Sodium–Glucose Cotransporter 2 Inhibitors and the Risk of Fractures Among Patients With Type 2 Diabetes

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Diabetes Care 2019;42:e150–e152 | https://doi.org/10.2337/dc19-0849

The association between sodium–glucose cotransporter 2 (SGLT2) inhibitors and the risk of fractures is controversial. In the Canagliflozin Cardiovascular Assessment Study (CANVAS), canagliflozin was associated with a significant increased risk of fractures compared with placebo (hazard ratio [HR] 1.26, 95% CI 1.04–1.52) (1). Possible mechanisms may involve elevated serum phosphate levels or reductions in bone mineral density (2). To date, three recent observational studies investigated this association, but these did not observe an increased risk of fractures (3–5). However, these studies had some limitations, including residual confounding, a limited outcome definition, or restriction to a single SGLT2 inhibitor.

To address these limitations, we conducted a population-based cohort study using the U.K. Clinical Practice Research Datalink (CPRD). We first assembled a base cohort of all individuals, at least 40 years old, newly treated with antidiabetic drugs between 1 January 1988 and 31 December 2017. We excluded individuals with <1 year of medical history, those initially prescribed insulin in monotherapy, and women with polycystic ovary syndrome (alternate metformin indication) at the time of the first-ever prescription of an antidiabetic drug. Using this base cohort, we then assembled a study cohort of individuals who initiated a new antidiabetic drug class as of 2013 (year the first SGLT2 inhibitor was introduced in the U.K.). Cohort entry was defined by the date of this new prescription. We excluded individuals with a diagnosis of Paget disease, osteomalacia, or hyperparathyroidism, rare risk factors associated with fracture incidence, at any time before cohort entry. Patients were monitored from cohort entry until the first of an incident diagnosis of fracture, death from any cause, an incident diagnosis of Paget disease, osteomalacia, or hyperparathyroidism, end of registration with the general practice, or end of the study period (31 March 2018).

We defined exposure using a time-varying definition, where each person-day of follow-up was classified into one of the following four mutually exclusive categories: *1*) current use of SGLT2 inhibitors; *2*) current use of dipeptidyl peptidase 4 (DPP-4) inhibitors (with initiation after 2013; i.e., new use); *3*) current use of DPP-4 inhibitors (with initiation before 2013; i.e., prevalent use); and *4*) other treatments. Current and new use DPP-4 inhibitors served as the reference group. For all exposure categories, exposed person-time was defined by the prescription duration plus a 90-day grace period to allow for a potential latent exposure effect on the outcome. Time-dependent Cox proportional hazards models were used to calculate HRs, adjusted for 45 covariates (Table 1), including smoking status, BMI, medications, and duration of treated diabetes. This study was approved by the CPRD Independent Scientific Advisory Committee (protocol 18_221) and by the Jewish General Hospital Research Ethics Board.

This study included 73,178 patients, with 9,454 SGLT2 inhibitor users (1,288 canagliflozin, 5,539 dapagliflozin, 2,133 empagliflozin, and 494 users of >1 SGLT2 inhibitor) and 18,410 DPP-4 inhibitor users, monitored for a median duration of 1.9 years (patient characteristics on file). There were 1,973 fracture events, corresponding to an incidence rate of 12.88 (95% CI 12.32–13.46) per 1,000 person-years.

