Lack of Evidence for a Harmful Effect of Sodium–Glucose Cotransporter 2 (SGLT2) Inhibitors on Fracture Risk among Type 2 Diabetes Patients: A Network and Cumulative Meta-Analysis of Randomized Controlled Trials

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Abstract

Aim: Given the conflicting evidence of sodium-glucose cotransporter 2 (SGLT2) inhibitors on bone health in patients with type 2 diabetes Mellitus (T2DM), we aimed to evaluate the comparative effects of SGLT2 inhibitors on risk of bone fracture.

Methods: PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov were systematically searched from inception to January 27, 2016 to identify RCTs reporting the outcome of fracture in T2DM patients with the use of SGLT2 inhibitors. A pairwise and network meta-analyses, as well as a cumulative meta-analysis were performed to calculate their odds ratios (ORs) and 95% confidence intervals (CIs).

Results: A total of 38 eligible RCTs (10 canagliflozin, 15 dapagliflozin, and 13 empagliflozin) involving 30,384 patients with periods of follow-up ranged from 24 to 160 weeks were included. The fracture event rates were 1.59% in the SGLT2 inhibitor groups and 1.56% in the control groups. The incidence of fracture event was similar among these three SGLT2 inhibitor groups. Compared with placebo, canagliflozin (OR, 1.15; 95%CI, 0.71 to 1.88), dapagliflozin (OR, 0.68; 95%CI, 0.37 to 1.25), and empagliflozin (OR, 0.93; 95%CI, 0.74 to 1.18) was not significantly associated with an increased risk of fracture. Our cumulative meta-analysis indicated the robustness of our null findings of SGLT2 inhibitors.

Conclusions: Our meta-analysis based on available RCT data does not support the harm effect of SGLT2 inhibitors on fracture, although future safety monitoring from RCT and real-world data with detailed information on bone health is warranted.

Keywords: SGLT2 inhibitor, Fracture, Type 2 diabetes, Meta-analysis

Introduction

Patients with type 2 diabetes mellitus (T2DM) are at high risk for fracture, especially in the elderly patients [1, 2]. Though the precise mechanisms are unclear, several diabetic complications, such as hypoglycemic events, sensory neuropathy, nephropathy, and retinopathy, contribute to increased fracture risk [3]. Furthermore, some glucose-lowering agents may have potential to affect the risk of fracture [4].

Sodium glucose cotransporter 2 (SGLT2) inhibitors were recently approved for treating T2DM [5], which offer a novel insulin independent hypoglycemia mechanism by selectively inhibiting renal glucose reabsorption to increase urinary glucose excretion [6, 7]. As a result, SGLT2 inhibitors cause osmotic diuresis effect that is related to volume depletion and maybe electrolytes imbalance. Possible changes of calcium and phosphate could adversely affect bone health [8].

Recently, the increased number of reports of bone fractures in clinical trials of SGLT2 inhibitors raised a safety concern [8]. One randomized trial in the elder patients with T2DM showed that canagliflozin slightly reduced the total hip bone mineral density (BMD) and increased the bone turnover markers over 104 weeks follow-up [9]. In September, 2015, the U.S. Food and Drug Administration (FDA) strengthened the fracture warning for canagliflozin by adding a new *Warning and Precaution* and revising the *Adverse Reactions* section of the labels [10]. A pooled analysis of 10 randomized trials suggested that the increased risk of fractures associated with canagliflozin was indeed driven by a significantly high fracture rate in patients with elevated cardiovascular disease risk [11]. One trial reported that patients with moderate renal impairment received dapagliflozin and experienced more bone fracture events than placebo over 104 weeks of

follow-up[12]. In contrast, fewer fracture events of empagliflozin were reported as compared with placebo in patients with chronic kidney disease [13].

Given conflicting results from individual RCTs, we therefore performed a comprehensive network meta-analysis to synthesize all available RCT data to evaluate the comparative effects of SGLT2 inhibitors on fracture risk in patients with T2DM. We also conducted a cumulative meta-analysis to assess the results robustness.

Methods

This review was performed according to the checklist of the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [14].

Search strategy

PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were comprehensively searched from inception to January 27, 2016 to identify eligible RCTs. We used the following relevant search terms: random, RCTs, sodium–glucose cotransporter, SGLT2, SGLT-2, and the names of individual SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, sotagliflozin, luseogliflozin, ipragliflozin, remogliflozin etabonate, tofogliflozin, and ertugliflozin). No restrictions of language, year of publication, or publication status were applied. In addition, a manual search was carried out by searching the references of included trials and relevant meta-analyses, as well as ClinicalTrials.gov to identify other published and unpublished trials. Detailed information about the search strategy is presented on **Table S1**.

Study selection and data extraction

We included RCTs that compared SGLT2 inhibitors with placebo or other active antidiabetic treatments in adult patients with T2DM. The follow-up periods required at least 24 weeks and fracture events were reported on published articles. In addition, the trials with results presented on ClinicalTrials.gov were also considered. Events of any type of fracture were considered the primary outcome and the change of BMD as the secondary outcome. The fracture event was reported by investigators as an adverse event (or serious adverse event) identified in the database using pre-specified lists from the Medical Dictionary for Regulatory Activities (MedDRA). Conference abstracts were excluded due to lack of detailed information assessing the trials' characteristics, definition of outcome, and trial quality.

