Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors and Fracture Risk in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

Short running title: SGLT2 inhibitors and fracture risk

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Abstract:

Introduction: Sodium glucose co-transporter 2 (SGLT2) inhibitors could potentially alter calcium and phosphate homeostasis and may increase the risk of bone fracture.

Methods: The current meta-analysis was conducted to investigate the fracture risk among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors. Randomized controlled trials that compared the efficacy of SGLT2 inhibitors to placebo were identified. The risk ratios of fracture among patients who received SGLT2 inhibitors versus placebo were extracted from each study. Pooled risk ratios and 95% confidence intervals (CI) were calculated using a random-effect, Mantel-Haenszel analysis.

Results: A total of 20 studies with 8,286 patients treated with SGLT2 inhibitors were included. The pooled risk ratio of bone fracture in patients receiving SGLT2 inhibitors versus placebo was 0.67 (95% CI, 0.42-1.07). The pooled RR for canagliflozin, dapagliflozin and empagliflozin was 0.66 (95% CI, 0.37-1.19), 0.84 (95% CI, 0.22-3.18) and 0.57 (95% CI, 0.20-1.59), respectively.

Conclusions: Increased risk of bone fracture among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors compared with placebo was not observed in this meta-analysis. However, the results were limited by short duration of treatment/follow-up and low incidence of the event of interest.

Introduction

Type 2 diabetes mellitus is associated with an increased risk of bone fracture due to several factors including diabetes related complications, increased fall risk and other co-morbidities (1-3). Chronic hyperglycemia could interfere with bone homeostasis, resulting in increased bone fragility (4, 5). Furthermore, use of certain glucose-lowering agents, such as thiazolidinediones, is an independent risk factor for bone fracture (6-8).

Sodium glucose co-transporter 2 (SGLT2) inhibitors are novel glucose lowering agents that inhibit glucose reuptake at the renal proximal tubule where majority of glucose is reabsorbed (9). Previous clinical trials have demonstrated use of canagliflozin and dapagliflozin were associated with increased fracture risk (10-11). Some studies have demonstrated a greater decline in bone mineral density and alteration of bone turnover markers that may lead to SGLT2 inhibitors associated bone fracture (12-15). Nonetheless, the observations on fracture risk are not consistent across studies (16-21). This meta-analysis was conducted with the aim to assess the fracture risk among patients with type 2 diabetes mellitus treated with Food and Drug Administration (FDA)-approved SGLT2 inhibitors compared with placebo, individually and as a single class, using the data from all available clinical trials.

Materials and Methods

A literature search was conducted through MEDLINE and EMBASE database from inception to November, 2015. The main search terms were “sodium-glucose transporter 2 inhibitors,” “SGLT2 inhibitors”, “sodium-glucose transporter 2 inhibitors”, “SGLT2 inhibitors”, “dapagliflozin”, “canagliflozin” and “empagliflozin” as described in

supplementary data 1. Completed but not yet published clinical trials were also identified from www.clinicaltrials.gov. The search methodology is described in detail in **supplementary figure 1**. Two investigators (D.R. and T.H.) independently performed this literature review. References of selected retrieved articles were also manually reviewed. The inclusion criteria were as follows: (1) randomized-controlled clinical trial assessing the efficacy of SGLT2 inhibitors versus placebo (2) duration of study was more than or equal to 24 weeks (3) incidence of bone fracture was reported in both arms.

Study eligibility was independently determined by each investigator noted above. The second investigator (P.U.) served as the deciding vote when different determinations regarding eligibility arose from the two investigators. The modified Jadad scale was used to evaluate the quality of the included studies. This scale assesses the study in three main domains including randomization, blinding and an account of all patients. A score of one is given for each category if randomization or blinding is mentioned, and one more point is given if it is conducted appropriately. A score of one under the category of an account of all patients is given if a statement of the number of and reasons for withdrawal is provided. Each study was considered to be of sufficient quality if the score was more than or equal to three (22).

Data extraction

A standardized data collection form was used to extract the following information: first author's name, title of the study, year of publication, year when the study was conducted, country of study, study population, number of participants in each arm, inclusion criteria, exclusion criteria, duration study, baseline characteristics for each group and incidence of bone fracture.

