JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

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

Kyoung Hwa Ha, Dae Jung Kim, Yong Jun Choi*
Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, South Korea

Keywords
Fracture, Sodium–glucose cotransporter 2 inhibitors, Type 2 diabetes mellitus

***Correspondence**
Yong Jun Choi
Tel.: +82-31-219-4491
Fax: +82-31-219-4497
E-mail address:
colsmile@ajou.ac.kr

J Diabetes Investig 2022; 13: 986–996

doi: 10.1111/jdi.13768

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[1,2]. Several older individuals have both conditions and take medications for these diseases concurrently. Fragility fractures are more common in people with type 2 diabetes[3]. 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[4]. 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[5].

Previous studies examined the association between SGLT2i monotherapy and fracture risk in people with type 2 diabetes, but yielded conflicting conclusions[6–8]. 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

Received 29 November 2021; revised 7 January 2022; accepted 6 February 2022

the canagliflozin group than in the placebo group[6]. However, the risks of canagliflozin on fracture were inconsistent between the CANVAS and CANVAS-Renal (CANVAS-R) trials[9]. 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[10].

Asians typically have pancreatic β-cell dysfunction and less obesity[11], but more visceral obesity than white people[12]. 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[13]. Lumbar spine bone density was also found to be lower than those for the femoral neck or hip of Koreans[14]. 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[15]. 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[16]. DPP-4i have been shown to be safe, with a neutral risk of cardiovascular complications and no risk of bone fracture[17]. Additionally, a recent study reported that DPP-4i have no discernible effect on the risk of fractures in a Korean population[18]. 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[19]. 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%), empagliflozin (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[20]. SGLT2i have been proven to have protective effects against cardiovascular disease in cardiovascular outcome clinical trials and in real-world settings[21–23]. 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[5,24]. 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[25,26]. Additionally, canagliflozin resulted in a decrease in total hip bone mineral density in a randomized controlled trial[27]. Conversely, ertugliflozin and dapagliflozin showed no negative effect on bone mineral density loss[28,29].

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)[6]. 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)[30]. However, the discordant risk between CANVAS and CANVAS-R was not clearly explained[31]. Furthermore, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial recently showed no significant difference in fracture risk between the canagliflozin and placebo groups[32].

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[7,8]. Recent meta-analyses of randomized controlled trials have shown that SGLT2i are not related to increased fracture risk[33–35].

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

Table 1 | Baseline characteristics of people with type 2 diabetes before and after propensity score matching

	Before PSM			After PSM		
	SGLT2i (*n* = 42,588)	DPP-4i (*n* = 436,238)	Standardized difference	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)	21.1	9,047 (21.4)	8,851 (21.0)	0.0
2017	18,288 (42.9)	185,176 (42.4)		18,167 (43.0)	18,190 (43.1)	
2018	15,216 (35.7)	123,577 (28.3)		15,016 (35.6)	15,189 (36.0)	
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)		14,763 (35.0)	14,782 (35.0)	
High	16,033 (37.6)	164,803 (37.8)		15,904 (37.7)	15,783 (37.4)	
Missing	1,746 (4.1)	24,762 (5.7)		1,740 (4.1)	1,780 (4.2)	
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)	42 (0.0)	1.5	11 (0.0)	13 (0.0)	0.3
Thiazolidinediones	1,816 (4.3)	22,346 (5.1)	4.1	1,809 (4.3)	1,790 (4.2)	0.2
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)	86,269 (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)	2,003 (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
Antiarrhythmic 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)	10,043 (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
Antiplatelet	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

Table 1. (*Continued*)

	Before PSM			After PSM		
	SGLT2i (*n* = 42,588)	DPP-4i (*n* = 436,238)	Standardized difference	SGLT2i (*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)	1,088 (2.6)	0.4
Anticonvulsants	4,236 (9.9)	56,199 (12.9)	9.2	4,203 (10.0)	4,122 (9.8)	0.6
Lithium	152 (0.4)	951 (0.2)	2.6	143 (0.3)	145 (0.3)	0.1
Benzodiazepines	11,208 (26.3)	138,232 (31.7)	11.9	11,138 (26.4)	10,993 (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
Teriparatide	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 ophthalmic manifestations	10,401 (24.4)	115,495 (26.5)	4.7	10,322 (24.4)	10,131 (24.0)	1.1
Retinal detachment, vitreous hemorrhage, vitrectomy	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)	1,020 (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	5,901 (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)	1.0	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*)

	Before PSM			After PSM		
	SGLT2i (*n* = 42,588)	DPP-4i (*n* = 436,238)	Standardized difference	SGLT2i (*n* = 42,230)	DPP-4i (*n* = 42,230)	Standardized difference
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)	232,926 (53.4)	8.8	24,359 (57.7)	24,250 (57.4)	0.5
Osteoarthritis	15,914 (37.4)	189,782 (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)	1.6	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.