Two reviewers independently did the study selection and data extraction, and any disagreements were resolved by consensus or referral to a third reviewer. A standardized data extraction form was developed to extract the following data: first author (publication year), study characteristics (country of origin, funding, and follow-up), characteristics of patients (inclusion criteria, background treatments, mean age, proportion of men, duration of T2DM, baseline glycated haemoglobin (HbA1c)%, body mass index (BMI), and pre-existing cardiovascular disease or chronic kidney disease, interventions (type and dose of SGLT2 inhibitors), and the outcomes (fracture events and BMD).

If multiple reports from the same population were retrieved, only the most complete

and/or more recently reported data were used. If fracture events were not reported in the manuscript, the data from the “Serious Adverse Events” section on the ClinicalTrials.gov were extracted. In addition, if fracture outcomes were not reported on ClinicalTrials.gov, the incidence of the events was assumed to be zero. If two different comparison groups of non-overlapping patients (ie, A vs B and C vs D) were included in the same report, each comparison was considered separately. If three arms (ie, A vs B vs A+B) were evaluated in the RCTs, only two arms (A vs B) were included. When placebo was switched to an active comparator in the extended period, only the period with the placebo was documented. If any data were unclear or missing, the authors of the original RCTs were contacted for further information.

Quality assessment—risk of bias

We used Cochrane risk of bias tool to assess the quality of RCTs on 5 domains [15]. Two authors independently reviewed and judged each RCT as low risk of bias, high risk of bias, or unclear risk of bias for each of the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

Statistical analysis

Two types of meta-analysis, pairwise and network meta-analysis were performed to calculate their odds ratios (ORs) and 95% confidence intervals (CIs). All meta-analysis was performed with STATA (Version 14; Stata Corp., College Station, TX).

For pairwise meta-analysis, Peto’s method was undertook to calculate the ORs for direct

comparisons between therapeutic regimens due to low event rate [16]. An I^2 statistic was used to evaluate the presence of heterogeneity within meta-analyses, with I^2 of 25, 50, and 75 indicating low, medium, and high heterogeneity, respectively [17]. The source of heterogeneity was further explored in the following pre-specified subgroups: 1) type of SGLT2 inhibitors (canagliflozin *vs.* dapagliflozin *vs.* empagliflozin); 2) type of control groups (placebo *vs.* active treatment); 3) length of trial duration (<52 *vs.* ≥52 weeks); 4) mode of therapy (monotherapy *vs.* combination therapy); 5) race/ethnicity (White *vs.* Asian); 6) pre-existing cardiovascular disease (Yes *vs.* No); 7) pre-existing chronic kidney disease (Yes *vs.* No); 8) age (<60 years *vs.* ≥ 60 years); and 9) data source (publications *vs.* Clinical trial registration). In addition, a cumulative meta-analysis was performed to test the stability of our findings with the accumulation of data over time. Finally, potential publication bias was assessed by Begg's or Egg's tests, as well as a visual inspection of the funnel plots.

For indirect and mixed comparisons, a network meta-analysis with a random-effects model was used to compare different interventions [18, 19]. The network meta-analysis was performed with STATA version 13.1 using the "mvmeta" command and programmed STATA routines [18, 19]. For zero-event RCT, a 0.5 zero-cell correction was applied before meta-analysis[20]. To rank the SGLT2 inhibitors for a specified outcome, we estimated the relative ranking probabilities of each treatment using surface under the cumulative ranking curve (SUCRA), and mean ranks. For incidence of fracture, large SUCRA probability and lower mean rank indicate a safer intervention[21]. The heterogeneity variance (tau) estimated by a restricted maximum likelihood method was employed to investigate between-study heterogeneity [22] .

To check for the presence of inconsistency, a loop inconsistency specific approach was introduced to evaluate the difference between direct and indirect estimates for a specific comparison [23]. To check the assumption of consistency in the entire network, a design-by-treatment interaction model by using the χ2 test was used [24]. In addition, a comparison-adjusted funnel plot was used to assess small study effects within a network of interventions [25].

Results

Study characteristics

A total of 1,268 citations were retrieved through electronic search, and then 172 potentially eligible reports were identified by reviewing study titles and abstracts. One hundred and thirty-four reports were excluded for the following reasons: conference abstracts (n= 75), no reporting fracture outcomes (n= 23), duplications with the same data source (n= 19), or follow-up period of less than 24 weeks (n=17). The RCTs registered on ClinicalTrials.gov were additionally checked and two RCTs were included. Finally, 38 RCTs were eligible and included in this meta-analysis (**Figure 1**).

The **Table S2** summarized the study characteristics of the 38 trials totaling 30,384 patients, who were randomly assigned to each of SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) or control groups (placebo or other active anti-diabetic treatments). Sample sizes of individual trials were between 180 and 7,020 participants and the periods of follow up ranged from 24 to 160 weeks. One trial provided two independent datasets for two different comparisons (empagliflozin *vs.* metformin and empagliflozin *vs.* sitagliptin), which we considered separately [26]. The data of two trials

were presented together on the ClinicalTrials.gov so we included the combined data as one independent trial [27, 28] .

