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ORIGINAL ARTICLE

Effectiveness and safety of ertugliflozin for type 2 diabetes: A meta-analysis of data from randomized controlled trials

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Keywords
Ertugliflozin, Meta-analysis, Type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: To evaluate the effectiveness and safety of the novel sodium–glucose cotransporter inhibitor, ertugliflozin, compared with a placebo or other antihyperglycemic agents for type 2 diabetes patients.

Materials and Methods: We carried out a meta-analysis of randomized controlled trials to assess the benefits and harms of ertugliflozin. Online database searches were carried out in PubMed, EMBASE, WEB OF SCIENCE and Cochrane from inception up to 11 March 2021. Our end-points were glycated hemoglobin, fasting plasma glucose and bodyweight. We analyzed the results using a random effects model, computed weighted mean differences and risk ratios.

Result: A total of 10 randomized controlled trials with 13,223 patients met the inclusion criteria. Compared with a placebo, the weighted mean differences in glycated hemoglobin were −0.77% (95% confidence interval [CI] −0.86 to −0.68%) for ertugliflozin 5 mg, and −0.82% (95% CI −1.01 to −0.63%) for ertugliflozin 15 mg. Ertugliflozin 5 mg daily was also associated with bodyweight loss (weighted mean difference −1.87 kg, 95% CI −2.12 to −1.6). When compared with a placebo, ertugliflozin significantly reduced fasting plasma glucose by −1.62 mmol/L (weighted mean difference, 95% CI −1.82 to −1.42 for 5 mg ertugliflozin). Yet, we observed a rising risk for genital mycotic infections (risk ratio 4.34, 95% CI 2.78–6.76). The results were similar for the 15 mg ertugliflozin group.

Conclusion: Ertugliflozin effectively reduces glycated hemoglobin levels and provides extra clinical benefits including bodyweight and fasting plasma glucose. Common adverse effects, including genital mycotic infections and so on, were reviewed.

INTRODUCTION

Diabetes is thought of as one of the largest widespread diseases the world has faced in the 21st century both in developed and developing nations[1]. Diabetes, which is characterized by hyperglycemia principally, can be simply classified into type 1 diabetes and type 2 diabetes[2]. Type 2 diabetes, mainly appearing in adulthood, is the result of insulin resistance and relative insulin deficiency. Diabetes usually gives rise to plenty of complications, owing to its insidious and chronic nature, which affect nearly every tissue of the body[3]. For type 2 diabetes, therapeutic drugs are involved in a step-up policy in which the regimens are increasingly complex should targets not be achieved[4]. There are a very diverse antihyperglycemic drugs, such as glucagon-like peptide, sodium–glucose cotransporter 2 (SGLT2) inhibitor, sulfonylurea and so on. SGLT2 inhibitor, an orally active antihyperglycemic drug, lowered blood glucose by suppressing sodium and glucose reabsorption from the proximal tubules[5]. Ertugliflozin, an orally active SGLT2 inhibitor, was authorized by the US Food and Drug Administration as adjuvant therapy to diet and exercise for adults with type 2 diabetes[6–8].

Although several previous meta-analyses have provided evidence for the effectiveness and safety of SGLT2 inhibitor, including canagliflozin, dapagliflozin and empagliflozin, for treatment of adults with type 2 diabetes[9–11], there were only

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thinly distributed data regarding the effectiveness and safety of ertugliflozin due to the lack of relevant studies on ertugliflozin. A previous study showed that ertugliflozin is effective to control glycated hemoglobin (HbA1c) levels, blood pressure and bodyweight[12]. However, to our knowledge, its effects on fasting plasma glucose (FPG) and accomplishing the target of HbA1c <7% are still unclear, as most trials carried out on this drug are small in size and heterogeneity is associated solely with methodological diversity. Meanwhile, adverse events consistent with genital mycotic infections (GMIs) and urinary tract infections (UTIs) among patients treated with SGLT2 inhibitor cannot be ignored on account of its glucosuria excretion to a certain extent. To obtain a more comprehensive profile, we carried out a meta-analysis of randomized controlled trials (RCTs) aiming to assess the benefits and harms of ertugliflozin in type 2 diabetes patients either as monotherapy or as add-on treatment.

