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Original article

Risk of bone fracture associated with sodium–glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials

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ABSTRACT

Aim. – To evaluate the association between sodium–glucose cotransporter-2 (SGLT2) inhibitors and risk of bone fractures in patients with type 2 diabetes mellitus (T2DM).
Methods. – A systematic literature search conducted of PubMed, Embase, the Cochrane Library and Web of Science from inception up to 31 August 2018 identified all eligible randomized controlled trials (RCTs). The following data were extracted from each study: first author; year of publication; sample size; patient characteristics; study design; intervention drug; control drug; follow-up durations; and incident bone-fracture events. A meta-analysis was performed using Review Manager 5.3 software to calculate odds ratios (ORs) and 95% confidence intervals (CI) for dichotomous variables.
Results. – A total of 30 studies involving 23,372 patients with T2DM were included in our analysis. There were 387 incident bone-fracture cases (245 in the SGLT2 inhibitor group, 142 in the control group). Compared with patients who received placebo, those receiving SGLT2 inhibitor treatment had a pooled OR of bone fracture of 0.86 (95% CI: 0.70–1.06). Also, there was no evidence that individual SGLT2 inhibitors across different doses were associated with any increased risk of bone fracture. After stratification by follow-up duration, an SGLT2 inhibitor treatment period of $\leq$ 52 weeks appeared to have beneficial effects against bone fracture; however, when the treatment period exceeded 52 weeks, these beneficial effects for preventing bone fracture disappeared.
Conclusion. – Our meta-analysis has indicated that SGLT2 inhibitors do not increase risk of bone fracture compared with placebo in patients with T2DM. However, these findings now need to be confirmed in well-designed RCT studies.

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Introduction

Bone fracture has recently been considered one of the complications of diabetes [1]. There is growing evidence to suggest that type 2 diabetes mellitus (T2DM) is associated with an increased risk of fragility fractures regardless of bone mineral density (BMD) [2–4]. Although the underlying mechanisms contributing to the decreased bone strength and bone quality in patients with T2DM are not yet fully understood, chronic hyperglycaemia has resulted in accumulation of advanced glycation end-products (AGEs), which downregulate osteocalcin gene expression and inhibit calcium uptake, both thought to be involved in the pathogenesis of bone fractures [5–7]. Moreover, T2DM has detrimental effects on bone-fracture healing, including delayed healing, non-union and post-surgical clinical complications (such as risk of infection, amputation), and even increased mortality [8,9]. Also, there are many different classes of antidiabetic drugs currently available for the treatment of T2DM, some of which might influence bone metabolism either directly or indirectly, thereby making it critically important to use antidiabetic drugs that do not increase the risk of bone fracture [10].

Sodium–glucose cotransporter-2 (SGLT2) inhibitors comprise a relatively new class of glucose-lowering medications that reduce

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plasma glucose concentrations by inhibiting proximal tubular reabsorption of glucose in the kidney while increasing its excretion *via* urine [11]. Given their unique insulin-independent mode of action and favourable efficacy and adverse-event profile, as well as their marked benefits to cardiovascular–renal outcomes in moderate-to-high risk patients with T2DM, the role of this drug class in T2DM is promising [12].

However, the osmotic diuresis effect of SGLT2 inhibitors could lead to volume depletion and electrolyte imbalances, while the possible changes in calcium and phosphate could also adversely affect bone health [13]. In fact, it has been reported that the use of SGLT2 inhibitors is associated with a decline in BMD and an increased risk of fractures, although such findings have not been consistent across studies [14,15]. Therefore, the present meta-analysis was conducted to evaluate fracture risk in patients with T2DM treated with SGLT2 inhibitors compared with placebo, using data from all available relevant clinical trials.

Methods

Search strategies

A search was made for randomized controlled trials (RCTs) of SGLT2 inhibitors in PubMed, Embase, the Cochrane Library and Web of Science databases from inception up to 31 August 2018 to identify relevant studies comparing the effects of SGLT2 inhibitors with placebo in patients with T2DM. The following terms were used: 'sodium–glucose cotransporter-2 inhibitors'; 'SGLT2 inhibitors'; 'dapagliflozin'; 'empagliflozin'; and 'canagliflozin'. These terms were adjusted to comply with the rules of each database.

Selection of studies

Publications were included in our meta-analysis if they met the following criteria:

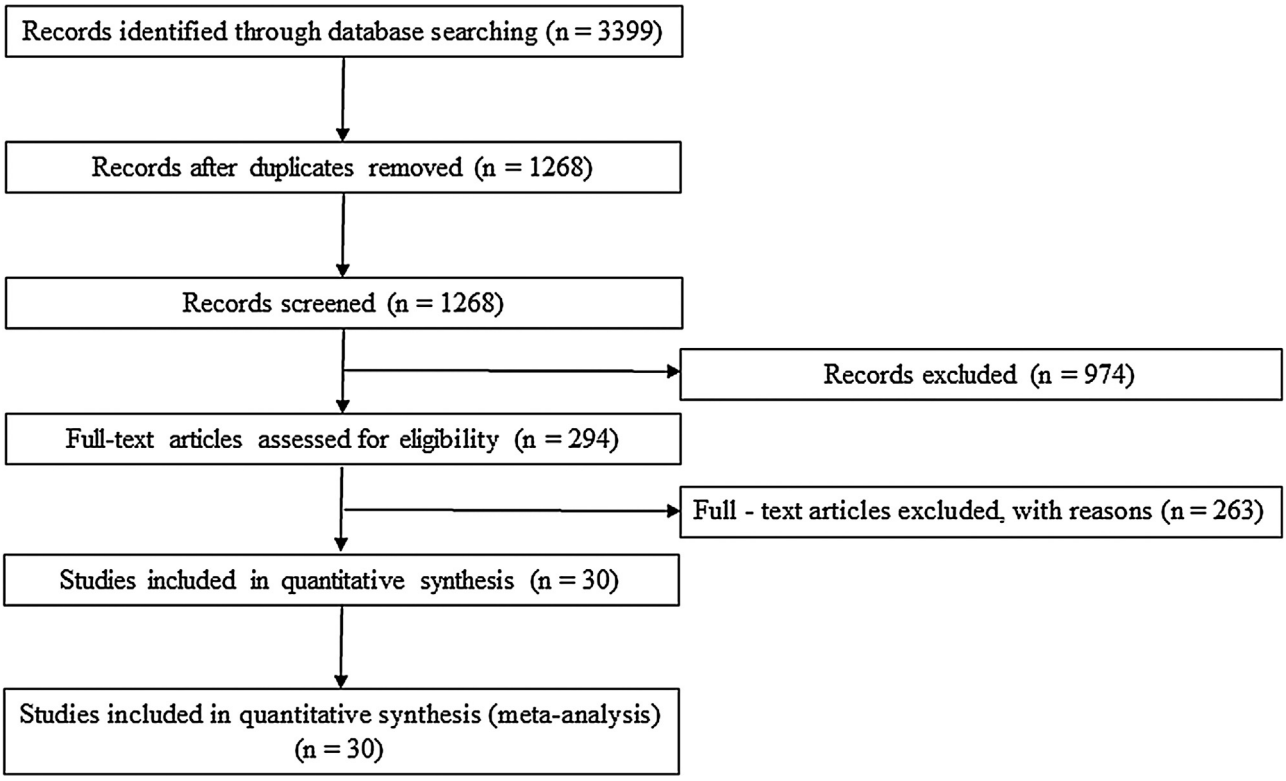

Fig. 1. Flow diagram of study selection for analysis.