Statistical analysis

Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). The pooled risk ratios (RR) of bone fracture across studies were calculated using a random-effect, Mantel–Haenszel analysis (23). The risk was evaluated for individual medication and for SGLT2 inhibitors as a single group. Statistical heterogeneity was assessed by Cochran's Q test and I^2 statistic. This statistic quantifies the proportion of total variation across studies that are due to heterogeneity rather than chance. A value of I^2 of 0% to 25% represents insignificant heterogeneity, more than 25% but less than or equal to 50% represents low heterogeneity, more than 50% but less than or equal to 75% represents moderate heterogeneity and more than 75% represents high heterogeneity (24). Funnel plot was used for the evaluation of publication bias.

This research was performed independently of any funding as part of institutional activities of the investigators.

Results

The search methodology and literature review process are outlined in **supplementary figure 1**. PRISMA (Preferred reporting Items for Systematic Reviews and Meta-Analysis) (25) is provided as **supplementary table 1**. The literature review process yielded 3,262 potentially relevant studies (2,308 articles from EMBASE, 750 articles from MEDLINE and 204 clinical trials from www.clinicaltrials.gov). After exclusion of 1,834 non-human studies, 906 non-randomized controlled trials, 59 non-type 2 diabetes studies and 304 studies with duration of less than 24 weeks, 159 studies underwent title, abstract and NCT number review. One hundred twenty articles were excluded at this stage due to duplication, leaving 39 studies for full-length article review. Of these 39 studies, 19 were excluded for various reasons (2 studies did not publish or disclose data, 8 studies did not

report the incidence of bone fracture and 9 studies did not have placebo arm), leaving 20 studies with 8,286 treated SGLT2 inhibitors for the meta-analysis (11, 26-44). The detailed characteristics and quality assessment of the included studies are illustrated in **table 1**.

Bone fractures occurred in 87 patients (54 patients in SGLT2 inhibitors arm and 33 patients in placebo arm). The pooled RR of bone fracture in patients receiving SGLT2 inhibitors versus placebo was 0.67 (95% CI, 0.42-1.07). The statistical heterogeneity was negligible with an I^2 of 0%. The forest plot of this overall analysis is shown in **figure 1**. The pooled RR for canagliflozin, dapagliflozin and empagliflozin was 0.66 (95% CI, 0.37-1.19; **figure 2**), 0.84 (95% CI, 0.22-3.18; **figure 3**) and 0.57 (95% CI, 0.20-1.59; **figure 4**), respectively.

Evaluation for publication bias

Funnel plot is shown as **supplemental figure 2**. The plot was symmetric and does not provide a suggestive evidence of publication bias.

Discussion

SGLT2 inhibitors, a novel class of anti-diabetic medication, are non-insulin dependent, reversible SGLT2 blockers that inhibit glucose reabsorption at the renal proximal tubule, leading to glycosuria and reduction in plasma glucose. Theoretically, SGLT2 inhibitors may have adverse skeletal effects by altering calcium and phosphate homeostasis which might lead to decline in bone density and increased risk of bone fracture. However, the current meta-analysis, which included data from 8,286 patients treated with SGLT2 inhibitors, did not observe a significantly increased risk of fracture when SGLT2 inhibitors were either evaluated individually or as a single class.

Our result is different from a previous pooled analysis of 9 studies that reported an increased risk of fracture among type 2 diabetic patients treated with canagliflozin (45). It should be noted that the previous pooled analysis included both placebo and active-controlled studies which was unlike our analysis that included only clinical trials with placebo as a comparator. Therefore, it is possible that the apparent increased risk of fracture among canagliflozin users might, indeed, from the protective effect of the active comparators rather than from the detrimental effect of canagliflozin (46-49). Moreover, the increased risk of fracture was primarily driven by one study (CANVAS study) that included older patients who had preexisting microvascular diseases, impaired baseline renal function and higher baseline risk of fall (45). Sensitivity analysis that excluded CANVAS study demonstrated a similar incidence of fracture between the canagliflozin and non-canagliflozin group (45). Similarly to CANVAS study, the increased fracture risk noted in dapagliflozin was occurred in type 2 diabetic patients who had moderate renal impairment (11).

The possible mechanism of SGLT2 inhibitors on bone metabolism was suggested by Taylor et al.,(50) that SGLT2 inhibitors can alter calcium homeostasis by inhibiting sodium and glucose co-transporter which enhances sodium transportation via sodium and phosphate cotransporter in apical membrane of renal proximal tubule. Thus, SGLT2 inhibitors increase serum phosphate resulted in increased fibroblast growth factor-23 (FGF-23) and parathyroid hormone leading to osteomalacia.