MATERIALS AND METHODS

Ethical review

The protocol of this review was registered in PROSPERO (CRD42021258614). Our research was a study-level meta-analysis of clinical trials. Therefore, ethical approval was not necessary for this study. The study was reported in conformity to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statements[13].

Date sources and searches

We selected relevant studies published from inception to 11 March 2021, by searching PubMed, Embase, Cochrane and Web of Science. Among the initially retrieved studies, we included only studies written in English, irrespective of primary outcome. We used the following keywords: Ertugliflozin OR PF 04971729 OR Steglatro OR 5-(4-chloro-3-(4-ethoxybenzyl) phenyl)-1-hydroxymethyl-6,8-dioxabicyclo (3.2.1) octane-2,3,4-triol OR 1,6 anhydro 1 C [4 chloro 3[(4 ethoxyphenyl) methyl] phenyl] 5 C (hydroxymethyl) beta I idopyranose OR MK8835 OR mk8835 OR PF4970729-00 OR pf04971729 OR pf04971729 00 OR pf4971729 OR ertugliflozin pyroglutamic acid.

Inclusion and exclusion criteria

Inclusion criteria included the following: (i) patients: inclusive of any ethnic origin and aged >18 years who had inadequate glycemic control (HbA1c >7%); (ii) interventions: any use of ertugliflozin either as monotherapy or add-on treatment, duration of the intervention was at least 12 weeks; (iii) control group: placebo or antihyperglycemic agents with or without background therapy; and (iv) report the following results: (a) HbA1c, (b) FPG, (c) bodyweight and (d) AEs.

Exclusion criteria included the following: (i) type 1 diabetes mellitus; (ii) non-randomized trials, non-human studies; (iii) study with <12 weeks duration of the intervention; and (iv) the studies did not measure the outcome of comparing ertugliflozin with other antidiabetic drugs or a placebo.

Data extraction

In the present meta-analysis, we incorporated RCTs comparing ertugliflozin as monotherapy or add-on treatment with a placebo or other antihyperglycemic drugs in adults with type 2 diabetes. With a view to observing changes in HbA1c levels, follow-up duration lasted at least 12 weeks. Records retrieved from some databases were sorted out in reference management software (EndNote X9, Clarivate Analytics, CT, USA).

Two authors (Fudan Zhang and Wenting Wang) extracted relevant data on their own from the selected eligible studies, and any discrepancies were resolved through consultation by both sides. Our primary outcome was HbA1c levels from baseline and the proportion of patients achieving the HbA1c target of <7%, FPG and bodyweight. Adverse outcomes included patients experiencing UTI, GMI and symptomatic hypoglycemia. We also extracted data for all-cause mortality results and cardiovascular outcomes. We were mainly concerned with the data for patients randomly assigned to ertugliflozin 5 mg/day and 15 mg/day.

Risk-of-bias assessment and publication bias

Two reviewers (Fudan Zhang and Wenting Wang) independently used the Cochrane Risk of Bias tool to evaluate the risk and quality in each collected study, including randomization implementation, proper allocation concealment, blinding, incomplete data, selective reporting, and other items (i.e., groups comparable at baseline, funder and incomplete information in the text). Figure 1 shows each part of the risk of the bias assessment. Meanwhile, we carried out funnel plots (including at least 10 studies) using (Revman5.3, Cochrane Collaboration, Oxford, UK). to evaluate the publication bias. The funnel plot of UTI did not detect obvious asymmetric distribution (Figure S1).