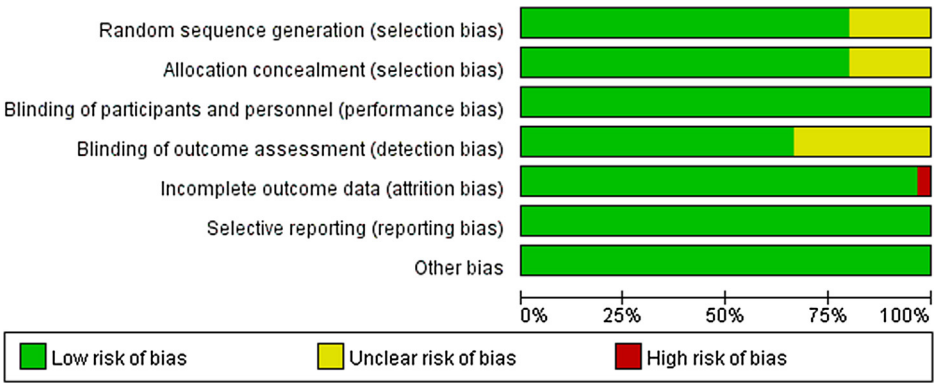

Fig. 2. Risk of bias for each study, as evaluated by the Cochrane Collaboration instrument.

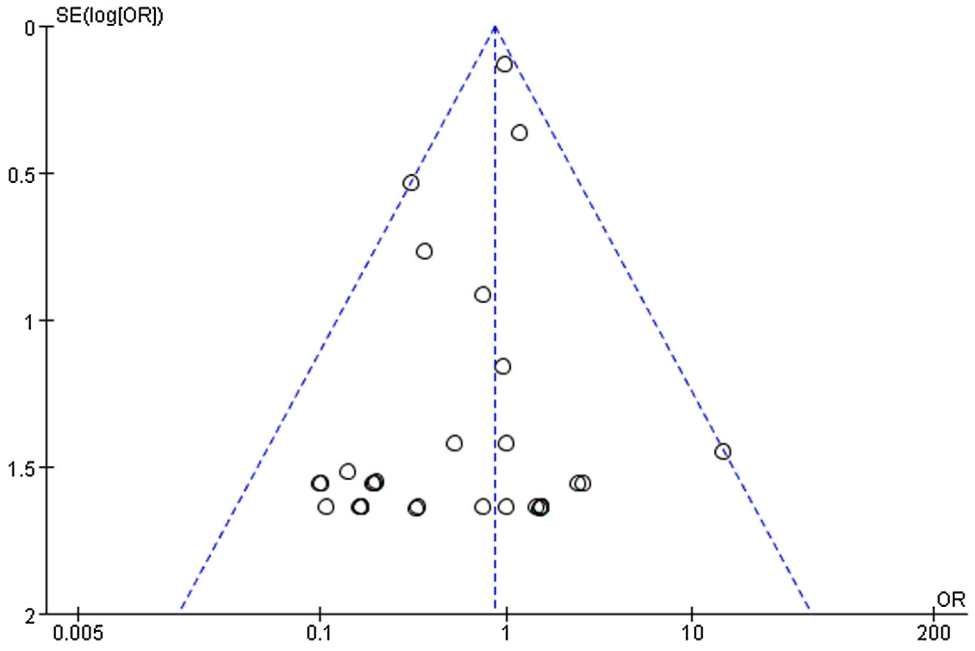

Fig. 3. Funnel plot of sodium–glucose cotransporter-2 (SGLT2) inhibitors *vs* placebo for risk of bone fracture.

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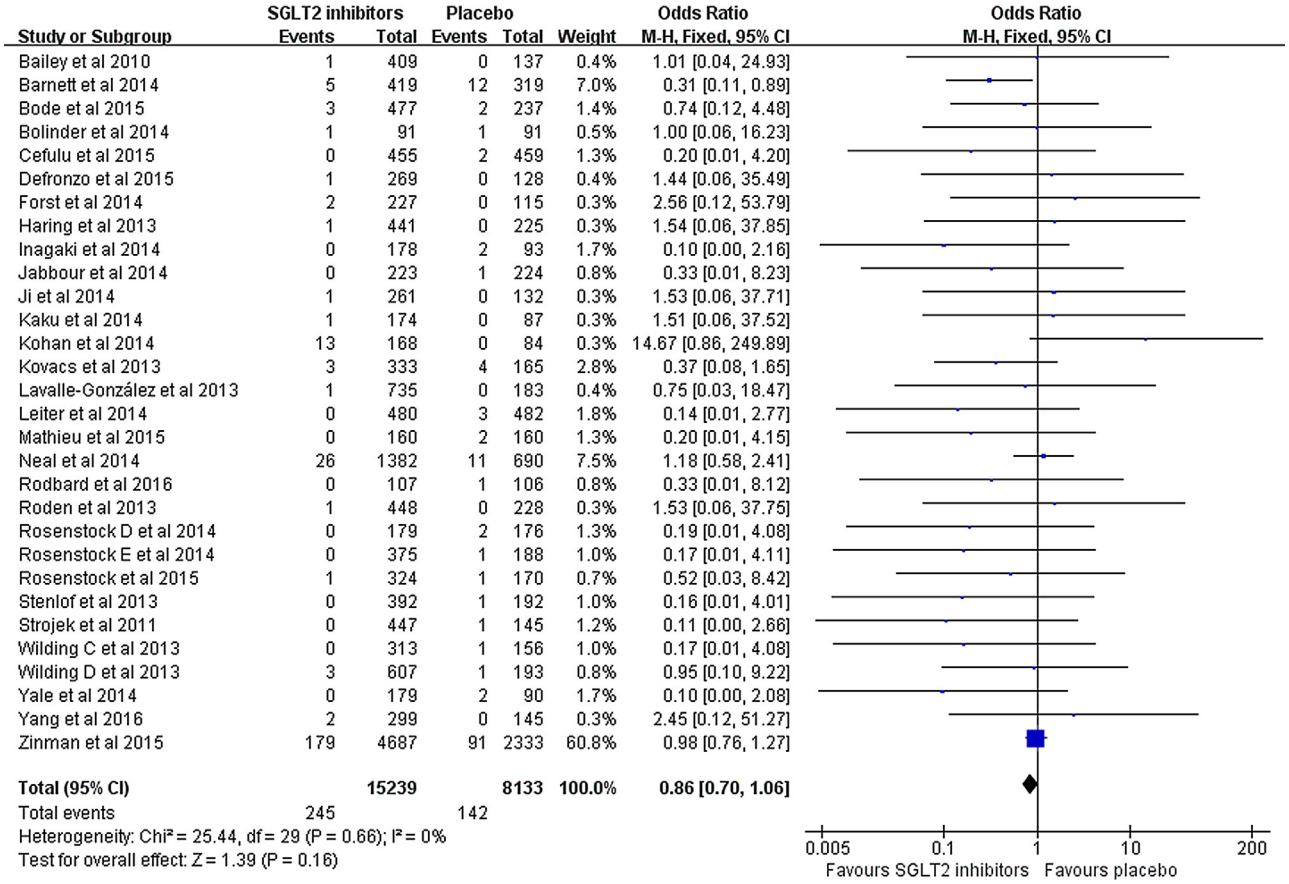