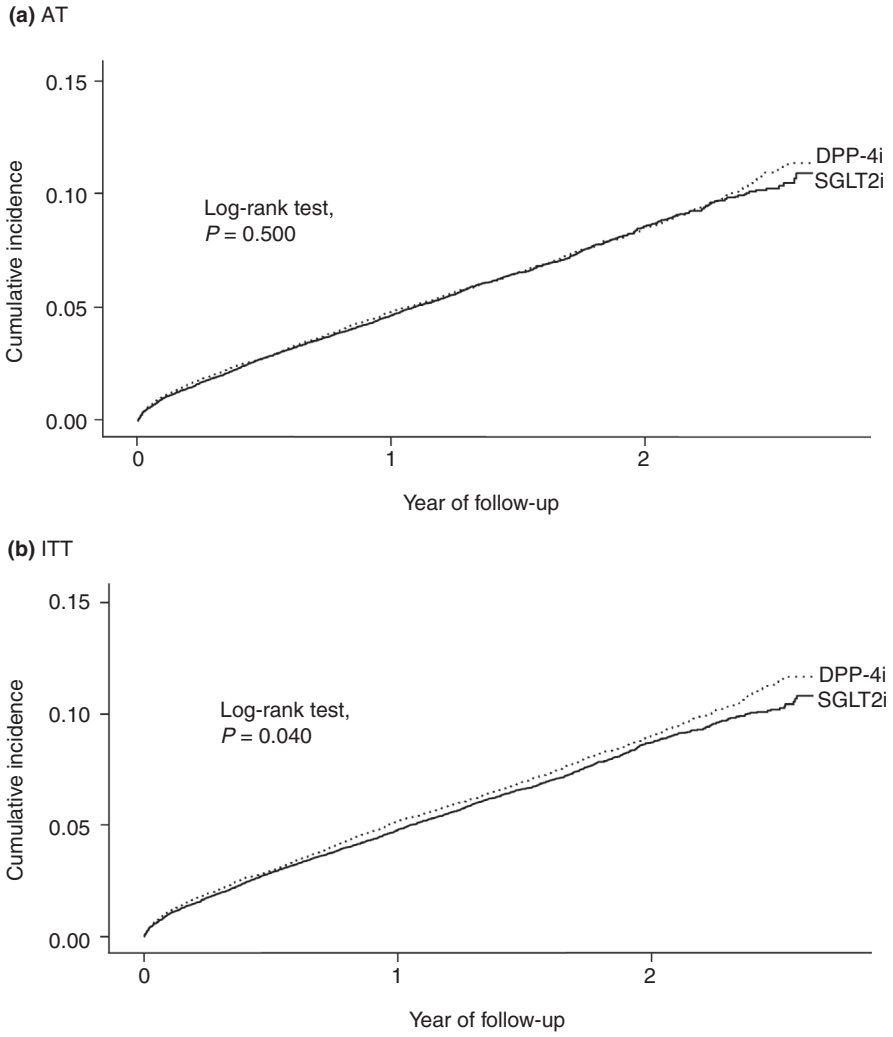

Figure 1 | Cumulative risk curve of incident fracture treated with sodium–glucose cotransporter 2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP-4i) in (a) as-treated (AT) and (b) in intention-to-treat (ITT) analysis.