Statistical analysis

We carried out the analysis on the basis of common doses of ertugliflozin (5 mg/day and 15 mg/day) and type of comparator (placebo or antihyperglycemic agents). All outcomes were analyzed according to Revman5.3 software. For continuous outcomes, such as HbA1c, bodyweight and FPG, weighted mean differences (WMD) using an inverse variance weighted random effects model and 95% confidence interval (95% CI). were calculated. For dichotomous outcomes, such as UTI, GMI and symptomatic hypoglycemia, we calculated risk ratios (RRs) by applying the Mantel–Haenszel formula assuming random effects and 95% confidence interval (95% CI). To minimize heterogeneity, we carried out subgroup analysis. Subgroup analysis was accomplished according to different dosage and comparators in measure. To explore the heterogeneity in the results of the 5 mg and 15 mg groups, we also carried out the sensitivity analysis to test the robustness of our findings. After excluding the patients compared with glimepiride[14], the heterogeneity decreased to a great extent in bodyweight and symptomatic hypoglycemic. Heterogeneity was assessed with I^2 statistics, with values >50% regarded as being indicative of moderate-to-high heterogeneity[15]. A fixed effects model was

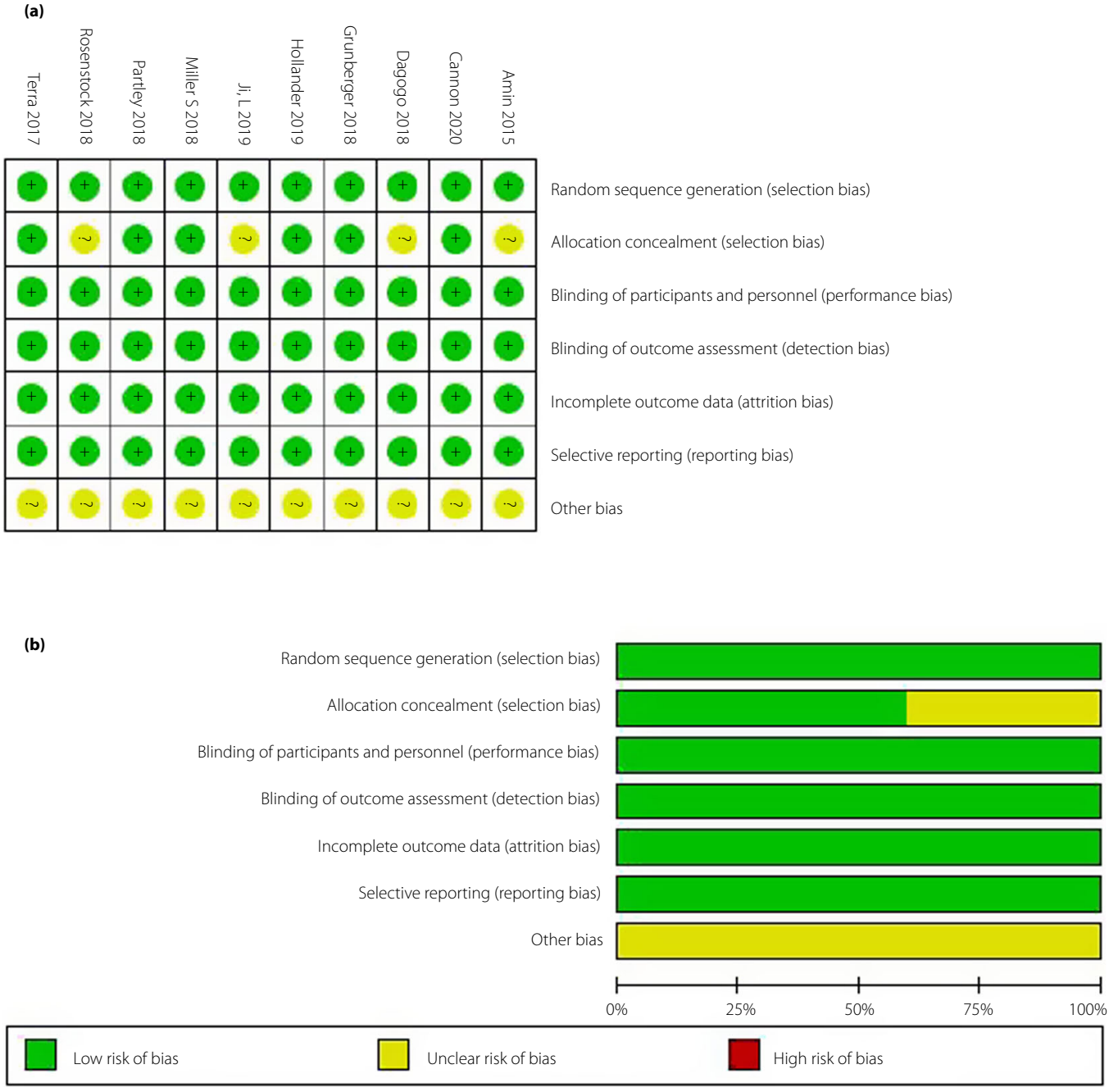

Figure 1 | Cochrane risk of bias graph and summary.

used for analysis if no heterogeneity was found (I^2 < 50%). We used the RevMan5.3 and Stata (version 16.0; StataCorp, College Station, TX, USA) for all statistical analyses.

RESULTS

Description of studies

The process of the study selection is shown in Figure 2. Therefore, 10 studies with a total of 13,223 participants were included in the meta-analysis. Among these people, 4,416 were in the control group and 8,807 (5 mg ertugliflozin group n = 4,447 participants, 15 mg ertugliflozin group n = 4,360 participants) were in the ertugliflozin group[14,16–24]. The characteristics of the included studies are summarized in Table 1. Study duration of the present trials ranged from 12 weeks to 104 weeks, and these trials were published between 2017 and 2020. In these studies, background antidiabetic drugs were multitudinous, such