Because fracture outcome could take long time to be observed, many clinical trials used changes in calcium metabolism, bone markers and bone mineral density as surrogates for bone health. Unfortunately, we were not able conduct any analyses based on surrogates because most of the studies included in our meta-analysis have inadequate data on calcium,

phosphate, bone turnover markers and bone mineral density to analyze and, more importantly, the data on the changes of these surrogate endpoints may not precisely reflect the actual fracture risk.

Although the primary studies included in this analysis were randomized controlled trials, we acknowledge that the meta-analysis had some limitations and the interpretation of the results should be done with cautions. The main limitations were the relatively short duration of treatment and follow-up in the primary studies. Decline in bone mineral density could take a longer period of time and the increased risk of fracture might not be apparent during the study period. Therefore, post-marketing surveillance is required to evaluate this risk among long-term users. Moreover, bone fracture was not the primary endpoint of the included studies and the absolute number of fractures occurred in those studies was relatively small, particularly for dapagliflozin and empagliflozin, leading to a concern over precision of the effect estimates. Thus, the completeness of the report and detection of fractures could be limited.

Conclusions

Increased risk of bone fracture among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors compared with placebo was not observed in this meta-analysis. However, the results were limited by short duration of treatment/follow-up and low incidence of event of interest of primary studies. Post-marketing surveillance is warranted to evaluate this risk.

Conflict of interest

None of the authors have any conflict of interest to disclose

Author contributions

T.H and D.R were involved in the conception and design of the study and draft the manuscript. P.U. performed the statistical analyses. T.H, D.R, P.U. and J.S. critically revised the manuscript. All authors contributed to data review, interpretation, writing process and approved the final manuscript. T.H is a guarantor of this work and takes responsibility of the integrity and accuracy of this work.

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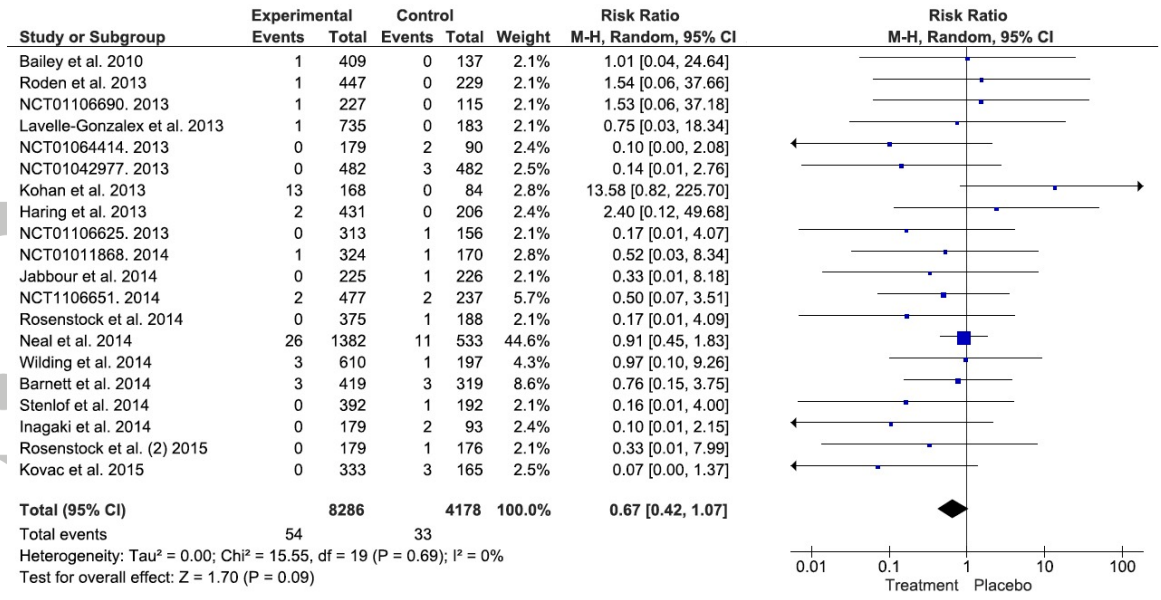