Study or Subgroup	SGLT2 inhibitors Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bailey et al 2010	1	409	0	137	0.4%	1.01 [0.04, 24.93]
Barnett et al 2014	5	419	12	319	7.0%	0.31 [0.11, 0.89]
Bode et al 2015	3	477	2	237	1.4%	0.74 [0.12, 4.48]
Bolinder et al 2014	1	91	1	91	0.5%	1.00 [0.06, 16.23]
Cefulu et al 2015	0	455	2	459	1.3%	0.20 [0.01, 4.20]
Defronzo et al 2015	1	269	0	128	0.4%	1.44 [0.06, 35.49]
Forst et al 2014	2	227	0	115	0.3%	2.56 [0.12, 53.79]
Haring et al 2013	1	441	0	225	0.3%	1.54 [0.06, 37.85]
Inagaki et al 2014	0	178	2	93	1.7%	0.10 [0.00, 2.16]
Jabbour et al 2014	0	223	1	224	0.8%	0.33 [0.01, 8.23]
Ji et al 2014	1	261	0	132	0.3%	1.53 [0.06, 37.71]
Kaku et al 2014	1	174	0	87	0.3%	1.51 [0.06, 37.52]
Kohan et al 2014	13	168	0	84	0.3%	14.67 [0.86, 249.89]
Kovacs et al 2013	3	333	4	165	2.8%	0.37 [0.08, 1.65]
Lavalle-González et al 2013	1	735	0	183	0.4%	0.75 [0.03, 18.47]
Leiter et al 2014	0	480	3	482	1.8%	0.14 [0.01, 2.77]
Mathieu et al 2015	0	160	2	160	1.3%	0.20 [0.01, 4.15]
Neal et al 2014	26	1382	11	690	7.5%	1.18 [0.58, 2.41]
Rodbard et al 2016	0	107	1	106	0.8%	0.33 [0.01, 8.12]
Roden et al 2013	1	448	0	228	0.3%	1.53 [0.06, 37.75]
Rosenstock D et al 2014	0	179	2	176	1.3%	0.19 [0.01, 4.08]
Rosenstock E et al 2014	0	375	1	188	1.0%	0.17 [0.01, 4.11]
Rosenstock et al 2015	1	324	1	170	0.7%	0.52 [0.03, 8.42]
Stenlof et al 2013	0	392	1	192	1.0%	0.16 [0.01, 4.01]
Strojek et al 2011	0	447	1	145	1.2%	0.11 [0.00, 2.66]
Wilding C et al 2013	0	313	1	156	1.0%	0.17 [0.01, 4.08]
Wilding D et al 2013	3	607	1	193	0.8%	0.95 [0.10, 9.22]
Yale et al 2014	0	179	2	90	1.7%	0.10 [0.00, 2.08]
Yang et al 2016	2	299	0	145	0.3%	2.45 [0.12, 51.27]
Zinman et al 2015	179	4687	91	2333	60.8%	0.98 [0.76, 1.27]
Total (95% CI)		**15239**		**8133**	**100.0%**	**0.86 [0.70, 1.06]**
Total events	245		142			

Heterogeneity: Chi² = 25.44, df = 29 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)

Fig. 4. Forest plot of SGLT2 inhibitors *vs* placebo for risk of bone fracture.

they were prospective, randomized and controlled clinical studies;
- they included adult patients diagnosed with T2DM;
- they were studies comparing SGLT2 inhibitors with placebo in T2DM;
- incidences of bone fracture were reported in both groups;
- duration of follow-up was $\geq$ 24 weeks; and;
- they were original studies published in the English language.

Studies were excluded if they did not provide original data, or included only type 1 diabetes mellitus (T1DM) patients or special populations, such as children or pregnant women.

Study quality assessment and risk of bias

Two independent reviewers evaluated the eligibility of each study and extracted the required data. The risk of bias in each study was also evaluated according to the recommended Cochrane Collaboration risk-of-bias tool, based on the following factors: randomization; allocation; blinding; incomplete outcome data; selective outcome reporting; and other biases. Each study was then assessed as having 'low risk of bias', 'unclear risk of bias' or 'high risk of bias'.

Data extraction

Two investigators independently extracted the following data after reviewing the full texts: first author; year of publication; sample size; patient characteristics; study design; intervention drug; control drug; follow-up durations; and incident bone-fracture events. These extracted data were further checked by another investigator, with any discrepancies resolved by discussion and consensus. If bone-fracture events were not reported in the published paper, then these data were instead extracted from