	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		

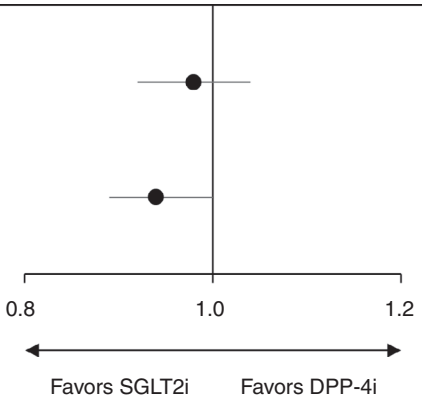

Figure 2 | Hazard ratio (HR) for fracture in people who were started on sodium–glucose cotransporter 2 inhibitor (SGLT2i) compared with that of individuals who were started on dipeptidyl peptidase-4 inhibitor (DPP-4i). AT, as-treated; CI, confidence interval; ITT, intention-to-treat; PY, person-years.

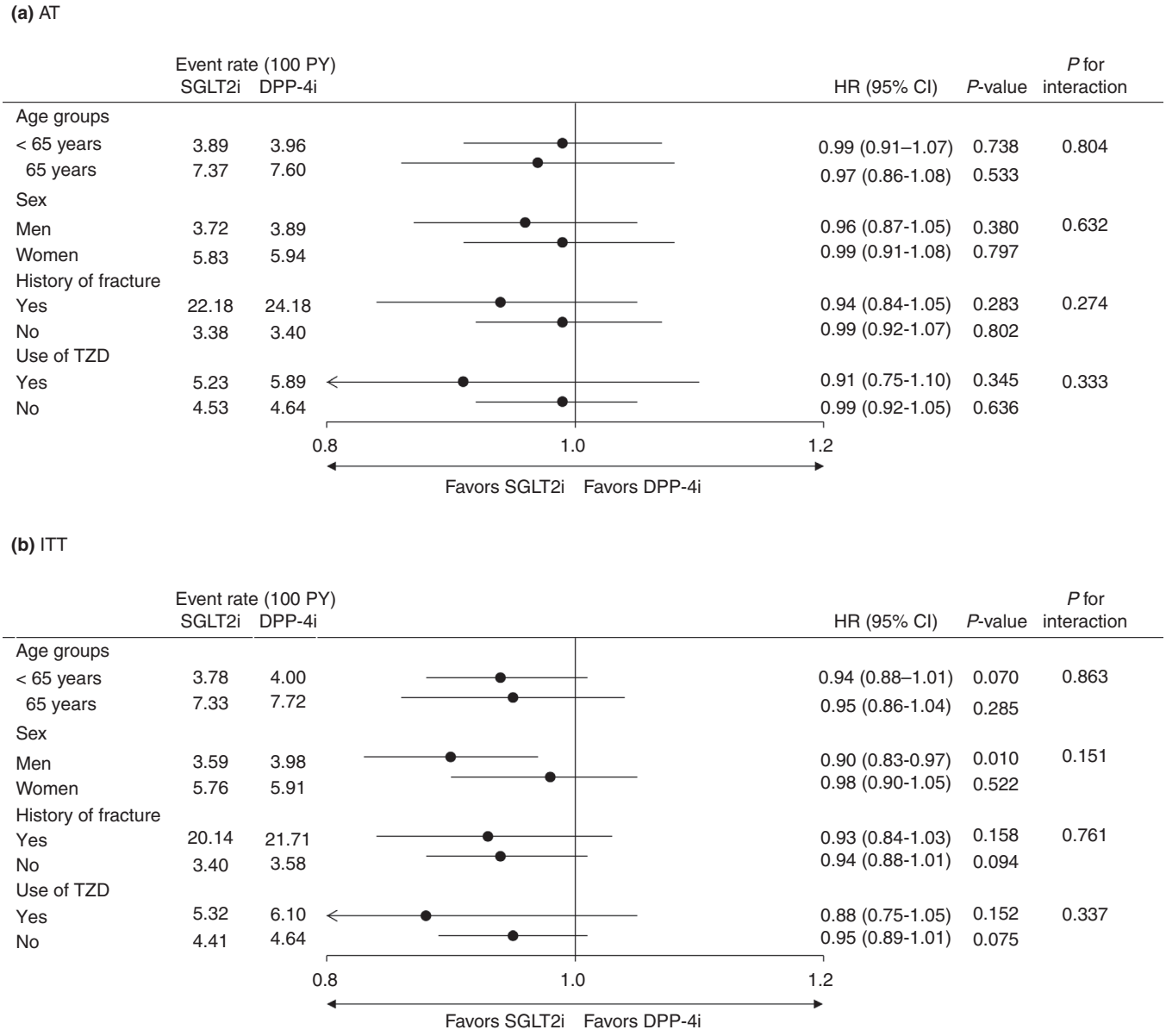

Figure 3 | Subgroup analysis of hazard ratio (HR) for fracture in people who were started on sodium–glucose cotransporter 2 inhibitor (SGLT2i) compared with that of individuals who were started on dipeptidyl peptidase-4 inhibitor (DPP-4i) in (a) as-treated (AT) and (b) intention-to-treat (ITT) analysis.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