The results of this study are presented in Table 1. Compared with use of DPP-4 inhibitors, use of SGLT2 inhibitors was not

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Received 29 April 2019 and accepted 23 June 2019

Table 1—Crude and adjusted HRs for the association between the use of SGLT2 inhibitors and the risk of fractures

Analysis	Events	Person-years	Incidence rate (95% CI)*	HR	
				Crude	Adjusted†
Primary analysis‡					
DPP-4 inhibitors	403	27,210	14.8 (13.4–16.3)	1.00 [Reference]	1.00 [Reference]
SGLT2 inhibitors	138	12,500	11.0 (9.3–13.0)	0.75	0.97 (0.79–1.19)
Type of SGLT2 inhibitor§					
Canagliflozin only	10	1,764	5.7 (2.7–10.4)	0.38	0.47 (0.25–0.88)
Dapagliflozin only	98	8,624	11.4 (9.2–13.8)	0.77	1.01 (0.81–1.27)
Empagliflozin only	30	2,031	14.8 (10.0–21.1)	1.00	1.29 (0.88–1.88)
Type of fracture‖					
Upper limb	57	12,500	4.6 (3.5–5.9)	0.85	1.00 (0.73–1.38)
Lower limb	46	12,500	3.7 (2.7–4.9)	0.68	0.93 (0.66–1.32)
Vertebral	11	12,500	0.9 (0.4–1.6)	1.23	1.76 (0.81–3.82)
Other	33	12,500	2.6 (1.8–3.7)	0.57	0.89 (0.60–1.33)
Effect measure modification¶					
No fracture history	129	12,170	10.6 (8.8–12.6)	0.74	0.95 (0.78–1.18)
History of fracture	9	330	27.3 (12.5–51.8)	0.95	1.18 (0.51–2.69)
No history of osteoporosis	130	12,180	10.7 (8.9–12.7)	0.80	0.97 (0.78–1.20)
History of osteoporosis	8	320	25.0 (10.8–49.3)	0.67	0.84 (0.39–1.81)
<65 years old	83	8,957	9.3 (7.4–11.5)	0.94	0.91 (0.69–1.22)
65–74 years old	45	3,063	14.7 (10.7–19.7)	1.13	1.11 (0.78–1.59)
≥75 years old	10	480	20.8 (10.0–38.3)	0.77	0.84 (0.44–1.61)
Female	68	4,845	14.0 (10.9–17.8)	0.63	0.88 (0.67–1.17)
Male	70	7,654	9.1 (7.1–11.6)	0.93	1.10 (0.82–1.47)
Sensitivity analyses					
Competing risk	138	12,500	11.0 (9.3–13.0)	0.76	0.98 (0.80–1.20)
High-dimensional disease risk score#	138	12,500	11.0 (9.3–13.0)	0.75	0.97 (0.80–1.18)
Marginal structural model**	137	153,736	0.9 (0.7–1.1)	0.73	0.95 (0.73–1.24)
Alternate reference group††	138	12,500	11.0 (9.3–13.0)	0.97	1.10 (0.82–1.48)