The risk of bias for the 38 RCTs was summarized as follows (**Figure S1**): 31 RCTs reported adequate random sequence generation; 28 RCTs reported adequate allocation concealment; masking conditions were high in 3 RCTs, of which 2 RCTs were open label in extended period and 1 RCT set one arm with open label; and 13 RCTs reported any fracture events. All of the trials were funded by industrial companies.

Risk of any types of bone fracture

Pairwise meta-analysis and cumulative meta-analysis

The analyses of fracture events included data from 38 trials reporting 496 events among 30,384 patients (a raw event rate of 1.63%). The event rates were 1.59% in the SGLT2 inhibitor treatment groups and 1.56% in the control groups. The results of pairwise meta-analysis were presented in **Figure 2**. There was no significant difference in the risk of fracture between SGLT2 inhibitors and controls (OR, 1.02; 95%CI, 0.84 to 1.23), with low statistical heterogeneity (I^2=22.8%). None of the subgroup analyses showed significant results. SGLT2 inhibitors appeared to increase the risk of facture in Asian population (OR, 2.05; 95%CI, 0.86 to 4.87), but there was not statistically significant. Furthermore, the cumulative meta-analysis by publication year showed that the result gradually became stable and toward the null (**Figure 3**). There was no evidence of substantial publication bias in our analysis, based on the Egger's test (*P* = 0.61), Begg's test (*P* = 0.43), and on visual inspection of the funnel plot (**Figure S2**).

Network meta-analysis

Figure S3 and **Figure 4** displayed the trial network and the results of network meta-analysis, respectively. Compared with placebo, Canagliflozin (OR, 1.15; 95%CI, 0.71 to 1.88), dapagliflozin (OR, 0.68; 95%CI, 0.37 to 1.25), and empagliflozin (OR, 0.93; 95%CI, 0.74 to 1.18) was not significantly associated with an increased risk of fracture.). The incidence of fracture was similar among these three SGLT2 inhibitors. There was a low level of statistical heterogeneity (tau≈0), no inconsistency between direct and indirect estimates (all 95%CIs across zero) and no global inconsistency within any network were detected (*P*=0.95). In addition, the comparison-adjusted funnel plot indicated absence of small-study effects (**Figure S4**).

Changes in bone mineral density

We identified 2 relevant RCTs that evaluated the effect of SGLT2 inhibitors on the changes in BMD [29, 30]. One RCT with 182 T2DM patients showed no significant differences between dapagliflozin and placebo in BMD expressed as adjusted mean percent change from baseline at week 102 in any of the three regions of lumbar spine, femoral neck and total hip [29]. However, the other RCT with 716 T2DM patients showed a small, statistically significant reduction in BMD at the total hip over 104 weeks follow-up with the use of canagliflozin [30] .

Discussion

Our meta-analysis included 38 RCTs (30,384 patients) that reported fracture risk and 2 RCTs with data on changes of BMD. The results from the direct and indirect evidence showed that SGLT2 inhibitors were not significantly associated with an increased risk of fracture. There was no evidence of any difference among these SGLT2 inhibitors. No significant difference was detected in the subgroup analyses. Our cumulative meta-analysis of RCTs ordered chronologically by publication year showed the robustness of our null findings.

Recently, some potential mechanisms by which SGLT2 inhibitors might affect bone metabolism were brought forward [8]. Due to their mechanism of action and the excretion of sodium in urine, SGLT2 inhibitors may alter serum calcium and phosphate levels, and thereby affect bone mass and fracture risk [31]. Some studies show that SGLT2 inhibitors are associated with small increases in serum inorganic phosphate and magnesium, but clinical relevance of these changes is unclear [32]. It is proposed that increased serum phosphate is likely to provoke secretion of parathyroid hormone (PTH), which enhances bone resorption and increase the risk of bone fractures [8]. Furthermore, serum PTH increases the concentrations of fibroblast growth factor 23 (FGF23), which has been associated with bone disease [33]. In addition, it is the fact that bone represents a substantial reservoir of sodium and that mobilization of bone sodium seems to require arginine vasopressin-dependent and independent mechanisms [34, 35]. Arginine vasopressin negatively regulates osteoblasts and stimulates osteoclasts [35]. Therefore, the hyponatremia caused by SGLT2 inhibitors might increase the osteoporosis and fracture risk. Previous studies showed that canagliflozin might increase bone turnover, with increases in serum of biomarkers for both bone resorption (collagen

type-1 beta-carboxytelopeptide) and bone formation (osteocalcin) [32], while dapagliflozin had no meaningful effect on makers of bone turnover [29]. Additionally, a decrease in BMD at total hip was detected in T2DM patients with the use of canagliflozin [30, 32], while dapagliflozin appeared to have no effect on BMD [29]. However, these limited data are preliminary and whether SGLT2 inhibitors have an effect on bone health biomarkers needed to be explored.