Figure 1: Forest plot of MH-OR (95% CI) for all included studies for fracture risk in type 2 diabetes who treated with all FDA approved SGLT 2 inhibitors and those with placebo; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

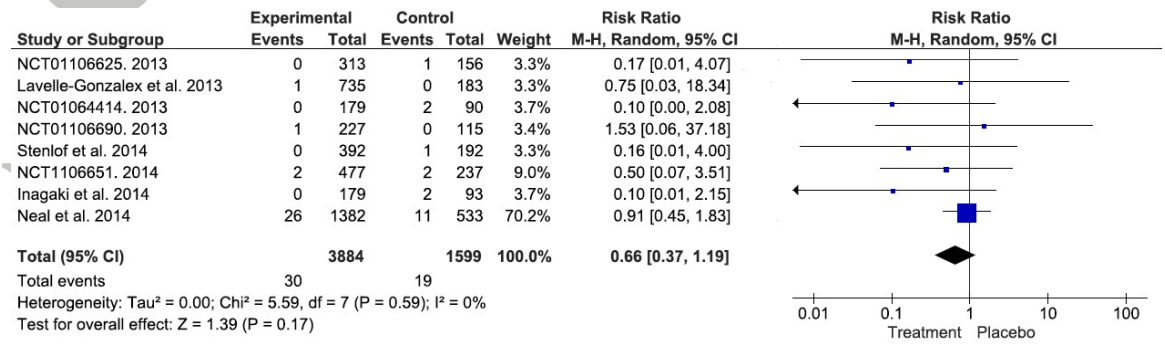

Figure 2: Forest plot of MH-OR (95% CI) for all included studies for fracture risk in type 2 diabetes who treated with canagliflozin and those with placebo; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

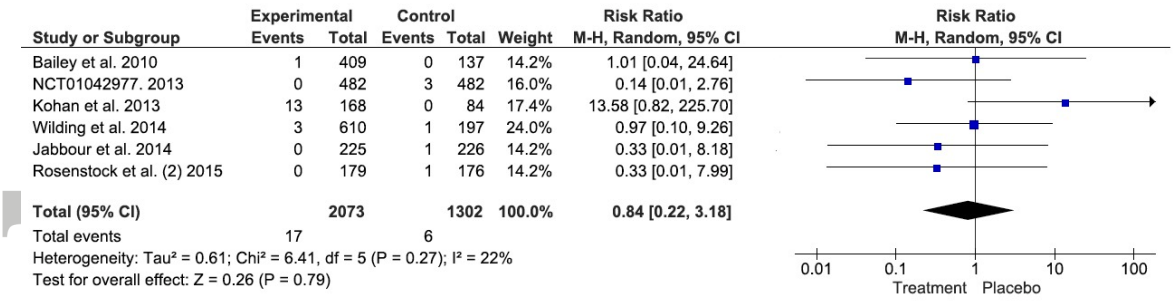

Figure 3: Forest plot of MH-OR (95% CI) for all included studies for fracture risk in type 2 diabetes who treated with dapagliflozin and those with placebo; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

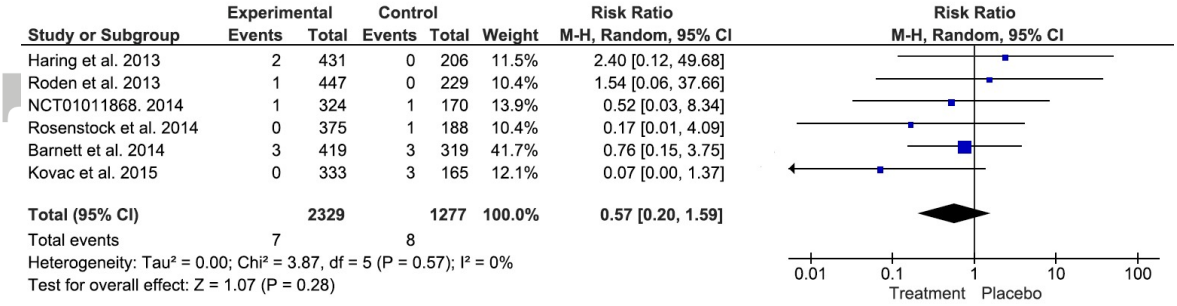

Figure 4: Forest plot of MH-OR (95% CI) for all included studies for fracture risk in type 2 diabetes who treated with empagliflozin and those with placebo; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

