Initiation of dapagliflozin and treatment-emergent fractures

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Title Page

Title: Initiation of dapagliflozin and treatment-emergent fractures.

Short Title: Fractures in patients under dapagliflozin

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Disclosure Page

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Non-structured abstract

An increase in the fracture risk was reported in patients with type 2 diabetes mellitus (T2DM) treated with canagliflozin, possibly mediated by effects induced by all members of the sodium-glucose co-transporter 2 inhibitors (SGLT2i) class. It is unclear whether initiation of dapagliflozin is followed by an increase in the risk of fracture. Therefore, we performed a population-based, open cohort study was performed (January 2013-January 2016) using The Health Improvement Network (THIN). 22,618 patients with T2DM (4,548 exposed to dapagliflozin and 18,070 under standard antidiabetic treatment, matched for age and sex) with no history of fractures at baseline. The primary outcome was the occurrence of any fragility fracture during the observation period. Risk of any fracture served as a secondary outcome. Adjusted Hazard Rate Ratios (aHR) with 95% confidence intervals (CI) were calculated using Cox regression. A total of 289 fractures (132 fragility fractures) were recorded during the observation period. No difference in the risk of fragility fracture was detected between patients prescribed dapagliflozin and matched controls (Crude HR: 0.90, 95% CI: 0.59-1.39, p -value = 0.645 and adjusted HR: 0.87, 95% CI: 0.56-1.35, p -value = 0.531). Similarly, no difference in the risk of any fracture was detected (aHR: 0.89, 95% CI: 0.66-1.20, p -value = 0.427). Sensitivity analyses limited to the subset of the population at high risk of fracture produced similar results. Thus, there was no evidence to suggest an increase in the risk of treatment-emergent fractures in patients with T2DM being initiated treatment with dapagliflozin.

Word count: 244

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Introduction

Patients with type 2 diabetes mellitus (T2DM) are at an increased risk for osteoporotic fractures (1). Notably, fragility fractures in the context of T2DM-related osteoporosis are associated with increased mortality (2). Therefore, any factor that might (even incrementally) affect this risk should be of concern in the management of T2DM.

The less-pronounced systemic effects of sodium-glucose co-transporters 2 (SGLT2i) inhibitors (canagliflozin, dapagliflozin and empagliflozin) are not yet fully elucidated. In specific, concerns are raised about their potential detrimental effect on the skeleton and eventually on the risk of fracture. In line with evidence suggesting a decrease in total hip body mass density (3) and increased risk of fractures in the upper and lower extremities (4), the rate of any fracture was recently found to be higher with canagliflozin in the CANVAS trial [hazard ratio (HR), 1.26] (5). Dapagliflozin was also associated with increased risk of fractures in patients with moderate renal impairment in a small study involving 252 individuals (6). However, outcomes were too few, sample was distinct from the general diabetic population and considering the neutral effect of dapagliflozin on bone turnover markers (7,8), it is still unclear whether the fracture risk is higher in these patients.

Therefore, we explored whether initiating treatment with dapagliflozin in patients with T2DM and no evidence of fractures at baseline is associated with an increased risk of fractures in the short term.

Materials and Methods

Study design: We designed and performed a population-based, retrospective open cohort study in which patients exposed to dapagliflozin (exposed cohort) were compared to matched patients with T2DM unexposed to SGLT2i (unexposed or

control cohort). Age, sex, body mass index (BMI) and duration of T2DM were used as matching parameters using a computerized procedure (9). Data were derived from The Health Improvement Network (THIN), a UK general practice electronic database, from 1st Jan 2013 (study start) to 1st Jan 2016 (study end, last collection date).

Study cohort: Individuals were included in the exposed cohort if they (i) were aged 40+ years, (ii) had more than three months of treatment with a dapagliflozin, (iii) remained at their practice at least three months after treatment initiation. For each exposed patient, up to four unexposed controls were selected by matching. Controls were also required to have a diagnosis of T2DM before or at their index date and were not exposed to any SGLT2i throughout the study.