as insulin, metformin, sitagliptin and so on. Participants in two trials did not receive background antidiabetic therapy[21,24]. In the rest of the trials, participants were on background treatment with metformin[14,16,20,22,23], metformin and sitagliptin,[18] and other antihyperglycemic drugs[19]. Beyond that, one trial did not mention the background therapy[17]. In all of the included trials, ertugliflozin monotherapy was compared with a placebo[16–20,23,24], whereas in two trials, ertugliflozin was compared with glimepiride[14] and sitagliptin[22] respectively. In one trial, the ertugliflozin group incorporated ertugliflozin with one active antidiabetic drug[21]. Finally, one trial registered patients solely with renal impairment (estimated glomerular filtration rate between 30 and 60 mL/min/1.73 m^2)[19], whereas one study recruited patients with atherosclerotic cardiovascular disease[17].

Glycemic efficacy (HbA1c)

In all included RCTs, ertugliflozin was compared with a placebo or other antidiabetic drugs (metformin, glimepiride etc.), we used random effects models and the subgroup analysis to analyze the outcome on account of its heterogeneity. Compared with the comparator, the treatment with ertugliflozin once daily improved glycemic efficacy (WMD in HbA1c −0.57%, 95% CI −0.77 to −0.37, I^2 = 94% for the ertugliflozin 5 mg group; WMD in HbA1c −0.61%, 95% CI −0.82 to −0.39, I^2 = 94% for the ertugliflozin 15 mg group; Figure 3). We carried out the subgroup analysis based on the dosage of ertugliflozin and the comparator. In the 5 mg ertugliflozin groups compared with a placebo, the pooled HbA1c WMD was −0.77% (95% CI −0.86 to −0.68, I^2 = 0%). In the 15 mg ertugliflozin groups compared with a placebo, the pooled HbA1c WMD was −0.82% (95% CI −1.01 to −0.63, I^2 = 66%; Figure 3). The ertugliflozin group showed that a large portion of participants achieved the target of HbA1c <7% (for the 5 mg ertugliflozin group, RR 1.80, 95% CI 1.37–2.37, I^2 = 85%, for the 15 mg ertugliflozin group, RR 1.75, 95% CI 1.28–2.38, I^2 = 88%). There were no conspicuous differences in the HbA1c <7% in the ertugliflozin group compared with the placebo group (for the 5 mg ertugliflozin group, RR 2.34, 95% CI 1.92–2.86, I^2 = 0%, for the 15 mg ertugliflozin group, RR 2.53, 95% CI 2.07–3.11, I^2 = 0%; Figure S2).