diabetes when compared with those who were newly prescribed glucagon-like peptide-1 receptor agonist[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[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)[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[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

in Korean men. Cheng *et al.*[38] 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[39]. SGLT2i are the only oral glucose-lowering medications with evidence of weight loss and visceral adiposity reduction[40]. 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[41]. SGLT2i have been shown to improve cardiac function and reduce the incidence of heart failure[42], suggesting that they might potentially be effective for bone fracture prevention. The hypothesis of higher fracture risk in Asian SGLTi 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[43]. 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[7,8,29]. 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.

REFERENCES

1. Kim B-Y, Won JC, Lee JH, *et al.* Diabetes fact sheets in Korea, 2018: an appraisal of current status. *Diabetes Metab J* 2019; 43: 487–494.
2. Ahn SH, Park S-M, Park SY, *et al.* Osteoporosis and osteoporotic fracture fact sheet in Korea. *J Bone Metab* 2020; 27: 281–290.
3. Epstein S, Leroith D. Diabetes and fragility fractures: a burgeoning epidemic? *Bone* 2008; 43: 3–6.
4. Gilbert MP, Pratley RE. The impact of diabetes and diabetes medications on bone health. *Endocr Rev* 2015; 36: 194–213.
5. Mannucci E, Monami M. Bone fractures with sodium-glucose co-transporter-2 inhibitors: how real is the risk? *Drug Saf* 2017; 40: 115–119.
6. Watts NB, Bilezikian JP, Usiskin K, *et al.* Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2016; 101: 157–166.
7. Wiviott SD, Raz I, Bonaca MP, *et al.* Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357.
8. Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
9. Neal B, Perkovic V, Matthews DR, *et al.* Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): a randomized, placebo-controlled trial. *Diabetes Obes Metab* 2017; 19: 387–393.
10. Fralick M, Kim SC, Schneeweiss S, *et al.* Fracture risk after initiation of use of canagliflozin: a cohort study. *Ann Intern Med* 2019; 170: 155–163.
11. Qian B-B, Chen Q, Li L, *et al.* Association between combined treatment with SGLT2 inhibitors and metformin for type 2 diabetes mellitus on fracture risk:a meta-analysis of randomized controlled trials. *Osteoporos Int* 2020; 31: 2313–2320.
12. Yabe D, Seino Y, Fukushima M, *et al.* β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. *Curr Diab Rep* 2015; 15: 602.
13. Choi HS. Vitamin D status in Korea. *Endocrinol Metab* 2013; 28: 12–16.