Follow-up, outcomes and covariates: The primary outcome was an incident fragility fracture (vertebral, femoral, humerus, distal radius) identified during the observation period. Incidence of any fracture served as a secondary outcome. Estimated glomerular filtration rate, HbA1c, insulin therapy, anti-osteoporotic medications, metastatic bone disease, connective tissue disorder, hyperthyroidism, active smoking, social deprivation quintile and oral steroid treatment were used as covariates in the primary analysis.

Sensitivity analyses: We performed pre-planned sensitivity analyses by (i) limiting to patients considered to be at a higher risk of fracture and (ii) adding use of thiazolidinediones (TZD) or sulfonylureas (SU) as covariates in the primary analysis. In the former, patients were considered to be at a higher risk of fracture if they were either at 65+ years old or having a diagnosis associated with altered bone turnover (hyperthyroidism, connective tissue disorder, metastatic bone disease, steroid use and osteoporosis under treatment). The latter analysis was performed to control for the

TZD-associated decrease in osteoblastogenesis (10) and the SU-associated increase in hypoglycaemic events (and possibly the resulting increased risk of falls) (11).

Statistical analysis Hazard rates of fractures were calculated and compared between cohorts, offset by the person-years of exposure using Cox regression in Stata MP 14.0. Missing data were handled by multiple imputation techniques (chained equations with predicted mean matching) and reported in the [Supplementary Material](#). This project was authorized by the relevant Scientific Review Committee (SRC Reference Number: 16THIN093).

Results

Cohort characteristics A total of 22,618 subjects (4,548 patients with T2DM exposed to dapagliflozin, thereafter “exposed cohort” and 18,070 patients with T2DM, unexposed to SGLT2i, thereafter “control cohort”) constituted the study population. The study population was followed-up for a mean of approximately 12.0 months (range 36 months) and a total of approximately 23,000 person-years. Men constituted 43% of the study population and virtually all subjects (99.7%) were over 50 years old. The mean age and BMI were 59.4 years and 34.5 kg/m² respectively, whereas the mean duration of diabetes was approximately ten years and the mean HbA1c in the total study population was 7.8% (62 mmol/mol).

A total of 289 fractures were recorded during the observation period, 132 of them were fractures of the proximal femoral, vertebrae, distal radius and humerus, collectively considered as fragility fractures. The event rate for any fracture was estimated at approximately 12 per 1000 person-years in the exposed cohort. A table summarizing key study characteristics on the basis of exposure to dapagliflozin is presented in [Table 1](#).

Risk of incident fragility fracture No difference in the risk of fragility fracture was detected between patients with diabetes who were administered dapagliflozin and matched controls (Crude HR: 0.90, 95% CI: 0.59-1.39, p -value = 0.645, [Table 2](#)). This finding did not change after adjusting for key covariates (Adjusted HR: 0.87, 95% CI: 0.56-1.35, p -value = 0.531, [Table 2](#)).

Risk of any fracture Similarly, no difference in the risk of any fracture was detected between patients with diabetes who were administered dapagliflozin and matched controls (Crude HR: 0.93, 95% CI: 0.69-1.23, p -value = 0.601 and aHR: 0.89, 95% CI: 0.66-1.20, p -value = 0.427, [Table 2](#)).

Sensitivity analyses No differences in the risk of fragility fracture or any fracture were detected when limiting the analysis to those patients at a higher risk of fracture and their respective controls (aHR: 0.79, 95% CI: 0.41-1.52, p -value = 0.476 and aHR: 0.99, 95% CI: 0.64-1.55, p -value = 0.981 respectively, [Supplementary Table 2](#)). Adding use of TZD and SU as covariates in the primary analysis did not change the findings (aHR for fragility fracture: 0.87, 95% CI: 0.56-1.36, p -value = 0.476 and aHR for any fracture: 0.88, 95% CI: 0.66-1.19, p -value = 0.422, [Supplementary Table 2](#)).