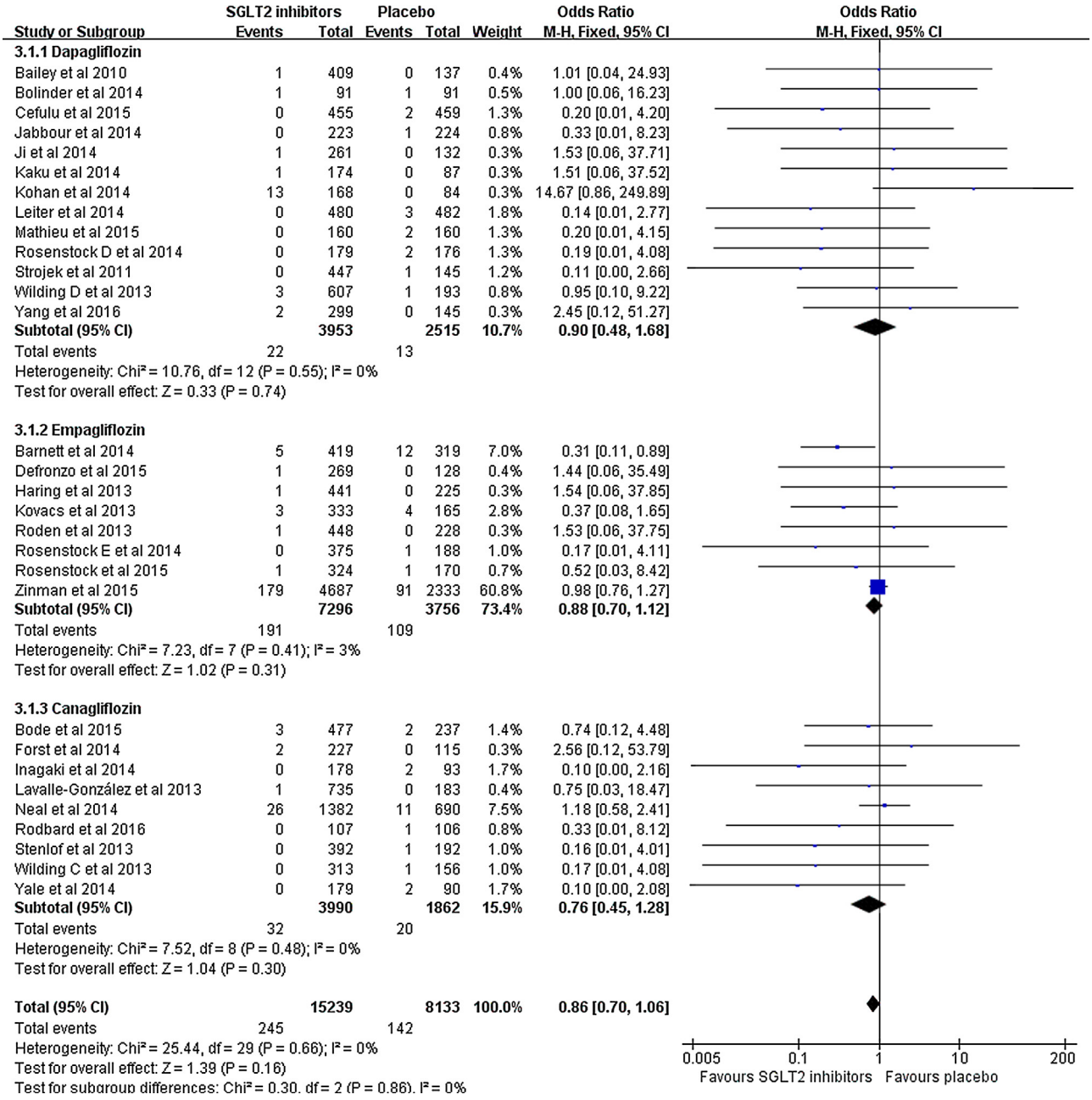

Fig. 5. Forest plot of different SGLT2 inhibitors vs. placebo for bone fracture.

the 'Serious adverse events' section of ClinicalTrials.gov; if bone-fracture events were not reported on ClinicalTrials.gov, then the incidence of such events was assumed to be zero.

For dichotomous data, the number of bone fracture events was categorized into high-dose, moderate-dose or low-dose subgroups for each specific SGLT2 inhibitor intervention. For dapagliflozin, 2.5 mg was considered the low dose, 5 mg was the moderate dose and 10 mg was the high dose; canagliflozin at 100 mg and 300 mg were considered the low-dose and high-dose subgroups, respectively, while empagliflozin 10 mg and 25 mg comprised the low-dose and high-dose subgroups, respectively. All bone-fracture events were then stratified by duration of follow-up into the $\leq$ 52-week group and the $>$ 52-week group.

Data synthesis and analysis

All statistical analyses were performed by Review Manager (RevMan) 5.3 software (The Cochrane Collaboration, London, England, UK). For dichotomous variables, odds ratios (ORs) and 95% confidence intervals (CI) were calculated to evaluate fracture risk with SGLT2 inhibitors. In addition, to assess whether this fracture risk could be modified by clinical variables, subgroup analyses were performed on the basis of each individual SGLT2 inhibitor and its most commonly used dosing regimens and follow-up durations. Heterogeneity across studies was assessed by chi-squared test and I^2 statistics, with I^2 values of 25%, 50% and 75% considered to have low, moderate and high heterogeneity, respectively. A fixed-effects model was used if no significant evidence of statistical heterogeneity or clinical diversity was found ($P \geq 0.10$, $I^2 \leq 50\%$); otherwise, if there was evidence of statistical heterogeneity or clinical diversity ($P < 0.10$, $I^2 > 50\%$), a random-effects model was used to account for interstudy heterogeneity. Publication bias was evaluated by visual inspection for funnel plot asymmetry.

Results

Our search methodology and literature review process are outlined in Fig. 1. The literature review process yielded 3399 potentially eligible articles, but after the exclusion of 3105 irrelevant articles based on their titles and abstracts, 294 articles were retained for full-text assessment. Of these 294 papers, 53 were excluded for being non-randomized controlled trials, 85 were excluded for having a follow-up duration $<$ 24 weeks, and 126 were excluded for not reporting fracture events. In the end, 30 articles involving a total of 23,372 patients with T2DM were included in our meta-analysis, comprising 15,239 patients who

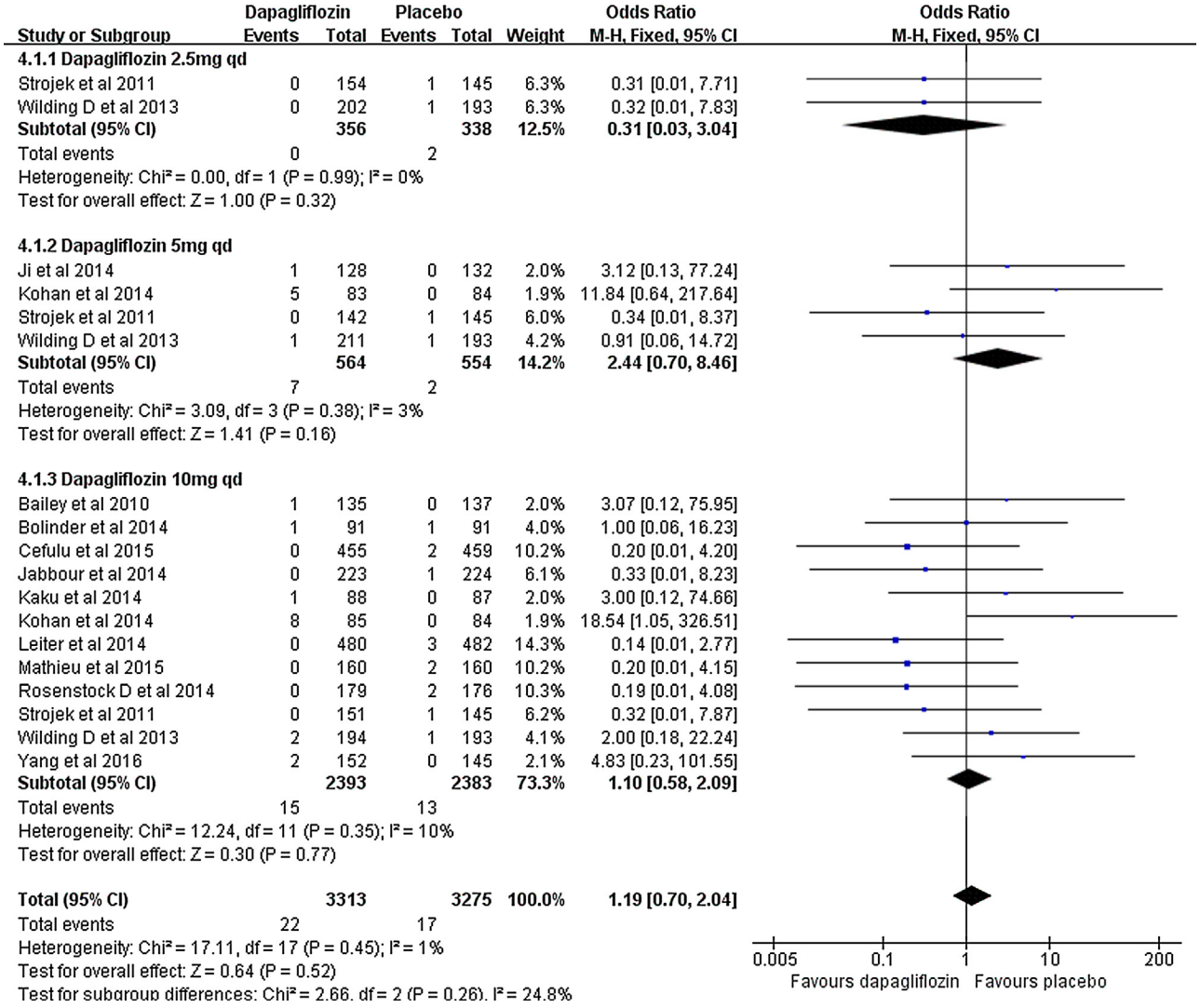

Fig. 6. Forest plot of the effect of different dose regimens of dapagliflozin on bone fracture.

