Do sodium–glucose cotransporter 2 inhibitors lead to fracture risk? A pharmacovigilance real-world study

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INTRODUCTION
Sodium–glucose cotransporter 2 inhibitors (SGLT2is) are insulin-independent targets that increase glucose excretion in the treatment of type 2 diabetes mellitus1. Currently approved SGLT2is include canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin and tofogliflozin. Based on recent studies2–6 of diabetes management and cardiovascular disease, indications for SGLT2is treatment have been expanding. The guidelines7,8 and consensus9–11 have undergone significant updates. With an emphasis on treatment strategy, diabetes management should be built on the prevention and treatment of cardiovascular disease. The primary criterion for evaluating hypoglycemic agents is whether the agent is beneficial to the improvement of cardiovascular outcomes. Among them, SGLT2is have become well-recognized ‘star drugs,’ given their clear cardiovascular and renal benefits12.

Nevertheless, safety issues of SGLT2is also represent an area of concern, such as urogenital infection, fracture, lower-
extremity amputation risk and ketoacidosis risk\textsuperscript{13–16}. SGLT2is has repeatedly received US Food and Drug Administration (FDA) safety warnings. In September 2015, the FDA strengthened the warning for canagliflozin, related to the increased risk of bone fractures, and added new information about reduced bone mineral density\textsuperscript{17}. Despite the increasing number of studies on SGLT2is-associated fractures, such as a meta-analysis based on nine clinical trials that showed that the fracture incidence was higher in the canagliflozin group\textsuperscript{18}, information on a relatively uncommon adverse event remains limited. Some studies even report the opposite view, indicating that SGLT2is did not increase fracture risk in patients compared with dipeptidyl peptidase-4 inhibitors (DPP-4) in a case-control study\textsuperscript{19}, and empagliflozin did not increase the fracture risk compared with a placebo or glimepiride in a placebo-controlled trial\textsuperscript{20}.

Considering the short time-to-market for such drugs and, until recently, the lack of pharmacovigilance studies illustrating SGLT2is-associated fractures, the knowledge about the bone safety profile after treatment with various SGLT2is is limited in real-world clinical practice. Therefore, we aimed to characterize the fractures potentially caused by various SGLT2is in a large population by using the FDA Adverse Event Reporting System (FAERS). We further examined and compared the timing and outcomes for fractures of different SGLT2is regimens.

**MATERIALS AND METHODS**

**Data source**

We carried out a retrospective pharmacovigilance study using the FAERS database from the first quarter in 2004 to the fourth quarter in 2019. The FAERS is a public spontaneous reporting system that contains information about adverse events and medication error reports provided by health professionals, patients and manufacturers, not only domestically, but also from other regions. FAERS data files comprehensively reflect demographic information, drug information, adverse events, patient outcomes, report sources, therapy dates, indications and deleted cases.

A total of 13,649,428 reports were obtained from the FAERS database. Records from deleted cases files and duplicated records were removed according to the FDA’s recommendations. In addition, the latest FDA_DT was selected when the CASEIDs were the same, and the higher PRIMARYID was chosen when the CASEID and FDA_DT were the same (Figure 1).

**Adverse event and drug identification**

Fracture information was obtained from adverse events files based on the Medical Dictionary for Regulatory Activities (version 23.0) at the preferred term level as follows: ‘Fractures’ [10017076], ‘Joint injury’ [10060820] and ‘Skeletal injury’ [10061363]. We chose generic and brand names of SGLT2is by utilizing the IBM Micromedex as the dictionary in the data mining process (Table 1).

![Figure 1](http://wileyonlinelibrary.com/journal/jdi)