Discussion

In this population-based study involving a total of 22,618 individuals with T2DM, we report that the risk of fracture is not affected in patients treated with dapagliflozin compared to appropriately matched controls receiving standard, background antidiabetic medication. This neutral effect of dapagliflozin on the risk of fracture (at least in the short-term) in patients with no record of fracture at baseline appears to be robust in sensitivity analysis limiting to those considered to be at an increased risk for fracture or when modelling the use of sulfonylureas and

thiazolidinediones. Our findings are reassuringly based on a total of 289 fractures observed during approximately 23000 person-years of follow-up in one of the largest to date cohorts of patients treated with dapagliflozin (n=4,548), collectively providing relative confidence in our estimates.

Our findings are also of clinical relevance, considering the prior knowledge of the increased risk of fracture in patients with T2DM and evidence suggesting that SGLT2i-related skeletal effects may be detrimental (12). Furthermore, the results of the sensitivity analyses suggest that the neutral effect of dapagliflozin on fracture risk may also apply to those patients with a higher baseline risk of fracture than the general diabetic population or even to patients who are usually excluded from trials, such as those with metastatic bone disease or those under glucocorticoid treatment. Unfortunately, it was not possible to explore the effects of the other SGLT2i, since the number of subjects receiving empagliflozin or canagliflozin was too small to permit analysis of rare events like the incidence of fractures.

The underlying pathophysiology between SGLT2i and bone metabolism is still unclear. It has been postulated that SGLT2i may lead to elevated serum phosphate, resulting in turn in a compensatory increase in PTH levels, thus further enhancing bone resorption (12) and that they may induce osmotic diuresis and volume depletion, which in turn may increase the susceptibility to falls (13). These effects, imposing an additional burden on skeletal health in T2DM, are not specific to a compound, instead they are noted with all members of the SGLT2i class. Our findings might challenge these postulated mechanisms suggesting a drug class-effect regarding fracture risk.

However, our findings should be considered in light of the study limitations. First, the duration of follow-up (mean follow-up a year, maximum follow-up three

years and shorter than the CANVAS trial) may not be long enough for a fracture to manifest. Therefore, the possibility of a cumulative negative effect on the skeletal health, provoked by the progressive accumulation of minimal yet detrimental skeletal effects induced by dapagliflozin, which would finally result in a fracture after a prolonged drug exposure cannot be excluded. On the other hand, the increase in the risk of fracture with SGLT2i was observed within first few weeks after drug initiation (4). Hence, our study would have captured this increase, considering its large sample size and the adequate follow-up.

In conclusion, we observed that the risk of treatment-emergent fractures in patients with T2DM receiving dapagliflozin is similar to that observed in those receiving standard antidiabetic medication. This neutral effect was also observed in patients at high risk of fracture.

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References

1. Nicodemus KK, Folsom AR, Iowa Women's Health S. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes care* 2001; 24:1192-1197

2. Nirantharakumar K, Toulis KA, Wijesinghe H, Mastan MS, Srikantharajah M, Bhatta S, Marshall T, Coleman JJ. Impact of diabetes on inpatient mortality and length of stay for elderly patients presenting with fracture of the proximal femur. *Journal of diabetes and its complications* 2013; 27:208-210
3. Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, Rosenthal N. 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
4. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, Meininger G. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab* 2016; 101:157-166
5. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondur N, Shaw W, Law G, Desai M, Matthews DR, Group CPC. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England journal of medicine* 2017;
6. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney international* 2014; 85:962-971
7. Ljunggren O, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, Sugg J, Parikh S. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. *Diabetes, obesity & metabolism* 2012; 14:990-999
8. Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, Sugg J, Parikh S. 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, obesity & metabolism* 2014; 16:159-169
9. Toulis KA, Willis BH, Marshall T, Kumarendran B, Gokhale K, Ghosh S, Thomas GN, Cheng KK, Narendran P, Hanif W, Nirantharakumar K. All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in THIN database. *J Clin Endocrinol Metab* 2017;
10. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009; 180:32-39
11. Eriksson JW, Bodegard J, Nathanson D, Thuresson M, Nystrom T, Norhammar A. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. *Diabetes research and clinical practice* 2016; 117:39-47
12. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. *The lancet Diabetes & endocrinology* 2015; 3:8-10
13. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. *Arch Intern Med* 2012; 172:1739-1744

Figure Legends.