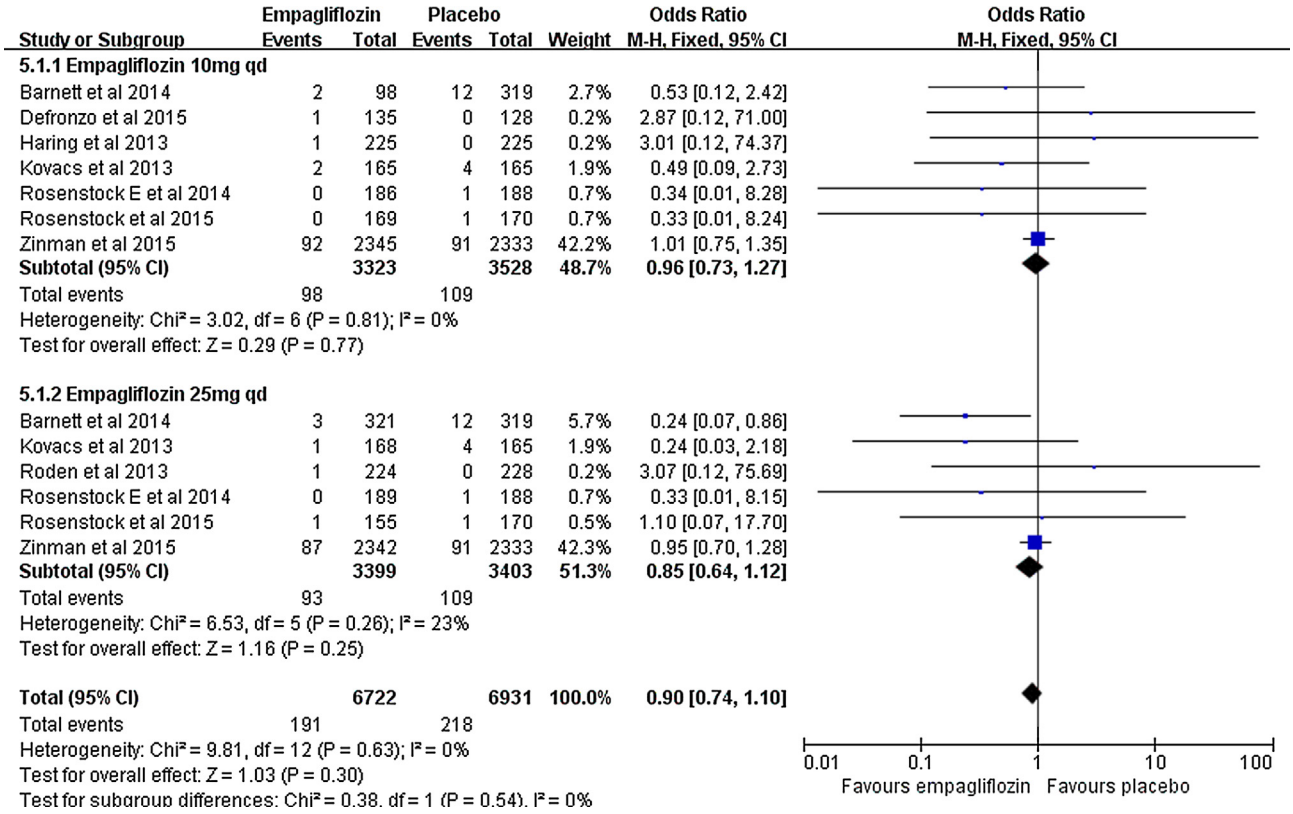

Fig. 7. Forest plot of the effect of different dose regimens of empagliflozin on bone fracture.

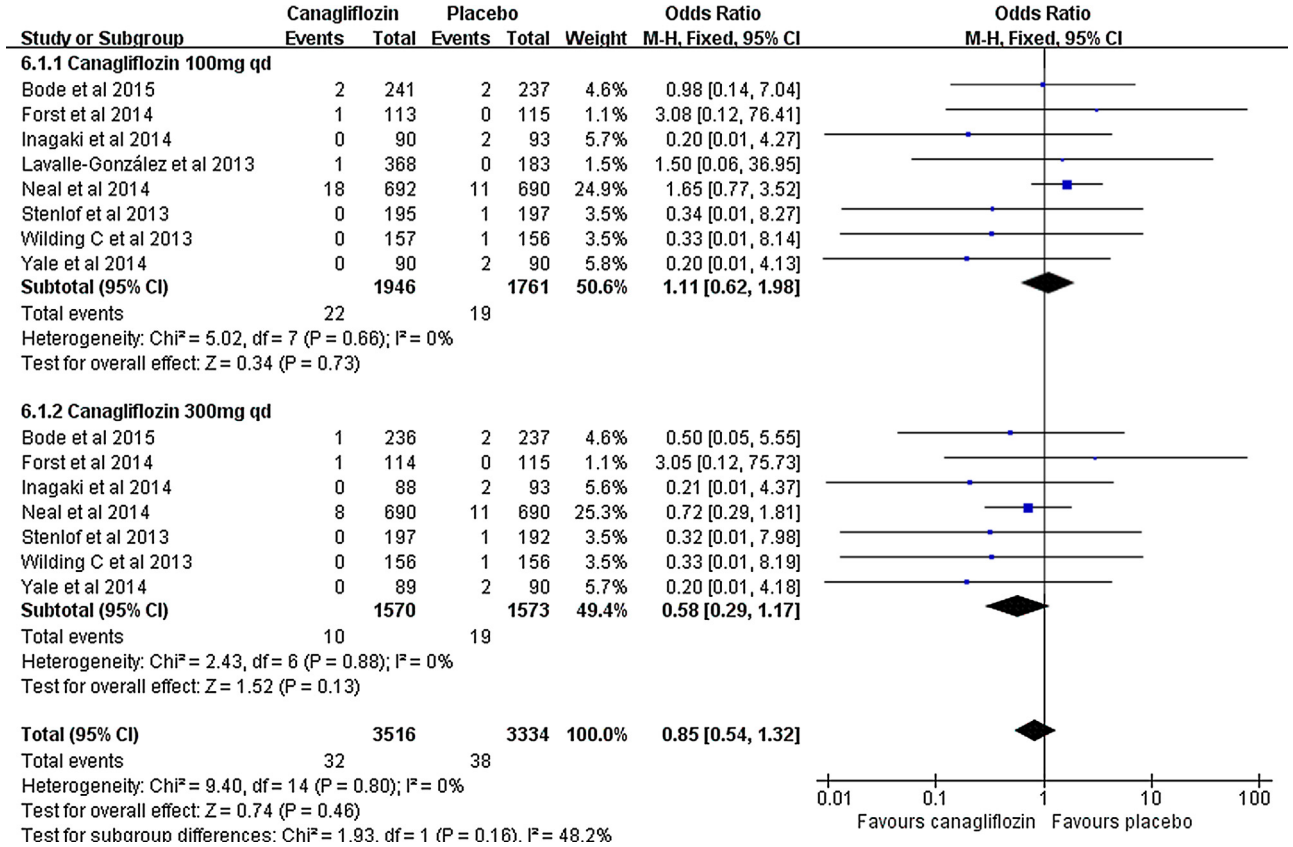

Fig. 8. Forest plot of the effect of different dose regimens of canagliflozin on bone fracture.