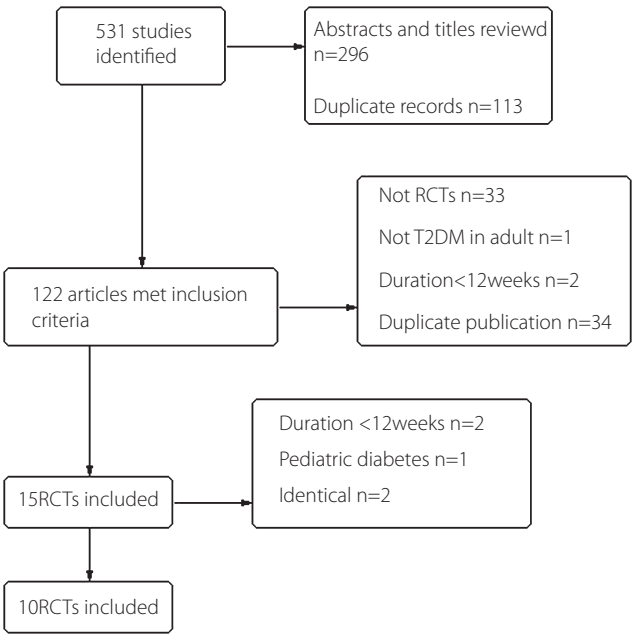

Figure 2 | Flow diagram selection of study. RCT, randomized controlled trial; T2DM, type 2 diabetes.

FPG

Treatment with ertugliflozin once daily had a favorable effect on FPG. Five trials[16,18,20,23,24] reported patients taking ertugliflozin compared with placebo monotherapy. The placebo subgroup was selected for the analysis. The subgroup analysis showed that 5 mg/day and 15 mg/day lowered FPG level compared with a placebo (for 5 mg ertugliflozin: WMD in FPG: −1.62 mmol/L, 95% CI −1.82 to −1.42, I^2 = 0%; for 15 mg ertugliflozin: WMD in FPG: −1.91 mmol/L, 95% CI −2.30 to −1.53, I^2 = 66%; Figure 4).

Bodyweight

Nine studies (n = 4810 participants) reported the results of bodyweight changes after treatment. The ertugliflozin group showed an evident bodyweight reduction compared with the comparator group (for 5 mg ertugliflozin, WMD: −2.17 kg, 95% CI −2.73 to −1.61, I^2 = 82%; for 15 mg ertugliflozin, WMD: −2.38 kg, 95% CI −3.10 to −1.65, I^2 = 87%; Figure S3). To probe heterogeneity in the results of the 5 mg and 15 mg groups, we carried out a sensitivity analysis (Figures S4a and S4b). Ruling out a specialized trial on patients compared with glimepiride[19] could explain the heterogeneity (for 5 mg ertugliflozin: WMD in bodyweight: −1.87 kg, 95% CI −2.12 to −1.62, P < 0.00001, I^2 = 0%; for 15 mg ertugliflozin :WMD in bodyweight: −2.06 kg, 95% CI −2.44 to −1.69, P < 0.00001, I^2 = 41%; Figure 5). Glimepiride, a kind of sulfonylurea, might be correlated with weight gain compared with other comparators[25].