Consistently, our findings and the results from one previous meta-analysis [36] do not support the adversely effect of SGLT2 inhibitors on fracture. Our meta-analysis included 38 RCTs with 496 events among 30,384 T2DM patients. Moreover, our cumulative meta-analysis showed that the overall evidence was sufficient and the null results were robust. In addition, there was no evidence that individual SGLT2 inhibitor (e.g., canagliflozin, dapagliflozin, or empagliflozin) increased the fracture rate or had different effects. One pooled analysis of data from more than 11,000 patients with T2DM reported that empagliflozin was not associated with an increased risk of bone fractures versus placebo [37]. However, another pooled analysis of 10 trials showed that fracture risk was increased with canagliflozin treatment only in the patients who were older, with a prior history/risk of cardiovascular disease, and with lower baseline estimated glomerular filtration rate and higher baseline diuretic use [11]. Also, the author indicated that the increased fracture rate of canagliflozin may be due to chance or possibly other risk factors [11]. We performed multiple subgroup analyses to identify any clinically relevant subgroup effects based on patients' characteristics (e.g., age, pre-existing cardiovascular disease, or chronic kidney disease). None of the subgroup analyses showed a significant difference in fracture risk. Intriguingly, our findings showed that

SGLT2 inhibitors had a tendency to increase the risk of fracture in Asian population. However, power was low because only 2,819 Asian patients with 24 events were included. Nevertheless, it is still difficult to draw the conclusion about long-term modest effect on fracture risk due to relatively short follow-up periods of included RCTs, which ranged from 24 to 160 weeks. Further studies with longer term follow-up are warranted to resolve uncertainty about the risk of fracture by SGLT2 inhibitors.

Be different from the previous pairwise meta-analysis which was conducted with bone fracture event as a secondary outcome [36], our network meta-analysis considered the fracture events as primary outcomes of interest. This meta-analysis included the data up to Sept 30, 2015 and just only separately pooled the data from regulatory submissions (462 events; 29503 patients; RR, 0.99, 95% CI: 0.85 to 1.34) and scientific reports (396 events; 13383 patients; RR, 0.96, 95% CI: 0.78 to 1.18) [36]. Conversely, our network meta-analysis with more restrict inclusion criteria provided more information and powerful evidence. First, we included more recent RCT data (38 RCTs with 496 events among 30,384 patients) from publications and clinical trial registration (up to Jan 27, 2016). Second, we have relatively large number of eligible RCTs to perform subgroup analyses to explore the impact by trial or patients' characteristics. Third, network meta-analysis was introduced to synthesize both direct and indirect evidence by maximizing available RCT data and explore the difference among these SGLT2 inhibitors. Fourth, we also used a cumulative meta-analysis to test the evidence sufficiency and finding robustness. Finally, more bone health outcomes (e.g., BMD) were assessed in our meta-analysis.

However, several limitations of our study merit consideration. First, some trials are less likely to report the events of fracture in the articles published on peer reviewed journals, though additional data on ClinicalTrials.gov were searched to minimize publication bias and the outcome reporting bias. Due to none of the trials considered fractures as pre-specified adverse event endpoints, it did not allow a clear report the incidence of any fracture (e.g., osteoporotic fracture) and other bone health parameters (e.g., BMD). Second, some trials were unable to ascertain fracture cases due to short follow-up periods (up to about 160 weeks). Third, background treatments and patient characteristics varied among the RCTs and might contribute to heterogeneity, although low statistical heterogeneity and absence of inconsistency of our network model were detected. Finally, risk of fracture for other novel SGLT2 inhibitors remains uncertain due to lack of RCT data.

In conclusions, current evidence suggested that SGLT2 inhibitors were not significantly associated with an increased risk of fracture in patients with T2DM. Since lack of detailed information on bone health outcome were reported and majority of RCTs were small and short term, future long term RCT and real-world data is warranted to draw more definitive conclusions regarding the bone effect of SGLT2 inhibitors.

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Disclosure Statement

The authors have nothing to disclose.

Contributor statements

H.T. and Y.S. had the idea for and designed the review. H.T. and D.L. identified and acquired reports of trials and extracted data. H.T., T.W., and Y.S. did all data analyses, checked for statistical inconsistency, and interpreted data. H.T. and Y.S. contributed to data interpretation. H.T. drafted the report and all other authors (D.L., J.Z., Y.H., T.W., S.Z., and Y.S.) critically reviewed the report.

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Figure Legend:

Figure 1. Flow chart of the identification of eligible trials.

Figure 2. Overall and subgroup pairwise meta-analysis of SGLT2 inhibitor on risk of fracture.

Figure 3. Cumulative meta-analysis of SGLT2 inhibitor on risk of fracture.

A null effect was stable after 24 RCTs and remained unchanged after additional inclusion of subsequent RCTs by publication years

Figure 4. Network meta-analysis of SGLT2 inhibitor on risk of fracture.

Common heterogeneity variables (tau) in the network meta-analysis were low (tau≈0). CANA, Canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; PLA, placebo; ACT, active treatments; CI, confidence interval.

Figure 1.

