture |        |        |             |         |                  |
| Yes        | 20.14  | 21.71  | 0.93 (0.84–1.03) | 0.158   | 0.761            |
| No         | 3.40   | 3.58   | 0.94 (0.88–1.01) | 0.094   |                   |
| Use of TZD |        |        |             |         |                  |
| Yes        | 5.32   | 6.10   | 0.88 (0.75–1.05) | 0.152   | 0.337            |
| No         | 4.41   | 4.64   | 0.95 (0.89–1.01) | 0.075   |                   |

Figure 3 | Subgroup analysis of hazard ratio (HR) for fracture in people who were started on sodium–glucose cotransporter 2 inhibitor (SGLT2i) compared with that of individuals who were started on dipeptidyl peptidase-4 inhibitor (DPP-4i) in (a) as-treated (AT) and (b) intention-to-treat (ITT) analysis. PY, person-years; T2D, type 2 diabetes.
in Korean men. Cheng et al. observed that SGLT2i did not increase fracture risk in people with type 2 diabetes and actually decreased fracture risk when compared with placebo after a maximum of 52 weeks of treatment. We recently showed that the trabecular bone score increases as visceral fat mass decreases in Koreans with type 2 diabetes. SGLT2i are the only oral glucose-lowering medications with evidence of weight loss and visceral adiposity reduction. Men, on average, have more visceral fat than women, and hence might benefit more from SGLT2i-induced visceral fat loss. Osteoporosis and fractures are related to heart failure. SGLT2i have been shown to improve cardiac function and reduce the incidence of heart failure, suggesting that they might potentially be effective for bone fracture prevention. The hypothesis of higher fracture risk in Asian SGLT2i users is also questionable. However, the study's apparent positive effect of SGLT2i on fracture risk should be evaluated cautiously. In a randomized clinical trial, ITT analysis evaluates the effect of differences in assigned intervention between groups and has become the 'gold standard' for analyzing the results. However, the AT analysis provides a better estimate effect than ITT analysis when participants had a poor adherence. In particular, because changes in drug treatment are greater in real-world clinical settings than in randomized clinical trials, AT analysis might more accurately represent the effects. However, the estimates of cumulative fracture incidence might be biased by changes in drug treatment, such as discontinuation, switch or concomitant use.

The present study had some limitations. First, as an observational cohort, individuals were not randomly assigned to the assessed medications. Despite the use of propensity score matching, residual confounding bias could have occurred due to unmeasured factors, such as diabetes duration, laboratory findings, such as vitamin D levels, and bone turnover marker. Second, long-term effects could not be examined due to the recent introduction of SGLT2i into clinical practice. Any drug's effect on fracture risk is difficult to determine, because a helpful or detrimental effect might become apparent only after prolonged exposure. Third, it is unclear whether the fracture risk of SGLT2i is a drug class effect or specific to individual compounds; canagliflozin increased fracture risk, but not dapagliflozin and empagliflozin in randomized control trials. Thus, it is necessary to evaluate the safety of all SGLT2i in the real-world clinical setting. However, we could not include canagliflozin as SGLT2i compounds, as it was unavailable in Korea.

In conclusion, the present study found no evidence of increased fracture risk associated with real-world clinical use of SGLT2i in people with type 2 diabetes. This study provided important clinical information by emphasizing the importance of understanding fracture safety when using SGLT2i within the limitations of a short treatment duration and follow up. Given that bone health issues and the related fracture risk impose a marked economic and social burden, additional research is required to determine the long-term safety of SGLT2i in fractures.

DISCLOSURES
The authors declare no conflict of interest.
Approval of the research protocol: The institutional review board of Ajou University Hospital approved this study protocol.
Informed consent: The institutional review board of Ajou University Hospital waived the requirement for informed consent due to the de-identification of all patient data.
Registry and the registration no. of the study/trial: Approval date: 17 August 2021, approval number: AJIRB-MED-EXP-21-526.
Animal studies: N/A.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Material