GMIs and UTIs

Nine out of 10 studies (n = 13,106 participants) evaluated the risk ratios of GMI in the treatment. Ertugliflozin compared with a comparator increased the risk of GMI (for 5 mg ertugliflozin, RR 4.34, 95% CI 2.78–6.76, I^2 = 29%; for 15 mg ertugliflozin, RR 4.63, 95% CI 2.95–7.26, I^2 = 30%; Figure S5). Regardless of the dose, women were at greater risk of GMI than men compared with a comparator (for women in the 5 mg ertugliflozin group, RR 1.60, 95% CI 1.22–2.27, I^2 = 0%; for men in the 5 mg ertugliflozin group, RR 2.75, 95% CI 1.70–4.45, I^2 = 19%; Figure S6). However, treatment with ertugliflozin 5 mg or 15 mg once daily did not increase the risk of UTI compared with the comparators (for 5 mg ertugliflozin, RR 1.01, 95% CI 0.74–1.36, I^2 = 44%; for 15 mg ertugliflozin, RR 1.09, 95% CI 0.89–1.34, I^2 = 16%; Figure S7).

Table 1 | Basic characteristics of included randomized controlled trials

Study	Year	Study duration weeks	Study arms	Background antidiabetic therapy	No. participants	HbA1c (%)†	FPG mmol/L†	Bodyweight, (kg)†	Mean age(years)†	BMI kg/m^{2}†	Duration of type 2 diabetes mellitus, year†	Gender male, *n* (%)
Amin	2015	12	Ertugliflozin 1 mg	MET	54	8.01 ± 0.17	9.03 ± 0.38	NR	53.1 ± 9.1	29.8 ± 0.67	6.3 (0.1-24.0)	34 (63.0)
			Ertugliflozin 5 mg		55	7.88 ± 0.13	8.69 ± 0.32		54.7 ± 7.7	31.1 ± 0.85	6.7 (0.3-30.0)	41 (74.5)
			Ertugliflozin 10 mg		55	8.13 ± 0.17	9.07 ± 0.35		57.3 ± 6.5	30.7 ± 0.80	6.1 (0.2-20.0)	31 (56.4)
			Ertugliflozin 25 mg		55	8.30 ± 0.16	9.52 ± 0.43		54.2 ± 8.8	29.8 ± 0.67	6.0 (0.3-18.2)	37 (67.3)
			Sitagliptin 100 mg		55	8.24 ± 0.15	9.23 ± 0.37		53.3 ± 10.7	30.4 ± 0.77	6.3 (0.3-20.0)	30 (55.6)
			Placebo		54	8.08 ± 0.14	9.18 ± 0.31		54 ± 8.1	30.6 ± 0.61	6.4 (0.3-20.5)	
Cannon	2020	52	Ertugliflozin 5 mg	NR	2752	8.3 (1.0)	9.78 (2.92)	91.9 (18.4)	64.3 (8.2)	31.9 ± 5.42	12.9 ± 8.3‡	3866 (70.3)‡
			Ertugliflozin 15 mg		2747	8.2 (1.0)	9.71 (2.87)	91.6 (18.6)	64.4 (8.0)	32.0 ± 5.5↗	13.1 ± 8.4↗	1903 (69.3)↗
			Placebo		2747	8.2 (0.9)	9.64 (2.74)	91.9 (18.3)	64.4 (8.0)			
Dagogo	2018	26	Ertugliflozin 5 mg	MET AND SITA	156	8.1 (0.9)	9.3 (2.1)	87.6 (18.6)	59.2 (9.3)	31.2 (5.5)	9.9 (6.1)	81 (51.9)
			Ertugliflozin 15 mg		153	8.0 (0.8)	9.5 (2.2)	86.6 (19.5)	59.7 (8.6)	30.9 (6.1)	9.2 (5.3)	82 (53.6)