**Data mining**

Based on the principles of Bayesian odds ratio and disproportionality analysis, we used the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network and the multi-item gamma Poisson shrinker algorithms to explore the associations between SGLT2is and fracture. The calculation and criteria\textsuperscript{21–27} of the four algorithms are reported as follows: ROR = (a / b) / (c / d), 95% confidence interval (CI) = e\textsuperscript{ln(ROR)} ± 1.96(1 / a + 1 / b + 1 / c + 1 / d)\textsuperscript{-0.5} (criteria: 95% CI >1, n ≥2); PRR = (a / (a + c)) / (b / (b + d)), \( \chi^2 = \sum((O - E)^2 / E); (O = a, E = [a + b] [a + c] / [a + b + c + d]) \) (criteria: PRR ≥2, \( \chi^2 ≥4, n ≥3 \)); with Bayesian confidence propagation neural network algorithms, IC = \( \log_2(a + b + c + d) / (a + c[a + b]) \), IC025 = e\textsuperscript{ic025} - 1.96 (17 / a + 1 / b + 1 / c + 1 / d)\textsuperscript{-0.5} (criteria: IC025 >0); with multi-item gamma Poisson shrinker algorithms, empirical Bayesian geometric mean (EBGM) = (a + b + c + d) / ((a + c)[a + b]), EBGM05 = e\textsuperscript{ebgm05} - 1.64(1 / a + 1 / b + 1 / c + 1 / d)\textsuperscript{-0.5} (criteria: EBGM05 >2, n >0). In these algorithms, ‘a’ is the number of reports containing both the suspect drug and the suspect adverse drug reaction; ‘b’ is the number of reports containing the suspect adverse drug
of adverse event reports on SGLT2is-related fractures collected in the FAERS database from the first quarter in 2004 to the fourth quarter in 2019 (Figure 1). Ultimately, 317 reports were screened with suspected SGLT2is-related fractures, and the clinical features of these patients are summarized in Table 2. Most cases were reported from North America (61.83%) and Europe (17.04%), and were reported by consumers (40.06%). Affected patients tend to be older than 45 years (68.76%), and were more often male than female (58.04% vs 34.07%). The most commonly reported SGLT2i-associated fractures were related to canagli- flozin (51.10%) followed by dapagliflozin (24.60%) and empagli- flozin (23.66%). Fracture cases are most commonly found in patients with type 2 diabetes mellitus (57.19%).

Disproportionality analysis and Bayesian analysis
No positive signals were detected among SGLT2is and GLMs plus SGLT2is. Just three of 14 GLMs posed one or two positive signals based on the criteria for the four algorithms: which are pioglitazone in ROR: 1.24 (1.10, 1.40) and IC: 0.31 (0.27), lixisenatide in PPR: 2.2 (3.32) and IC: 1.14 (0.47), and aloglip- tin in IC: 0.24 (0.13; Table 3).

Onset times of fracture
Overall, the median onset times of SGLT2is, GLMs and GLMs plus SGLT2is were 150 days (interquartile range [IQR] 56–313 days), 534 days (IQR 153–1,247 days) and 184 days (IQR 58–481 days), respectively. The onset times of fracture for each regimen are described in Figure 2. Of note, a significant difference in median onset times of fracture was found between GLMs versus GLMs plus SGLT2is (P < 0.0001). However, the median onset times of fracture for SGLT2is versus GLMs (P = 0.7050) or SGLT2is versus GLMs plus SGLT2is (P = 0.6299) were not significantly different. Significant differences were noted for SGLT2is versus metformin (P < 0.0001), SGLT2is versus thiazolidinedione (P < 0.0001), metformin versus glucagon-like peptide-1 receptor agonists (P < 0.0001), metformin versus DPP-4 inhibitors (P < 0.0001), metformin versus

Statistical analysis
Descriptive analyses were used to summarize the characteristics of adverse event reports on SGLT2is-related fractures collected from the FAERS database. The onset time of fracture was defined as the interval between the EVENT_DT (fracture onset date) and the START_DT (start date of SGLT2is use). Reports with input error (EVENT_DT earlier than START_DT) or inaccurate date entry were excluded.

The onset times among SGLT2is were compared using non-parametric tests (the Mann–Whitney test was used for dichotomous variables, and the Kruskal–Wallis test was used when there were more than two subgroups of respondents). Pearson’s χ²-test or Fisher’s exact test was used to compare the outcome between SGLT2is. The statistical significance was set at P < 0.05 with 95% confidence intervals. All data mining and statistical analyses were carried out using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).
Table 2 | Clinical characteristics of patients with fracture sourced from the US Food and Drug Administration’s Adverse Event Reporting System database (2004q1 to 2019q4)