Table 1: Characteristics of included randomized controlled trials

	Bailey et al (26)	**Kohan et al (11)**	**NCT01042977 (27)**	**Wilding et al (28)**	**Jabbour et al (29)**
Year of publication	2010 (24 weeks)	2013 (24 weeks)	2013 (24 weeks)	2014 (24 weeks)	2014 (24 weeks)
Study design	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded
Intervention	Dapagliflozin 2.5, 5, 10 mg	Dapagliflozin 5, 10 mg	Dapagliflozin plus usual care	Dapagliflozin 2.5, 5, 10 mg	Dapagliflozin 10 mg added to Sitagliptin +/- metformin
Comparison	Placebo	Placebo	Placebo plus usual care	Placebo	Placebo added to Sitagliptin +/- metformin
Country where study was conducted	75 sites USA, Canada, Mexico, Argentina, Brazil	111 sites United States, Argentina, Australia, Canada, Denmark, France, India, Italy, Mexico, Peru, Puerto Rico, Singapore, Spain	135 sites United States, Argentina, Australia, Austria, Bulgaria, Canada, Chile, Germany, Hungary, Poland	96 sites United States, Austria, Bulgaria, Canada, Finland, Germany, Hungary, Netherlands, Romania, Russian Federation, Slovakia, Spain, United Kingdom	88 sites Argentina, Germany, Mexico, Poland, the United Kingdom, United States
Fracture	**Open Fracture** Dapagliflozin 2.5 mg + metformin 0/137 Dapagliflozin 5 mg + metformin 0/137 Dapagliflozin 10 mg + metformin 1/135 Placebo + metformin 0/137	**Fracture** Dapagliflozin 5 mg 5/83 Dapagliflozin 10 mg 8/85 Placebo 0/84	**Cervical vertebral fracture** 0/482, 1/482 (Dapagliflozin, placebo) **Clavicle fracture** 0/482, 1/482 (Dapagliflozin, placebo) **Femoral neck fracture** 0/482, 1/482 (Dapagliflozin, placebo)	**Ankle Fracture** 0/202, 0/212, 1/196, 1/197 (Dapagliflozin 2.5, 5, 10 mg and placebo) **Hip Fracture** 0/202, 0/212, 1/196, 0/197 (Dapagliflozin 2.5, 5, 10 mg and placebo) **Tibial Fracture** 0/202, 1/212, 0/196, 0/197 (Dapagliflozin 2.5, 5, 10 mg and placebo)	**Upper limb Fracture** Dapagliflozin 0/225 Placebo 1/226

Primary outcome	Change in HbA1c	Adjusted mean change in HbA1c Levels	Change in HbA1c Proportion of responders meeting all criteria (A1C drop of 0.5% or more HbA1c, relative drop of 3% or more total BW, and drop of 3 mmHg or more seated SBP)	Adjusted mean change in HbA1c	Adjusted mean change in HbA1c
Major secondary outcome	- Change from baseline in total BW, FPG - Proportion of patients achieving HbA1c <7%	- Change in estimated GFR, CrCl, FPG, BW	- Change in eGFR - Change in FPG, BW	- Change in BW, insulin dose and FPG	- Change in BW, total BW, seated SBP, 2 hour post liquid meal glucose rise - Proportion of participants achieving a reduction in HbA1c of ≥0.7%
Number of treatment group	137, 137, 135	83, 85	482	202, 211, 194	223
Number of control group	137	84	483	193	224
Percentage of male in treatment and control group	Treatment 51.1, 50.4, 57.0 Control 55.5	Treatment 66.3, 65.9 Control 63.1	Treatment 66.9 Control 67.0	Treatment 49.5, 47.4, 44.8 Control 49.2	Treatment 57 Control 52.7
Average age of treatment and control group (years)	Treatment 55, 54.3, 52.7 Control 53.7	Treatment 66, 68 Control 67	Treatment 63.9 Control 63.6	Treatment 59.8, 59.3, 59.3 Control 58.8	Treatment 54.8 Control 55

Baseline HbA1c	Treatment 7.99, 8.17, 7.92 Control 8.11	Treatment 8.3, 8.22 Control 8.53	Treatment 8.04 Control 8.08	Treatment 8.46, 8.62, 8.57 Control 8.47	Treatment 7.9 Control 8
Jadad scale	Randomization 2 Blinding 2 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1	Randomization 1 Blinding 1 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1