Table 1: Baseline characteristics of the study population on the basis of exposure to dapagliflozin

	Exposed to dapagliflozin	Unexposed cohort
N	4,548 (20.1)	18,070 (79.9)
Age (years)	59.4 (9.4)	59.4 (9.4)
Male	1,968 (43.3)	7,829 (43.3)
Body Mass Index	34.7 (6.8)	34.4 (6.6)
Current smoking	603 (13.3)	2,903 (16.1)
Estimated Glomerular Filtration Rate	90.8 (21.8)	87.0 (24.8)
Townsend		
1	916 (20.1)	3226 (17.9)
2	841 (18.5)	3377 (18.7)
3	1047 (23.0)	3874 (21.4)
4	917 (20.2)	3891 (21.5)
5	679 (15.0)	3022 (16.7)
Not available	148 (3.3)	680 (3.8)
Follow-up (months)	12.9 (8.4)	11.9 (8.2)
Diabetes-specific characteristics		
Duration (years)	9.9 (5.8)	9.6 (5.7)
Glycated Hemoglobin A1c (% - mmol/mol)	9.1 (3.8) 75.7 (17.3)	7.5 (3.8) 60.5 (18.8)
Insulin use	1,226 (26.7)	4,047 (22.4)
Drugs or co-morbidities potentially affecting risk of fracture		
Hyperthyroidism	61 (1.3)	262 (1.5)
Antiestrogenic medication	93 (2.0)	466 (2.6)
Glucocorticoid	289 (6.4)	1,382 (7.7)
Metastatic bone disease	8 (0.2)	52 (0.3)
Connective tissue disorder	88 (1.9)	582 (3.2)
Charlson's Comorbidity Index		

1	2115 (46.5)	7874 (43.57)
2	1446 (31.79)	5456 (30.19)
3	579 (12.73)	2667 (14.76)
4	267 (5.87)	1196 (6.62)
5 or more	141 (3.1)	877 (4.85)

Continuous data presented as mean (standard deviation) unless otherwise specified. Dichotomous and ordinal data presented as N (%). Townsend index is a measure of material deprivation (1 denotes the least deprived and 5 the most deprived individuals)

Table 2: Risk of fragility fracture and any fracture in the exposed cohort compared to standard treatment cohort

	Exposed to dapagliflozin	Controls	Crude HR (95%CI)	P-value	Adjusted HR* (95%CI)	P-value
Fragility fracture						
Person-years	4,881.69	17,994.32				
Fragility fracture (events)	26	106				
Event rate (per 1000 person-years)	5.33	5.89	0.90 (0.59-1.39)	0.645	0.87 (0.56-1.35)	0.531
Any fracture						
Person-years	4,851.14	17,892.61				
Any fracture (events)	58	231				
Event rate (per 1000 person-years)	11.96	12.91	0.93 (0.69-1.23)	0.601	0.89 (0.66-1.20)	0.427

CI: Confidence Interval, HR: Hazard Rate Ratio, *Adjusted for age, gender, body mass index, smoking, glycated haemoglobin A1c, duration of diabetes, insulin use, estimated glomerular filtration rate, social deprivation index, presence of hyperthyroidism, metastatic bone disease or connective tissue disorder | P-values derived from Cox regression | Proximal femoral, vertebral, distal radius and humerus fractures were considered as fragility fractures.