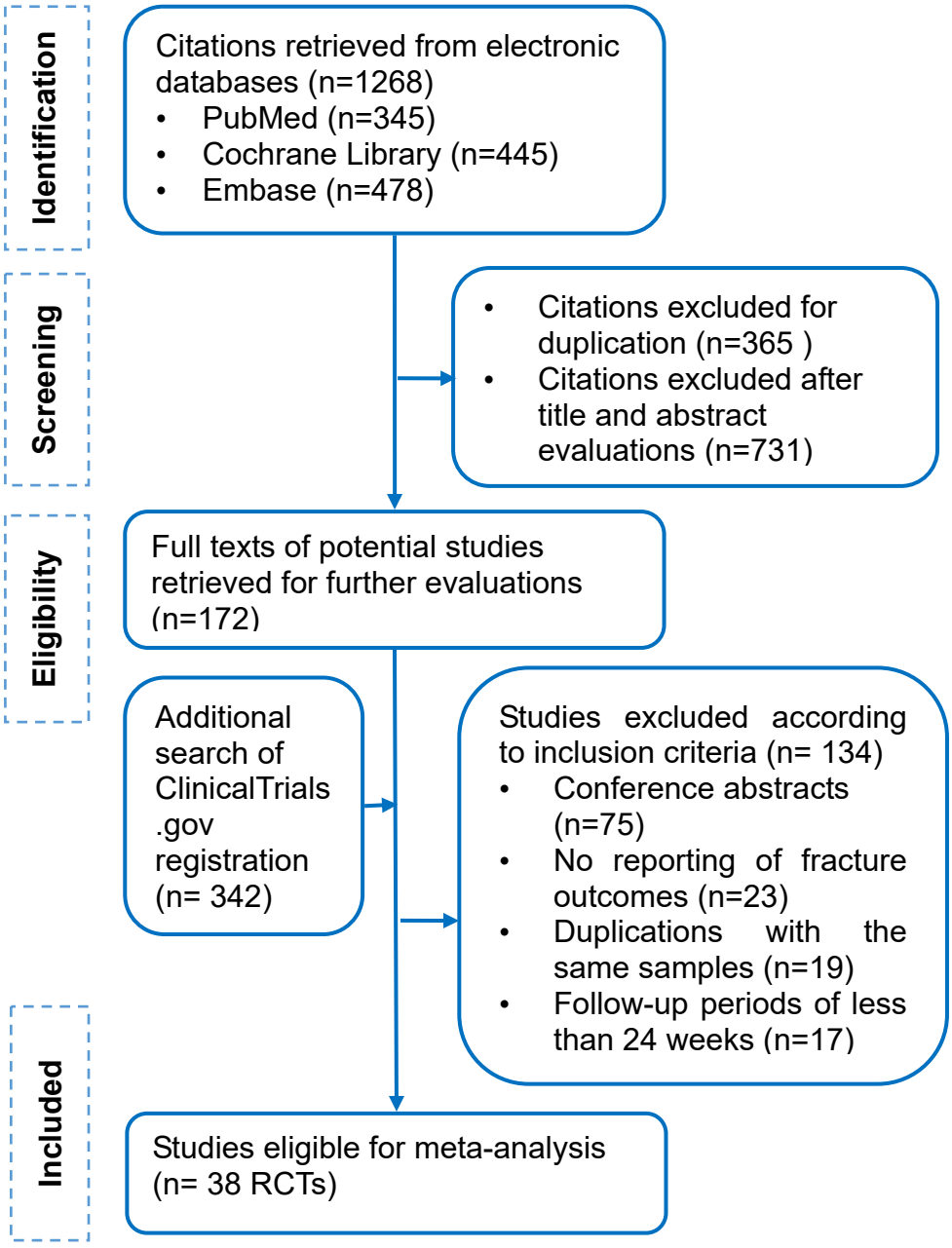