| Characteristics                | Reports, n (%) |
|---------------------------------|----------------|
| Reporting region                |                |
| Europe                          | 54 (17.04%)    |
| North America                   | 196 (61.83%)   |
| South America                   | 8 (2.52%)      |
| Asia                            | 55 (17.35%)    |
| Oceania                         | 4 (1.26%)      |
| Reporters                       |                |
| Consumer                        | 127 (40.06%)   |
| Other health professional       | 38 (11.99%)    |
| Pharmacist                      | 21 (6.62%)     |
| Physician                       | 115 (36.28%)   |
| Unknown or missing              | 16 (5.05%)     |
| Reporting year                  |                |
| 2019                            | 66 (20.82%)    |
| 2018                            | 95 (29.97%)    |
| 2017                            | 52 (16.40%)    |
| 2016                            | 65 (20.50%)    |
| 2015                            | 28 (8.83%)     |
| 2014                            | 8 (2.52%)      |
| 2013                            | 2 (0.63%)      |
| Unknown or missing              | 1 (0.32%)      |
| Sex of patients                 |                |
| Male                            | 184 (58.04%)   |
| Female                          | 108 (34.07%)   |
| Unknown or missing              | 25 (7.89%)     |
| Age groups (years)              |                |
| <18                             | 1 (0.32%)      |
| 18–44                           | 8 (2.52%)      |
| 45–64                           | 105 (33.12%)   |
| 65–74                           | 65 (20.50%)    |
| >75                             | 48 (15.14%)    |
| Unknown or missing              | 90 (28.39%)    |
| SGLT2is                         |                |
| Canagliflozin                   | 162 (51.10%)   |
| Dapagliflozin                   | 78 (24.60%)    |
| Empagliflozin                   | 75 (23.66%)    |
| Ertugliflozin                   | 2 (0.63%)      |
| Ipragliflozin                   | 0 (0%)         |
| Luseogliflozin                  | 0 (0%)         |
| Remogliflozin                   | 0 (0%)         |
| Tofogliflozin                   | 0 (0%)         |
| Indications                     |                |
| Cardiac disorder                | 5 (1.64%)      |
| Chronic kidney disease          | 2 (0.65%)      |
| Diabetes mellitus               | 46 (15.04)     |
| Glycosylated hemoglobin increased| 4 (1.31)      |
| Obesity                         | 1 (0.33)       |
| Type 1 diabetes mellitus        | 3 (0.98)       |
| Type 2 diabetes mellitus        | 175 (57.19%)   |
| Unknown                         | 70 (22.88)     |

SGLT2is, sodium–glucose cotransporter 2 inhibitors.

metformin plus SGLT2is (P < 0.0001), metformin versus DPP-4 inhibitors plus SGLT2is (P = 0.0109), glucagon-like peptide-1 receptor agonists versus thiazolidinedione (P < 0.0001), thiazolidinedione versus DPP-4 inhibitors (P < 0.0001) and thiazolidinedione versus metformin plus SGLT2is (P < 0.0001).

Outcomes due to fracture

To analyze the prognosis of SGLT2is-associated fractures, we assessed the rate of outcomes (death, disability, hospitalization, life-threatening, other serious and required intervention) due to fracture after various SGLT2is and GLMs treatments, and the results are shown in Table 4. The outcome of fracture tends to be poor, resulting in hospitalization in 66.64% patients and death in 9.38%. GLMs result in a higher hospitalization rate (69.72%) than SGLT2is (55.14%, P < 0.0001) and GLMs plus SGLT2is (61.20%, P = 0.0197). No significant difference was noted between SGLT2is and GLMs + SGLT2is (P = 0.2619). Similarly, fatality rates for GLMs (11.10%) were significantly higher than SGLT2is (5.61%, P < 0.0001) and GLMs plus SGLT2is (0.55%, P < 0.0001).

DISCUSSION

It is believed that SGLT2is might change the balance of calcium and phosphorus in the body, leading to decreased bone density and increased fracture risk. The mechanism causing this imbalance is potentially attributed to the fact that SGLT2is inhibit sodium and glucose transporters, and increase serum phosphorus levels, leading to increased levels of fibroblast growth factor-23 and parathyroid hormone, and ultimately causing osteomalacia29. The incidence of all fractures for canaglifl zinc was increased compared with a placebo (15.4 vs 11.9 fracture patients per 1,000 patient-years; HR 1.26, 95% CI 1.04–1.52) in the Canagliflzin Cardiovascular Assessment Study (CANVAS) trial, which involved a total of 10,142 participants with type 2 diabetes and high cardiovascular risk12. Another study showed that during the first year of canagliflzin administration, the incidence of fractures increases in the second year30. In a 104-week follow-up of 716 diabetes patients, canagliflzin significantly reduced bone mineral density in patients compared with a placebo, which might be related to fracture events31.