14. Choi YJ, Oh HJ, Kim DJ, *et al*. The prevalence of osteoporosis in Korean adults aged 50 years or older and the higher diagnosis rates in women who were beneficiaries of a national screening program: the Korea National Health and Nutrition Examination Survey 2008–2009. *J Bone Miner Res* 2012; 27: 1879–1886.
15. Kim MK, Ko S-H, Kim B-Y, *et al*. 2019 clinical practice guidelines for type 2 diabetes mellitus in Korea. *Diabetes Metab J* 2019; 43: 398–406.
16. Korean Diabetes Association. Diabetes Fact Sheet in Korea 2018 [Internet]. Seoul, Korea: Korean Diabetes Association; 2018. Available from: https://www.diabetes.or.kr/pro/news/admin.php?code=admin&category=A&mode=view&number=1615 Accessed December 24, 2021.
17. Sesti G, Antonelli Incalzi R, Bonora E, *et al*. Management of diabetes in older adults. *Nutr Metab Cardiovasc Dis* 2018; 28: 206–218.
18. Ustulin M, Park SY, Choi H, *et al*. Effect of dipeptidyl peptidase-4 inhibitors on the risk of bone fractures in a Korean population. *J Korean Med Sci* 2019; 34: e224.
19. Cheol Seong S, Kim YY, Khang YH, *et al*. Data resource profile: the national health information database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2017; 46: 799–800.
20. Jung CH, Jang JE, Park JY. A novel therapeutic agent for type 2 diabetes mellitus: SGLT2 inhibitor. *Diabetes Metab J* 2014; 38: 261–273.
21. Zelniker TA, Wiviott SD, Raz I, *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; 393: 31–39.
22. Kosiborod M, Cavender MA, Fu AZ, *et al*. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). *Circulation* 2017; 136: 249–259.
23. Kosiborod M, Lam CSP, Kohsaka S, *et al*. Cardiovascular events associated with sglt-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. *J Am Coll Cardiol* 2018; 71: 2628–2639.
24. Ye Y, Zhao C, Liang J, *et al*. X. Effect of sodium-glucose co-transporter 2 inhibitors on bone metabolism and fracture risk. *Front Pharmacol* 2019; 9: 1517.
25. Thrailkill KM, Clay Bunn R, Nyman JS, *et al*. SGLT2 inhibitor therapy improves blood glucose but does not prevent diabetic bone disease in diabetic DBA/2J male mice. *Bone* 2016; 82: 101–107.
26. Thrailkill KM, Nyman JS, Bunn RC, *et al*. The impact of SGLT2 inhibitors, compared with insulin, on diabetic bone disease in a mouse model of type 1 diabetes. *Bone* 2017; 94: 141–151.
27. Bilezikian JP, Watts NB, Usiskin K, *et al*. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. *J Clin Endocrinol Metab* 2016; 101: 44–51.
28. Rosenstock J, Frias J, Páll D, *et al*. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET*)*. *Diabetes Obes Metab* 2018; 20: 520–529.
29. Bolinder J, Ljunggren Ö, Johansson L, *et al*. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab* 2014; 16: 159–169.
30. Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.
31. Zhou Z, Jardine M, Perkovic V, *et al*. Canagliflozin and fracture risk in individuals with type 2 diabetes: results from the CANVAS Program. *Diabetologia* 2019; 62: 1854–1867.
32. Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
33. Tang HL, Li DD, Zhang JJ, *et al*. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2016; 18: 1199–1206.
34. Ruanpeng D, Ungprasert P, Sangtian J, *et al*. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: a meta-analysis. *Diabetes Metab Res Rev* 2017; 33: e2903.
35. Qian B-B, Chen Q, Li L, *et al*. Association between combined treatment with SGLT2 inhibitors and metformin for type 2 diabetes mellitus on fracture risk: a meta-analysis of randomized controlled trials. *Osteoporos Int* 2020; 31: 2313–2320.
36. Ueda P, Svanström H, Melbye M, *et al*. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ* 2018; 363: k4365.
37. Abrahami D, Douros A, Yin H, *et al*. Sodium-glucose cotransporter 2 inhibitors and the risk of fractures among patients with type 2 diabetes. *Diabetes Care* 2019; 42: e150–e152.
38. Cheng L, Li Y-Y, Hu W, *et al*. Risk of bone fracture associated with sodium-glucose cotransporter-2 inhibitor treatment: a meta-analysis of randomized controlled trials. *Diabetes Metab* 2019; 45: 436–445.
39. Moon HU, Lee N, Chung Y-S, *et al*. Reduction of visceral fat could be related to the improvement of TBS in diabetes mellitus. *J Bone Miner Metab* 2020; 38: 702–709.
40. Sheu W-H, Chan SP, Matawaran BJ, *et al*. Use of SGLT-2 inhibitors in patients with type 2 diabetes mellitus and

abdominal obesity: an Asian perspective and expert recommendations. *Diabetes Metab J* 2020; 44: 11–32.
41. Aluoch AO, Jessee R, Habal H, *et al*. Heart failure as a risk factor for osteoporosis and fractures. *Curr Osteoporos Rep* 2012; 10: 258–269.
42. Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 inhibitors in heart failure: diabetes and beyond. *Curr Treat Options Cardiovasc Med* 2017; 19: 23.
43. DeMets DL, Cook T. Challenges of non-intention-to-treat analyses. *JAMA* 2019; 321: 145–146.

SUPPORTING INFORMATION

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

Supplementary Material