received SGLT2 inhibitors and 8133 who received a placebo. The characteristics of these included studies are detailed in Table I. Of the 30 included studies, 22 (73.3%) had a low risk of bias across all domains, one (3.3%) had a high risk of bias for attrition, and six (20%) had unclear risks of biases for allocation concealment and/or detection (Fig. 2). A funnel plot of SGLT2 inhibitors *vs* placebo for fracture risk (Fig. 3) shows symmetry with no evidence of publication bias.

Overall, bone fracture was seen in 387 patients (245 patients in the SGLT2 inhibitor group, 142 in the control group). There was no significant difference in risk of bone fracture between SGLT2 inhibitors and placebo: the pooled OR for bone fracture with the former was 0.86 (95% CI: 0.70–1.06) compared with placebo, and there was no significant heterogeneity between studies (I^2 = 0%, P = 0.66; Fig. 4). Similarly, the pooled ORs for bone fracture with dapagliflozin, empagliflozin and canagliflozin were 0.90 (0.48–1.68), 0.88 (0.70–1.12) and 0.76 (0.45–1.28), while their statistical heterogeneity was negligible with I^2 values of 0%, 3% and 0%, respectively (Fig. 5).

When assessing the effects of different doses of SGLT2 inhibitors on risk of fractures, the pooled ORs for dapagliflozin 2.5 mg, 5 mg and 10 mg were 0.31 (0.03–3.04), 2.44 (0.70–8.46) and 1.10 (0.58–2.09), respectively (Fig. 6); the pooled ORs for empagliflozin 10 mg and 25 mg were 0.96 (0.73–1.27) and 0.85 (0.64–1.12), respectively (Fig. 7); and the pooled ORs for canagliflozin 100 mg and 300 mg were 1.11 (0.62–1.98) and 0.58 (0.29–1.17), respectively (Fig. 8). In addition, in a subgroup analysis where studies were divided according to follow-up duration, the pooled OR for bone fracture for follow-ups $\leq$ 52 weeks was 0.55 (0.37–0.81) vs. 1.04 (0.81–1.33) for follow-ups $>$ 52 weeks (Fig. 9).

Discussion

In the present meta-analysis, no significantly increased risk of bone fracture was observed with SGLT2 inhibitors whether evaluated singly or as a class. There was also no evidence that different doses of the SGLT2 inhibitors dapagliflozin, empagliflozin and canagliflozin were associated with any greater risk of bone fracture compared with placebo. When stratified by follow-up duration, an SGLT2 inhibitor treatment period of $\leq$ 52 weeks appeared to have beneficial effects for preventing bone fracture

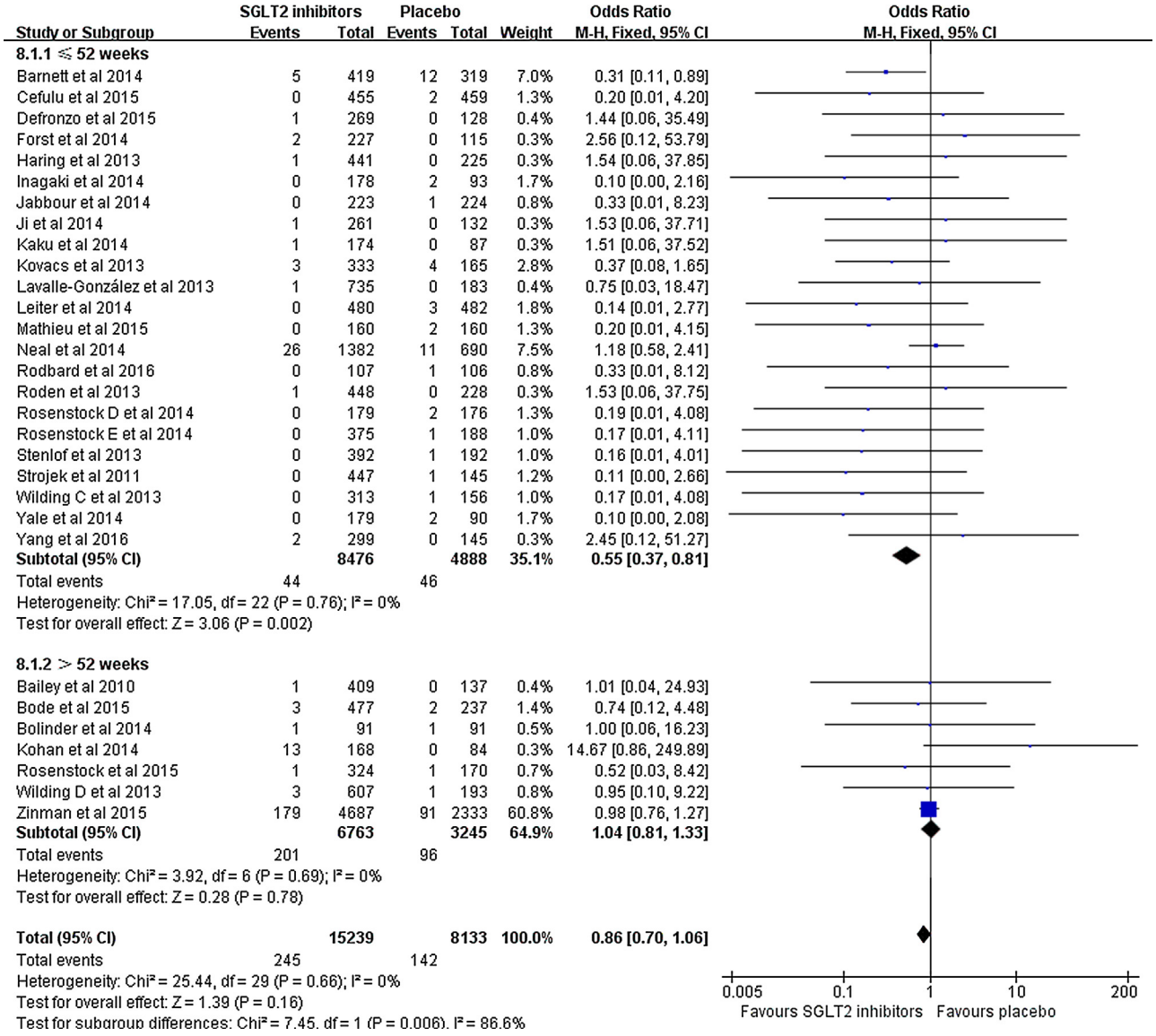

Fig. 9. Forest plot of the effects of SGLT2 inhibitor treatment duration on risk of bone fracture.