However, neither empagliflozin nor dapagliflzin increased the risk of fracture compared with a placebo32–34. Of note, although the experimental SGLT2is used in these studies were different, the proportion of women and obese patients, and the type 2 diabetes mellitus duration in the CANVAS trial was higher and longer. Considering that being female, obesity and longer duration of type 2 diabetes mellitus are risk factors for fractures, these differences might increase fracture risk, as observed in the CANVAS trial. In a meta-analysis study that included 20 randomized controlled trials of 8,266 patients reported that SGLT2is did not increase fracture risk (relative risk 0.67, 95% CI 0.42–1.07) compared with a placebo35. Another systematic review showed similar results in which the use of SGLT2i (relative risk 1.02, 95% CI 0.91–1.16) was not
associated with the risk of fracture. Therefore, based on the results of existing clinical trials, it is difficult to determine the correlation between SGLT-2 inhibitors and fracture occurrence.

Similarly, we cannot exclude the possibility that a patient had been using GLM for many years, and fractures occur after replacement with SGLT2is and may be attributed to SGLT2is as noted in the study. However, these fractures are likely to be the result of a combination of GLM and disease.

Clinical trials studies still lack enough power to draw definitive conclusions about drug safety due to the strict inclusion criteria, limited sample sizes and relatively short observation periods. In our pharmacovigilance analysis, surprisingly, no association between SGLT2is and fracture was detected. Additionally, the association between GLMs plus SGLT2is with fracture was not detected.

Interestingly, we found positive signals of pioglitazone in ROR and IC. When pioglitazone was combined with SGLT2is, the signals became negative. This suggests that the signals observed were not due to the drugs themselves but rather to their interactions.
associated with an increased risk of fracture. However, this result might not be sufficient to show that SGLT2is help prevent bone fractures. A possible explanation for this finding might be that pioglitazone was approved for marketing in 1999, and there are a large number of patients with long-term use. In contrast, SGLT2is has been on the market for just a few years. Therefore, in the combined therapy group, the possibility of shorter durations of pioglitazone in some patients cannot be excluded. Furthermore, as diabetes progresses, the disease itself might also cause osteoporosis and fractures. Similarly, the short-term use of SGLT2is might not pose a fracture risk.

Another finding is that the median onset times of fracture are 242 (IQR 56–313) days for SGLT2is. This time is considerably reduced compared with that reported in another study carried out by Meier et al., showing that the median duration between diabetes mellitus onset and fracture date was 4.5 years based on a large population of 354,438 type 2 diabetes mellitus patients. This result is also increased compared with the data of the other two groups in the present study; that is, 534 (IQR 153–1247) for GLMs and 184 (IQR 58–481) for GLMs plus SGLT2is. The difference in results might be explained by the fact that the present study used data on adverse drug events, namely, fractures suspected to be caused by the drug rather than those caused by trauma. Nevertheless, Meier’s study used a UK-based primary care database and identified patients with a low-trauma fracture (non-vertebral fractures of the proximal and distal upper and lower extremities, ribs and thorax, hip and foot) during the study period.

The predictable increase in the number of patients who will receive SGLT2is in the future implies that close monitoring and constant epidemiological surveillance are required, even if the adverse event of fracture occurs rarely. It is still recommended to include fractures in post-marketing risk management plans, especially in the context of falls, reduced bone density,
advanced age, alcoholism, low weight, presence of certain diseases (such as electrolyte disorders, epilepsy, chronic obstructive pulmonary disease etc.) and the simultaneous use of certain drugs (such as glucocorticoids, antidepressants, anti-epileptic drugs etc.).

We acknowledge certain limitations of the present study. First, data mining technology fails to fully reflect all clinical information from patients. It also requires detailed information from clinical follow up and other surveys to verify data mining hypotheses. Also, most of the patients came from North America (61.83%), Asia (17.35%) and Europe (17.04%). There was indeed some uncertainty in other regions and ethnicities. Second, data mining technology cannot remedy the inherent limitations of adverse drug reaction reporting systems, such as underreporting, false reporting, incomplete reporting, inaccuracy and arbitrariness. Third, some relevant statistics, such as the incidence rate for each suspicious drug, cannot be calculated due to the lack of total numbers of patients receiving treatment.

The present study showed that SGLT2is used in type 2 diabetes mellitus seems to have no safety profile regarding fracture events. It is recommended to assess fractures as the primary outcome, at long-term follow up, and in high-quality real-world studies to further verify and explore the relationship between SGLT2is and fractures.

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DISCLOSURE
The authors declare no conflict of interest.

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