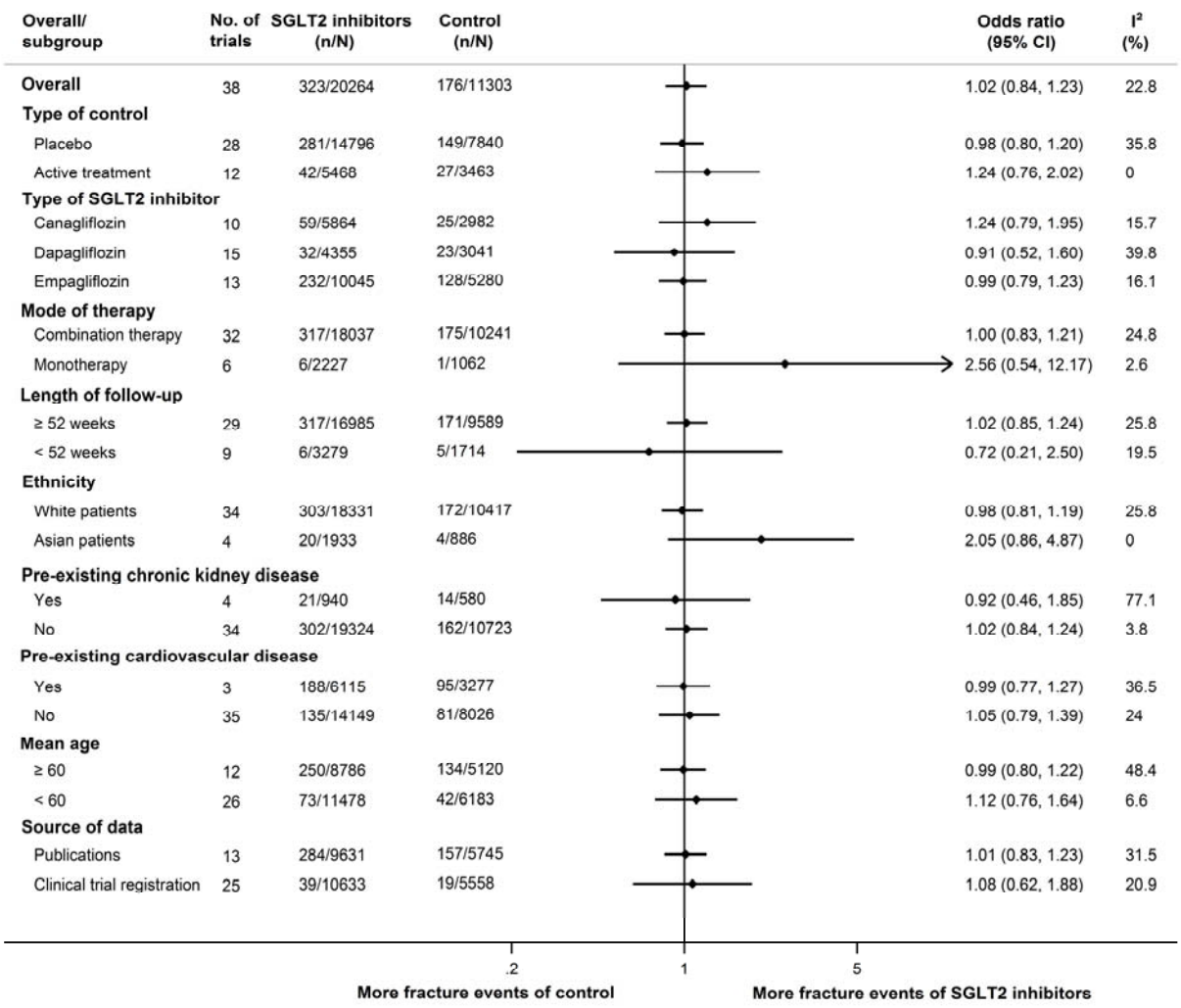