*Per 1,000 person-years. †Adjusted for age, sex, year of cohort entry, alcohol-related disorders (including alcohol dependency, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure), smoking status, BMI, inflammatory bowel disease, rheumatoid arthritis, hemoglobin A_{1c}, duration of treated diabetes, macrovascular complications of diabetes (including stroke, myocardial infarction, and peripheral vascular disease), microvascular complications of diabetes (including nephropathy, neuropathy, and retinopathy), cancer, fracture history, osteoporosis, and use of bisphosphonates, use of antidiabetic drugs in the year before cohort entry, use of calcium and vitamin D, number of unique nonantidiabetic drugs in the year before cohort entry, use of benzodiazepines, sedative-hypnotics, opioids, selective serotonin reuptake inhibitors, tricyclic antidepressants, anti-Parkinson disease drugs, centrally acting antihypertensive drugs, nitrates, nonnitrate antianginal agents, thiazide and thiazide-like diuretics, inhaled glucocorticoids, oral glucocorticoids, proton pump inhibitors, H2 receptor antagonists, anticonvulsants, atypical antipsychotics, typical antipsychotics, and loop diuretics in the year before cohort entry. Variables with missing data were imputed using multiple imputation, using results from five imputations. ‡The median duration of DPP-4 inhibitor use was 366 days, and the median duration of SGLT2 inhibitor use was 343.5 days. Current use of DPP-4 inhibitors (with initiation before 2013) and use of other treatments were considered in the model but not presented in the table. These groups generated 67 events from 4,357 person-years and 1,365 events from 109,113 person-years, respectively. §Drug switchers (individuals who used more than one type of SGLT2 inhibitor) were considered in a separate category. This group generated 0 events from 81 person-years. ‖DPP-4 inhibitor users (reference) generated 148, 146, 19, and 128 upper-limb, lower-limb, vertebral, and other fractures, respectively, in 27,210 person-years of follow-up. ¶DPP-4 inhibitor users without a fracture history generated 382 events in 26,481 person-years, and those with a history of fracture generated 21 events in 729 person-years. DPP-4 inhibitor users without a history of osteoporosis generated 337 events in 25,471 person-years, and those with a history of osteoporosis generated 66 events in 1,739 person-years. DPP-4 inhibitor users aged <65 years old generated 124 events in 12,567 person-years, users aged 65–74 generated 108 events in 8,318 person-years, and users aged ≥75 generated 171 events in 6,325 person-years. Female DPP-4 inhibitor users generated 242 events in 10,879 person-years, and male DPP-4 inhibitor users generated 161 events in 16,331 person-years. #Adjusted for high-dimensional disease risk score, which included all variables listed above and 200 variables empirically selected by the high-dimensional disease risk score algorithm. **This model considered person-months of follow-up and generated marginal HRs. DPP-4 inhibitor users generated 406 events in 336,321 person-months. ††Use of glucagon-like peptide-1 receptor agonists was considered as the reference group, which generated 65 events during 5,675 person-years of follow-up.

associated with fracture risk (HR 0.97, 95% CI 0.79–1.19). When stratifying by SGLT2 molecule, use of canagliflozin was associated with a decreased risk of fractures (HR 0.47, 95% CI 0.25–0.88), but this finding was based on few events (n = 10). There were no differences in risk according to fracture type, except for a numerically elevated HR with vertebral fractures (HR 1.76, 95% CI 0.81–3.82). Similarly, the association was not modified by history of fracture, osteoporosis, age, or sex. Finally, the results remained consistent in several sensitivity analyses investigating death as a competing risk (using the Fine and Gray method), when controlling for confounding using the high-dimensional disease risk score, when using a marginal structural model with inverse probability of treatment and censoring weighting, or when comparing to glucagon-like peptide 1 receptor agonists, as was done in a previous study (5).

In summary, the results of this large population-based cohort study indicate that use of SGLT2 inhibitors is not associated with an increased risk of fractures compared with use of DPP-4 inhibitors. Although our stratified analysis by SGLT2 molecule revealed a protective effect for canagliflozin, this finding should be interpreted with caution given that it was based on few exposed events. Overall, our real-world study provides further reassurance on the safety of this

new class of drugs on bone health among patients with type 2 diabetes.

Funding. This research was funded by a Foundation Scheme grant from the Canadian Institutes of Health Research (FDN-333744). D.A. is the recipient of a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research and recipient of a training grant from the Canadian Institutes of Health Research Drug Safety and Effectiveness Training Program. O.H.Y.Y. holds a Chercheur-Boursier Clinicien Junior 1 award from the Fonds de Recherche du Québec – Santé. L.A. holds a Chercheur-Boursier Senior award from the Fonds de Recherche du Québec – Santé and is the recipient of a William Dawson Scholar Award from McGill University.
Duality of Interest. L.A. received consulting fees from Janssen for work unrelated to this study. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. D.A. wrote the manuscript. D.A., A.D., H.Y., O.H.Y.Y., and L.A. critically revised the manuscript. All authors conceived and designed the study, analyzed and interpreted the data, approved the final version of the manuscript, and are accountable for its accuracy. D.A., H.Y., and L.A. did the statistical analyses. L.A. acquired the data and supervised the study. L.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation. Parts of this study were presented in poster form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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