	Rosenstock et al (30)	**NCT01064414 (31)**	**Lavelle Gonzalex et al (32)**	**Neal et al (33)**	**Stenlof et al (34)**	**NCT01106651 (35)**
Year of publication	2015 (24 weeks)	2013 (52 weeks)	2013 (26 weeks)	2014 (52 weeks)	2014 (26 weeks)	2014 (104 weeks)
Study design	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, open label extension	RCT, double-blinded
Intervention	-Saxagliptin+ metformin+placebo, -Dapagliflozin+ metformin+Placebo, -Saxagliptin, Dapagliflozin+ metformin	Canagliflozin 100, 300 mg	Canagliflozin 100, 300 mg	Canagliflozin 100, 300 mg	Canagliflozin 100, 300 mg	Canagliflozin 100, 300 mg + antihyperglycemic
Comparison		Placebo	Placebo/Sitagliptin, Sitagliptin 100 mg	Placebo	Placebo	Placebo + antihyperglycemic
Fracture	**Patella fracture** -Saxagliptin+ metformin+Placebo -Dapagliflozin+ metformin+Placebo -Saxagliptin+ Dapagliflozin+ metformin 1/176, 0/179, 0/179	**Fibular fracture** Canagliflozin 100 mg, 300 mg, placebo 0/90, 0/89, 1/90 **Tibial fracture** 0/90, 0/89, 1/90	**Cervical Fracture** 26 weeks Canagliflozin 100 mg, 300 mg, Sitagliptin, placebo 1/368, 0/367, 0/366, 0/183 Excluded week 52 given placebo was switched to Sitagliptin at week 26	**Fracture** Canagliflozin 100 mg, 300 mg, placebo 18/692, 8/690, 11/533	**Ankle fracture** Canagliflozin 100 mg, 300 mg, placebo 0/195, 0/197, 1/192	**Ankle fracture** 26week Canaglifozin 100 mg, 300 mg, placebo 1/241, 0/236, 0/237 104week Canagliflozin 100 mg, 300 mg, placebo 2/241, 0/236, 0/237 **Cervical fracture** 26week Canaglifozin 100 mg, 300 mg, placebo 0/241, 0/236, 1/237

						104 week Canagliflozin 100 mg, 300 mg, placebo 0/241, 0/236, 1/237 **Hand fracture** 26 week Canaglifozin 100 mg, 300 mg, placebo 0/241, 0/236, 0/237 104 week Canagliflozin 100 mg, 300 mg, placebo 0/241, 0/236, 1/237 **Hip fracture** 26 week Canaglifozin 100 mg, 300 mg, placebo 0/241, 0/236, 0/237 104 week Canagliflozin 100 mg, 300 mg, placebo 0/241, 1/236, 0/237
Primary outcome	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c
Major secondary	- Change in, BW, FPG, PPG	- Percentage of	- Percentage of patients with HbA1c	HbA1c <7.0%, BW, SBP, DBP, and	- Percentage of patients With	- Percentage of patients with HbA1c

outcome		patients with HbA1c <7% at - Change in FPG	<7% - Change in SBP, BW, TG, FPG, HDL	fasting plasma lipids and the ratio of LDL to HDL	HbA1c <7% - Change in FPG, 2h PPG, SBP, BW, TG	<7% - Change in BMD, SBP, BW, TG, body fat, FPG
Number of treatment group	176, 179, 179	90, 89	368, 367	692, 690	195, 197	241, 236
Number of control group	N.A.	90	183 (placebo/Sitagliptin) 366 (Sitagliptin)	690	192	237
Percentage of male in treatment and control group	Treatment 53.4, 49.7 47.5	Treatment 64.4, 53.9 Control 63.3	47.3, 45.0, 51.4 (placebo/Sitagliptin), 47 (Sitagliptin)	Treatment 67, 65 Control 66	Treatment 41.5, 45.2 Control 45.8	Treatment 51.4, 54.7 Control 60.3
Average age of treatment and control group (year)	Treatment 55, 54, 53	Treatment 69.5, 67.9, Control 68.2	55.5, 55.3, 55.3 (placebo/Sitagliptin), 55.5 (Sitagliptin)	Treatment 62, 63 Control 63	Treatment 55.1, 55.3 Control 55.7	Treatment 64.3, 64.4, Control 64.2
Baseline A1c	Treatment 9.03, 8.87, 8.92	N.A.	7.9, 7.9, 8.0 (placebo/Sitagliptin), 7.9 (Sitagliptin)	Treatment 8.3, 8.3, Control 8.3	Treatment 8.1, 8.0 Control 8.1	N.A.
Jadad scale	Randomization 2 Blinding 2 An account for all patient 1	Randomization 1 Blinding 1 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1