Identification
Citations retrieved from electronic databases (n=1268)
• PubMed (n=345)
• Cochrane Library (n=445)
• Embase (n=478)
Screening
• Citations excluded for duplication (n=365)
• Citations excluded after title and abstract evaluations (n=731)
Eligibility
Full texts of potential studies retrieved for further evaluations (n=172)
Additional search of ClinicalTrials .gov registration (n= 342)
Studies excluded according to inclusion criteria (n= 134)
• Conference abstracts (n=75)
• No reporting of fracture outcomes (n=23)
• Duplications with the same samples (n=19)
• Follow-up periods of less than 24 weeks (n=17)
Included
Studies eligible for meta-analysis (n= 38 RCTs)

Figure 2.


Overall/ subgroup
No. of trials
SGLT2 inhibitors (n/N)
Control (n/N)
Odds ratio (95% CI)
I² (%)
Overall 38 323/20264 176/11303 1.02 (0.84, 1.23) 22.8
Type of control
Placebo 28 281/14796 149/7840 0.98 (0.80, 1.20) 35.8
Active treatment 12 42/5468 27/3463 1.24 (0.76, 2.02) 0
Type of SGLT2 inhibitor
Canagliflozin 10 59/5864 25/2982 1.24 (0.79, 1.95) 15.7
Dapagliflozin 15 32/4355 23/3041 0.91 (0.52, 1.60) 39.8
Empagliflozin 13 232/10045 128/5280 0.99 (0.79, 1.23) 16.1
Mode of therapy
Combination therapy 32 317/18037 175/10241 1.00 (0.83, 1.21) 24.8
Monotherapy 6 6/2227 1/1062 2.56 (0.54, 12.17) 2.6
Length of follow-up
≥ 52 weeks 29 317/16985 171/9589 1.02 (0.85, 1.24) 25.8
< 52 weeks 9 6/3279 5/1714 0.72 (0.21, 2.50) 19.5
Ethnicity
White patients 34 303/18331 172/10417 0.98 (0.81, 1.19) 25.8
Asian patients 4 20/1933 4/886 2.05 (0.86, 4.87) 0
Pre-existing chronic kidney disease
Yes 4 21/940 14/580 0.92 (0.46, 1.85) 77.1
No 34 302/19324 162/10723 1.02 (0.84, 1.24) 3.8
Pre-existing cardiovascular disease
Yes 3 188/6115 95/3277 0.99 (0.77, 1.27) 36.5
No 35 135/14149 81/8026 1.05 (0.79, 1.39) 24
Mean age
≥ 60 12 250/8786 134/5120 0.99 (0.80, 1.22) 48.4
< 60 26 73/11478 42/6183 1.12 (0.76, 1.64) 6.6
Source of data
Publications 13 284/9631 157/5745 1.01 (0.83, 1.23) 31.5
Clinical trial registration 25 39/10633 19/5558 1.08 (0.62, 1.88) 20.9
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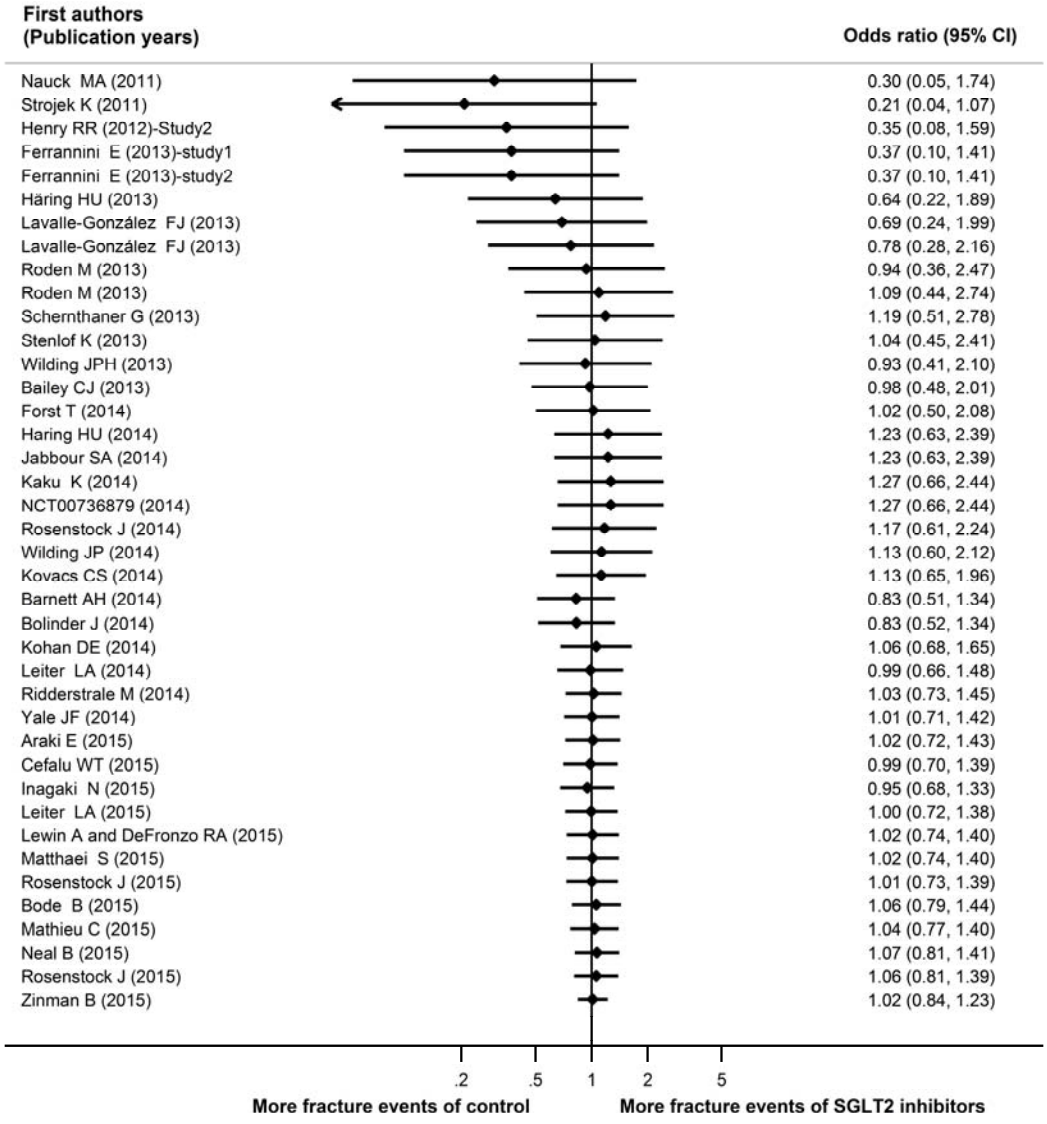
More fracture events of control
More fracture events of SGLT2 inhibitors

Figure 3.