Table 1
Characteristics of the randomized controlled studies (RCTs) included in the meta-analysis.

Study	Year of publication	Study design	Study duration	Intervention	Control	Patients (*n*)		Age (years)		HbA_{1c} (%)		Cases of fracture (n)	
						Intervention	Controls	Intervention	Controls	Intervention	Controls	Intervention	Controls
Bailey et al. [1]	2010	RCT, db	102 weeks	Dapa 2.5 mg, 5 mg, 10 mg	Placebo	137, 137, 135	137	55.0 ± 9.3, 54.2 ± 9.4, 52.7 ± 9.9	53.7 ± 10.3	7.99 ± 0.90, 8.17 ± 0.96, 7.92 ± 0.82	8.11 ± 0.96	0, 0, 1	0
Barnett et al. [2]	2014	RCT, db	52 weeks	Empa 10 mg, 25 mg	Placebo	98, 321	319	63.2 ± 8.5, 63.9 ± 9.0	64.1 ± 8.7	8.02 ± 0.84, 7.96 ± 0.73	8.09 ± 0.80	2, 3	12
Bode et al. [3]	2015	RCT, db	104 weeks	Cana 100 mg, 300 mg	Placebo	241, 236	237	64.3 ± 6.5, 63.4 ± 6.0	63.2 ± 6.2	7.8 ± 0.8, 7.8 ± 0.8	7.8 ± 0.8	2, 1	2
Bolinder et al. [4]	2014	RCT, db	102 weeks	Dapa 10 mg	Placebo	91	91	60.6 ± 8.16	60.8 ± 6.82	7.19 ± 0.44	7.16 ± 0.53	1	1
Cefulu et al. [5]	2015	RCT, db	52 weeks	Dapa 10 mg	Placebo	455	459	62.8 ± 7.0	63.0 ± 7.7	8.18 ± 0.84	8.08 ± 0.80	0	2
Defronzo et al. [6]	2015	RCT, db	52 weeks	Empa 10 mg, 25 mg	Placebo	135, 134	128	56.2 ± 10.3, 57.1 ± 10.2	56.2 ± 10.0	7.95 ± 0.80, 7.90 ± 0.79	8.02 ± 0.90	1, 0	0
Forst et al. [7]	2014	RCT, db	52 weeks	Cana 100 mg, 300 mg	Placebo	113, 114	115	56.7 ± 10.4, 57.0 ± 10.2	58.3 ± 9.6	8.0 ± 0.9, 7.9 ± 0.9	8.0 ± 1.0	1, 1	0
Haring et al. [8]	2013	RCT, db	24 weeks	Empa 10 mg, 25 mg	Placebo	225, 216	225	57.0 ± 9.2, 57.4 ± 9.3	56.9 ± 9.2	8.07 ± 0.81, 8.10 ± 0.83	8.15 ± 0.83	1, 0	0
Inagaki et al. [9]	2014	RCT, db	24 weeks	Cana 100 mg, 300 mg	Placebo	90, 88	93	58.4 ± 10.4, 57.4 ± 11.1	58.2 ± 11.0	7.98 ± 0.73, 8.04 ± 0.77	8.04 ± 0.70	0, 0	2
Jabbour et al. [10]	2014	RCT, db	24 weeks	Dapa 10 mg	Placebo	223	224	54.8 ± 10.4	55.0 ± 10.2	7.90 ± 0.81	7.97 ± 0.78	0	1
Ji et al. [11]	2014	RCT, db	24 weeks	Dapa 5 mg, 10 mg	Placebo	128, 133	132	53.0 ± 11.07, 51.2 ± 9.89	49.9 ± 10.87	8.14 ± 0.74, 8.28 ± 0.95	8.35 ± 0.95	1, 0	0
Kaku et al. [12]	2014	RCT, db	24 weeks	Dapa 5 mg, 10 mg	Placebo	86, 88	87	58.6 ± 10.4, 57.5 ± 9.3	60.4 ± 9.7	7.50 ± 0.72, 7.46 ± 0.61	7.50 ± 0.63	0, 1	0
Kohan et al. [13]	2014	RCT, db	104 weeks	Dapa 5 mg, 10 mg	Placebo	83, 85	84	66 ± 8.9, 68 ± 7.7	67 ± 8.6	8.30 ± 1.04, 8.23 ± 0.98	8.53 ± 1.28	5, 8	0
Kovacs et al. [14]	2013	RCT, db	24 weeks	Empa 10 mg, 25 mg	Placebo	165, 168	165	54.7 ± 9.9, 54.2 ± 8.9	54.6 ± 10.5	8.1 ± 0.89, 8.1 ± 0.82	8.2 ± 0.92	2, 1	4
Lavalle- González et al. [15]	2013	RCT, db	52 weeks	Cana 100 mg, 300 mg	Placebo	368, 367	183	55.5 ± 9.4, 55.3 ± 9.2	55.3 ± 9.8	7.9 ± 0.9, 7.9 ± 0.9	8.0 ± 0.9	1, 0	0
Leiter et al. [16]	2014	RCT, db	52 weeks	Dapa 10 mg	Placebo	480	482	63.9 ± 7.6	63.6 ± 7.0	8.0 ± 0.8	8.1 ± 0.8	0	3
Mathieu et al. [17]	2015	RCT, db	52 weeks	Dapag 10 mg	Placebo	160	160	55.2 ± 8.6	55.0 ± 9.6	8.24 ± 0.96	8.17 ± 0.98	0	2
Neal et al. [18]	2014	RCT, db	52 weeks	Cana 100 mg, 300 mg	Placebo	692, 690	690	62.0 (32–83), 63.0 (37–85)	63.0 (38–83)	8.3 ± 0.9, 8.3 ± 0.9	8.3 ± 0.9	18, 8	11
Rodbard et al. [19]	2016	RCT, db	26 weeks	Cana	Placebo	107	106	57.4 ± 9.3	57.5 ± 10.1	8.5 ± 0.9	8.4 ± 0.8	0	1
Roden et al. [20]	2013	RCT, db	24 weeks	Empa 10 mg, 25 mg	Placebo	224, 224	228	56.2 ± 11.6, 53.8 ± 11.6	54.9 ± 10.9	7.87 ± 0.88, 7.86 ± 0.85	7.91 ± 0.78	0, 1	0
Rosenstock et al. [21]	2014	RCT, db	24 weeks	Dapa 10 mg	Placebo	179	176	53 ± 10	55 ± 10	8.92 ± 1.18	9.03 ± 1.05	0	2
Rosenstock et al. [22]	2014	RCT, db	52 weeks	Empa10 mg, 25 mg	Placebo	186, 189	188	56.7 ± 8.7, 58.0 ± 9.4	55.3 ± 10.1	8.39 ± 0.05, 8.29 ± 0.05	8.33 ± 0.05	0, 0	1
Rosenstock et al. [23]	2015	RCT, db	78 weeks	Empa 10 mg, 25 mg	Placebo	169, 155	170	58.6 ± 9.8, 59.9 ± 10.5	58.1 ± 9.4	8.3 ± 0.1, 8.3 ± 0.1	8.1 ± 0.1	0, 1	1
Stenlof et al. [24]	2013	RCT, db	52 weeks	Cana 100 mg, 300 mg	Placebo	195, 197	192	55.1 ± 10.8, 55.3 ± 10.2	55.7 ± 10.9	8.1 ± 1.0, 8.0 ± 1.0	8.0 ± 1.0	0, 0	1
Strojek et al. [25]	2011	RCT, db	24 weeks	Dapa 2.5 mg, 5 mg, 10 mg	Placebo	154, 142, 151	145	59.9 ± 10.1, 60.2 ± 9.7, 58.9 ± 8.3	60.3 ± 10.2	8.11 ± 0.75, 8.12 ± 0.78, 8.07 ± 0.79	8.15 ± 0.74	0, 0, 0	1
Wilding et al. [26]	2013	RCT, db	52 weeks	Cana 100 mg, 300 mg	Placebo	157, 156	156	57.4 ± 10.5, 56.1 ± 8.9	56.8 ± 8.3	8.1 ± 0.9, 8.1 ± 0.9	8.1 ± 0.9	0, 0	1
Wilding et al. [27]	2013	RCT, db	104 weeks	Dapa 2.5 mg, 5 mg, 10 mg	Placebo	202, 211, 194	193	59.8 ± 7.6, 59.3 ± 7.9, 59.3 ± 8.8	58.8 ± 8.6	8.46 ± 0.78, 8.62 ± 0.89, 8.57 ± 0.82	8.47 ± 0.77	0, 1, 2	1
Yang et al. [28]	2016	RCT, db	24 weeks	Dapa 5 mg, 10 mg	Placebo	147, 152	145	53.1 ± 9.1, 54.6 ± 9.5	53.5 ± 9.2	8.09 ± 0.72, 8.17 ± 0.84	8.13 ± 0.85	0, 2	0
Yale et al. [29]	2014	RCT, db	52 weeks	Cana 100 mg, 300 mg	Placebo	90, 89	90	69.5 ± 8.2, 67.9 ± 8.2	68.2 ± 8.4	7.9 ± 0.9, 8.0 ± 0.8	8.0 ± 0.9	0, 0	2
Zinman et al. [30]	2015	RCT, db	4.6 years	Empa 10 mg, 25 mg	Placebo	2345, 2342	2333	63.0 ± 8.6, 63.2 ± 8.6	63.2 ± 8.8	8.07 ± 0.86, 8.06 ± 0.84	8.08 ± 0.84	92, 87	91