	NCT01106690 (36)	Inagaki et al (37)	NCT01106625 (38)	NCT01011868 (39)	Haring et al (40)	Barnett et al (41)
Year of publication	2013(26weeks)	2014 (24 weeks)	2013 (52 weeks)	2014 (78/82 weeks)	2013(24weeks)	2014(52weeks)
Study design	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded
Intervention	Canagliflozin 100, 300 mg	Canagliflozin 100, 200 mg	Canagliflozin 100, 300 mg	Empagliflozin 10, 25 mg	Empagliflozin 10, 25 mg add on to metformin plus SU	Empagliflozin 10,25 mg
Comparison	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Country where study was conducted	83 sites United States, Canada, Finland, France, Germany, Greece, India, Mexico, Spain, Thailand, United Kingdom	5 sites in Japan	76 sites United States, Australia, Belgium, France, Guatemala, Hungary, Israel, Mexico, Puerto Rico, Russian Federation, Spain, United Kingdom	99 sites United States, Denmark, France, Ireland, Korea, Portugal, United Kingdom	148 sites United States, Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey	127 sites United States, Canada, France, Hong Kong, India, Malaysia, Netherlands, Philippines, Poland, Portugal, Russian Federation, Slovakia, South Africa, Spain, United Kingdom
Fracture	**Periprosthetic Fracture** **26 weeks** Canagliflozin 100, 300 mg, Placebo 1/113, 0/114, 0/115 **Tibial Fracture** **26 weeks** 0/113, 0/114, 0/115 Exclude week 52 given placebo was switched to sitagliptin at week 26	**Forearm fracture** Canagliflozin 100, 200 mg, Placebo 0/90, 0/89, 1/93 **Spinal compression fracture** Canagliflozin 100, 200 mg, Placebo 0/90, 0/89, 1/93	**Ankle fracture** **Week 26** Canagliflozin 100, 300 mg, placebo 0/157, 0/156, 0/156 **Week 52** 0/157, 0/156, 1/156	**Radial fracture** Empagliflozin 10, 25 mg, placebo 0/169, 0/155, 1/170 **Wrist fracture** 0/169, 1/155, 0/170	**Comminuted fracture** -metformin+placebo 0/206 -metformin +empagliflozin 10 mg 1/217 -metformin +empagliflozin 25 mg 0/214 -metformin +empagliflozin 25 mg open label	**Clavicle fracture** Empagliflozin 10, 25 mg, placebo 0/98, 0/321, 1/319 **Humeral fracture** 0/98, 0/321, 2/319 **Pelvic fracture** 0/98, 1/321, 0/319 **Rib fracture** 0/98, 1/321, 0/319 **Spinal fracture** 0/98, 1/321, 0/319

					0/69 -metformin +SU+placebo 0/225 metformin +SU+empagliflozin 10 mg 0/224 metformin +SU+empagliflozin 25 mg 0/217 metformin +SU+empagliflozin 25 mg open label 0/101 **Facial bone fracture** 0/206 1/217 0/214 0/69 0/225 0/224 0/217 0/101 **Lumbar vertebral fracture** 0/206 0/217 0/214 0/69	

					0/225 0/224 0/217 1/101 **Femoral neck fracture** 0/206 0/217 0/214 0/69 0/225 1/224 0/217 0/101	
Primary outcome	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c
Major secondary outcome	- %A1C<7%, BW, SBP, TG, HDL - Change in FPG, HOMA-2%, - %change in BW	- Change in BW, FBG, BP, PPG, adverse event, hypoglycemic event, labs, EKG, vitals	- Change in, BW, FPG, SBP, TG, HDL % patient with A1C<7	- HbA1c Lowering by at least 0.5 - Change in FPG, basal insulin dose/day, BW, HbA1c - HbA1c <7.0%	- BW change, mean daily plasma glucose change	N.A.
Number of treatment group	113, 114	90, 89	157, 156	169, 155	217, 213, 69 225, 516, 101	98, 321
Number of control group	115	93	156	170	Metformin+placebo 207 metformin+SU+ placebo 225	319
Percentage of	Treatment 68.1, 55.3	Treatment 65.6, 82.0	Treatment 48.4, 55.8	Treatment 55.0, 60 Control 52.9	Treatment 57.6, 56.3, 59.4	Treatment 61.2, 58.9 Control 56.7