First authors
(Publication years)
Odds ratio (95% CI)
Nauck MA (2011) 0.30 (0.05, 1.74)
Strojek K (2011) 0.21 (0.04, 1.07)
Henry RR (2012)-Study2 0.35 (0.08, 1.59)
Ferrannini E (2013)-study1 0.37 (0.10, 1.41)
Ferrannini E (2013)-study2 0.37 (0.10, 1.41)
Häring HU (2013) 0.64 (0.22, 1.89)
Lavalle-González FJ (2013) 0.69 (0.24, 1.99)
Lavalle-González FJ (2013) 0.78 (0.28, 2.16)
Roden M (2013) 0.94 (0.36, 2.47)
Roden M (2013) 1.09 (0.44, 2.74)
Schernthaner G (2013) 1.19 (0.51, 2.78)
Stenlof K (2013) 1.04 (0.45, 2.41)
Wilding JPH (2013) 0.93 (0.41, 2.10)
Bailey CJ (2013) 0.98 (0.48, 2.01)
Forst T (2014) 1.02 (0.50, 2.08)
Haring HU (2014) 1.23 (0.63, 2.39)
Jabbour SA (2014) 1.23 (0.63, 2.39)
Kaku K (2014) 1.27 (0.66, 2.44)
NCT00736879 (2014) 1.27 (0.66, 2.44)
Rosenstock J (2014) 1.17 (0.61, 2.24)
Wilding JP (2014) 1.13 (0.60, 2.12)
Kovacs CS (2014) 1.13 (0.65, 1.96)
Barnett AH (2014) 0.83 (0.51, 1.34)
Bolinder J (2014) 0.83 (0.52, 1.34)
Kohan DE (2014) 1.06 (0.68, 1.65)
Leiter LA (2014) 0.99 (0.66, 1.48)
Ridderstrale M (2014) 1.03 (0.73, 1.45)
Yale JF (2014) 1.01 (0.71, 1.42)
Araki E (2015) 1.02 (0.72, 1.43)
Cefalu WT (2015) 0.99 (0.70, 1.39)
Inagaki N (2015) 0.95 (0.68, 1.33)
Leiter LA (2015) 1.00 (0.72, 1.38)
Lewin A and DeFronzo RA (2015) 1.02 (0.74, 1.40)
Matthaei S (2015) 1.02 (0.74, 1.40)
Rosenstock J (2015) 1.01 (0.73, 1.39)
Bode B (2015) 1.06 (0.79, 1.44)
Mathieu C (2015) 1.04 (0.77, 1.40)
Neal B (2015) 1.07 (0.81, 1.41)
Rosenstock J (2015) 1.06 (0.81, 1.39)
Zinman B (2015) 1.02 (0.84, 1.23)
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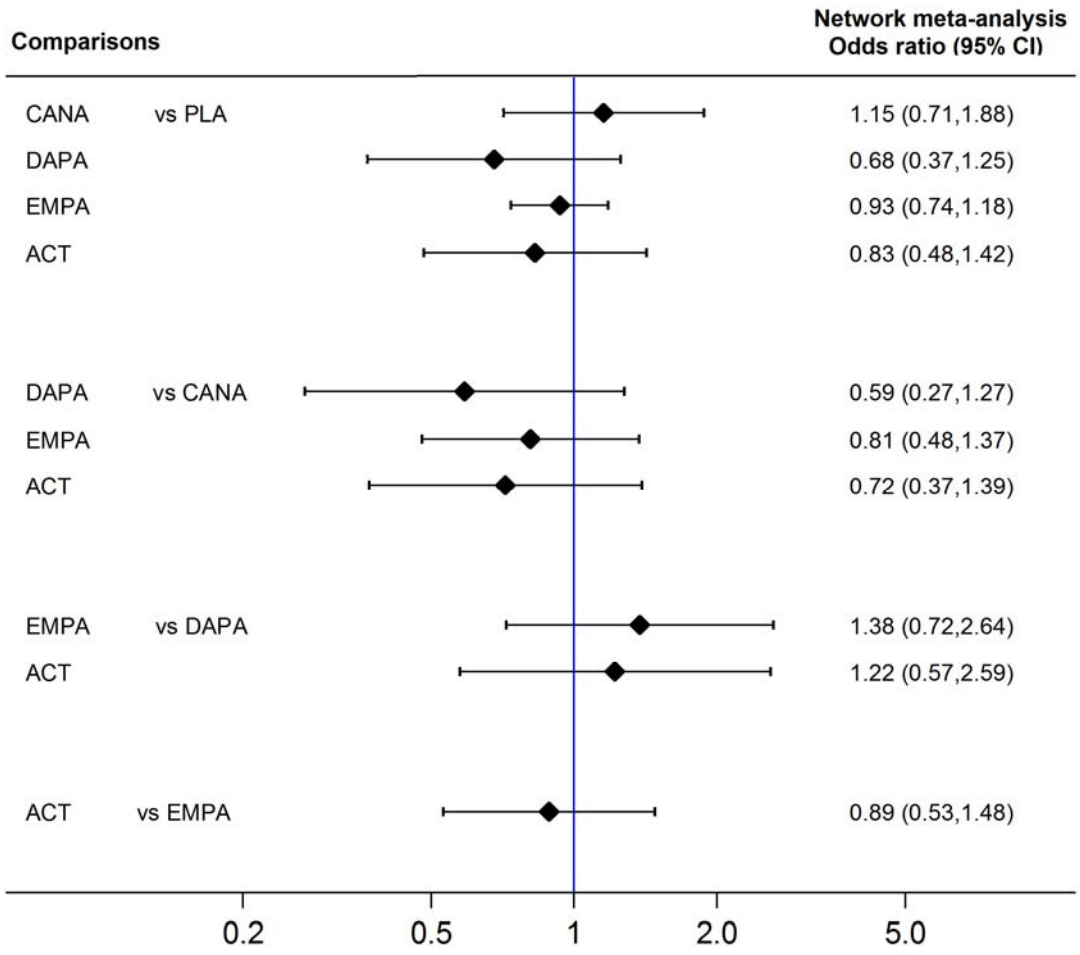
More fracture events of control
More fracture events of SGLT2 inhibitors

Figure 4.


Comparisons
Network meta-analysis
Odds ratio (95% CI)
CANA vs PLA
1.15 (0.71,1.88)
DAPA
0.68 (0.37,1.25)
EMPA
0.93 (0.74,1.18)
ACT
0.83 (0.48,1.42)
DAPA vs CANA
0.59 (0.27,1.27)
EMPA
0.81 (0.48,1.37)
ACT
0.72 (0.37,1.39)
EMPA vs DAPA
1.38 (0.72,2.64)
ACT
1.22 (0.57,2.59)
ACT vs EMPA
0.89 (0.53,1.48)
0.2
0.5
1
2.0
5.0