HbA_{1c}: haemoglobin A_{1c}; db: double-blinded; Dapa: dapagliflozin; Empa: empagliflozin; Cana: canagliflozin.

whereas, if the treatment lasted > 52 weeks, these beneficial effects disappeared Table 1.

Our findings are consistent with the results of two previous meta-analyses that also found no evidence that SGLT2 inhibitors increase the risk of bone fracture [16,17]. However, a previous pooled analysis of 10 trials by Watts et al. [18] showed, in contrast to our present results, an increased risk of bone fracture with canagliflozin. In this case, it should be noted that this increased risk was observed only in older patients with pre-existing cardiovascular disease, impaired renal function at baseline and greater baseline diuretic use [19]. On the other hand, one study of canagliflozin in our meta-analysis that included subjects with established cardiovascular or chronic kidney disease did show a trend towards an increased risk of fracture with the drug [20]. A similar trend was also observed in patients with moderate renal impairment taking dapagliflozin [21], although a study of empagliflozin, which enrolled patients with similar characteristics, revealed no increased incidence of bone fracture [22]. When patients with cardiovascular and kidney disease were excluded, the risk of bone fracture with SGLT2 inhibitors did not differ from that of their comparators. Thus, these trials suggest that canagliflozin and dapagliflozin might have adverse effects on bone in patients at high risk of cardiovascular or kidney disease that now need to be clarified in future studies.

After stratification by follow-up duration, beneficial effects against bone fracture were observed in studies with follow-ups ≤ 52 weeks. It was also reported that blood glucose levels were positively associated with BMD, and that patients with poor glycaemic control were at higher risk of fracture than those with lower HbA_{1c} levels [23,24]. Indeed, diabetes-related complications could reduce bone strength and increase the risk of falls, thereby leading to more frequent fractures [25,26]. On the other hand, SGLT2 inhibitor treatment may improve glycaemic control and prevent or delay the development of complications such as diabetic kidney disease [27,28] and could, in turn, help to reduce the incidence of bone fracture. Moreover, heart failure is associated with an increased risk for osteoporosis and fracture [29], whereas SGLT2 inhibitors have been demonstrated to improve cardiac function and decrease heart failure risk [30,31], which may also be beneficial for the prevention of bone fracture.

When SGLT2 inhibitor treatment exceeded 52 weeks, the beneficial effects of these drugs in preventing bone fracture disappeared. To date, a few potential mechanisms of SGLT2 inhibitors on bone metabolism have been proposed. While SGLT2 is not expressed in bone, SGLT2 inhibition might modulate calcium/phosphate homoeostasis and, thus, indirectly affect bone metabolism [32]. There have been reports that SGLT2 inhibitors could alter calcium and phosphate homoeostasis by increasing phosphate reabsorption in the proximal tubules [33]. Elevated serum phosphate levels can result in an increase in parathyroid hormone (PTH) and fibroblast growth factor (FGF)-23, which might stimulate bone resorption, thereby increasing the risk of bone fracture [34,35]. Moreover, SGLT2 inhibitor treatment is associated with body weight loss [36], which might lead to decreases in BMD and increases in bone turnover [37–39]. Therefore, the increased serum phosphate and decreased body weight due to SGLT2 inhibitors might be detrimental to bone metabolism, thus diminishing the potential protective effects of SGLT2 inhibitors over time.

Conclusion

The present meta-analysis has demonstrated that SGLT2 inhibitors do not increase the risk of bone fracture in patients with T2DM but, instead, result in beneficial effects against bone fractures with treatment periods ≤ 52 weeks. However, these results need to be interpreted with caution, as the durations of the included studies were relatively short and the number of bone-fracture events per study was low. Thus, large-scale RCTs with prespecified, well-defined safety outcomes are now warranted to assess the impact of SGLT2 inhibitors on fracture outcomes.

Ethics statement

The study protocol was in accordance with the principles of the Helsinki Declaration. All extracted data originated from research publications. There were no data containing sensitive information concerning participants in the studies included in our meta-analysis. The authors of all studies included in this meta-analysis claimed to have obtained approval from their appropriate institutional review boards.

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Author contributions

Liang Cheng, Yun-Yun Li and Xiao-Ming Mao were all involved in the study concept, design and performance, as well as the data extraction, data analysis and manuscript preparation.

Wen Hu, Feng Bai, Hai-Rong Hao and Wei-Nan Yu were all involved in carrying out the study, extracting data, data analysis and manuscript preparation.

Disclosure of interest

The authors declare that they have no competing interest.

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