male in treatment and control group	Control 66.1	Control 66.7	Control 48.7		Placebo 56.0 Treatment 50.2, 52.8, 53.5, Placebo 49.8	
Average age of treatment and control group (year)	Treatment 56.7, 57 Control 58.3	Treatment 58.4, 57.3 Control 58.2	Treatment 57.3, 56 Control 56.7	Treatment 58.6, 59.9 Control 58.1	Treatment 55.5, 55.6, 49.8 Placebo 56.0 Treatment 57, 57.4, 53.4 Placebo 56.9	Treatment 63.2, 63.9 Control 64.1
Baseline A1c	N.A.	Treatment 8.05, 8.09 Control N.A.	N.A.	N.A.	Treatment 8.07, 8.1, 11.18 Control 8.15	Treatment 8.02, 7.96 Control 8.09
Jadad scale	Randomization 1 Blinding 1 An account for all patient 1	Randomization 1 Blinding 1 An account for all patient 1	Randomization 1 Blinding 1 An account for all patient 1	Randomization 1 Blinding 1 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1	Randomization 2 Blinding 2 An account for all patient 1

	Roden et al (42)	**Kovacs et al (43)**	**Rosenstock et al (44)**
Year of publication	2013(24weeks)	2015(24weeks)	2014 (52 weeks)
Study design	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded
Intervention	Empagliflozin 10, 25, 25 mg open label extension	Empagliflozin 10, 25 mg	Empagliflozin 10, 25 mg
Comparison	Placebo, sitagliptin 100 mg	Placebo	Placebo
Country where study was conducted	124 sites United States, Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland	68 sites United States, Canada, Greece, India, Philippines, Thailand, Ukraine	103 sites United States, Belgium, Bulgaria, Colombia, Czech Republic, Finland, France, Germany, Guatemala, Mexico, Peru, Russian Federation, Spain, Ukraine
Fracture	**Tibial fracture** Empagliflozin 10 mg, 25 mg, Sitagliptin 100 mg, Empagliflozin 25 open label, Placebo 0/224, 1/223, 0/223, 0/87, 0/229	**Hand fracture** Empagliflozin 10 mg, 25 mg, Placebo 0/165, 0/168, 1/165 **Humeral fracture** 0/165, 0/168, 1/165 **Traumatic fracture** 0/165, 0/168, 1/165	**Humeral fracture** Empagliflozin 10 mg, 25 mg, Placebo 0/186, 0/189, 1/188
Primary outcome	Change in DBP, SBP, BW	Change in, BW, FPG	Change insulin dose, BW, HA1c
Number of treatment group	224, 224, 223, 87	165, 168	186, 189
Number of control group	228	165	188
Percentage of male in treatment and control group	Treatment 63.4, 64.7, 63.2, 73.6, Control 53.9	Treatment 50.3, 50.6, Control 44.2	Treatment 52.2, 44.4, Control 39.9
Average age of treatment and control group (year)	Treatment 56.2, 53.8, 55.1, 50.2, Control 54.9	Treatment 54.7, 54.2 Control 54.6	Treatment 56.7, 58.0 Control 55.3
Baseline HbA1c	Treatment 7.87, 7.86, 7.85, 11.5 Control 7.91	Treatment 8.07, 8.06 Control 8.16	Treatment 8.39, 8.29 Control 8.33
Jadad scale	Randomization 2, Blinding 2, An account for all patient 1	Randomization 2, Blinding 2, An account for all patient 1	Randomization 2, Blinding 2, An account for all patient 1

Abbreviations

RCT indicates randomized controlled trial; HbA1c, Hemoglobin A1c; FPG, fasting plasma glucose; PPG, postprandial glucose; T2DM, type 2 diabetes mellitus; BW, body weight;

BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; SU, Sulfonylurea; N.A., not available;