			Placebo		153	8.0 (0.9)	9.4 (2.1)	86.4 (20.8)	58.3 (9.2)	30.3 (6.4)	9.4 (5.6)	100 (65.4)
Grunberger	2018	52	Ertugliflozin 5 mg	(AHAS)	158	8.2 (1.0)	8.94 (3.13)	89.4 (22.5)	66.7 (8.3)	32.6 (6.8)	14.9 (9.0)	84 (53.2)
			Ertugliflozin 15 mg		155	8.2 (0.9)	8.75 (2.66)	85.8 (17.4)	67.5 (8.5)	31.7 (5.3)	14.5 (8.5)	75 (48.4)
			Placebo		154?	8.1 (0.9)	8.72 (3.13)	90.4 (18.9)	67.5 (8.9)	33.2 (6.1)	13.1 (8.1)	72 (46.8)
Hollander	2019	104	Ertugliflozin 5 mg	MET	445	7.8 ± 0.6	9.0 ± 1.9	88.0 ± 19.0	58.7 ± 9.8	31.7 ± 5.6	7.3 ± 5.7	227 (51.0)
			Ertugliflozin 15 mg		435	7.8 ± 0.6	9.0 ± 2.0	85.7 ± 19.1	58.0 ± 9.9	31.3 ± 6.2	7.5 ± 5.7	191 (43.9)
			Glimepiride		435	7.8 ± 0.6	8.8 ± 1.9	86.9 ± 20.8	57.9 ± 9.1	31.2 ± 6.4	7.6 ± 5.6	224 (51.5)
Ji	2019	26	Ertugliflozin 5 mg	MET	170	8.1 (0.9)	9.45 (2.0)	71.4 (11.1)	56.1 (9.0)	26.0 (2.8)	7.0 (5.0)	95 (55.9)
			Ertugliflozin 15 mg		169	8.1 (0.9)	9.29 (2.28)	69.5 (10.9)	56.3 (9.3)	25.7 (3.2)	7.5 (5.1)	98 (58.0)
			Placebo		167	8.1 (1.0)	9.21 (2.09)	70.1 (12.4)	56.9 (9.0)	26.1 (3.4)	6.4 (5.1)	88 (52.7)
Miller	2018	26	Ertu5 mg/St100 mg	DIET AND	98	8.9 (0.9)	11.0 (2.6)	90.8 (20.7)	56.4 (9.3)	32.0 (6.3)	5.7 (5.0)	57 (58.2)
			Ertu15 mg/St100 mg	EXERCISE	96	9.0 (0.9)	10.4 (2.6)	91.2 (22.5)	56.1 (10.1)	32.1 (5.8)	6.5 (6.5)	53 (55.2)
			Placebo		97	9.0 (0.9)	11.5 (2.5)	95.0 (20.5)	54.3 (10.3)	32.7 (6.2)	6.8 (6.5)	57 (58.8)
Partley	2018	52	Ertugliflozin 5 mg	MET	250	8.6 (1.0)	10.23 (2.9)	88.6 (22.2)	55.1 (10.1)	31.8 (6.2)	7.1 (5.4)	127 (50.8)
			Ertugliflozin 15 mg		248	8.6 (1.0)	9.97 (2.54)	88.0 (20.3)	55.3 (9.5)	31.5 (5.8)	7.3 (5.4)	134 (54.0)
			Stiaglptin 100 mg		247	8.5 (1.0)	9.86 (2.59)	89.8 (23.5)	54.8 (10.7)	31.7 (6.5)	6.2 (5.2)	154 (62.3)
Rosentock	2017	104	Ertugliflozin 5 mg	MET	207	8.1 ± 0.9	9.3 ± 2.5	84.8 ± 17.2	56.6 ± 8.1	30.8 ± 4.8	7.9 ± 6.1	97 (46.9)
			Ertugliflozin 15 mg		205	8.1 ± 0.9	9.3 ± 2.5	85.3 ± 16.5	56.9 ± 9.4	31.1 ± 4.5	8.1 ± 5.5	93 (45.4)
			Placebo		209	8.2 ± 0.9	9.4 ± 2.3	84.5 ± 17.1	56.5 ± 8.7	30.7 ± 4.7	8.0 ± 6.3	98 (46.9)
Terra	2017	26	Ertugliflozin 5 mg	DIET AND	156	8.16 (0.88)	10.0 (2.7)	94.0 (25.4)	56.8 (11.4)	33.2 (7.4)	5.11 (5.09)	89 (57.1)
			Ertugliflozin 15 mg	EXERCISE	152	8.35 (1.12)	9.9 (2.7)	90.6 (18.3)	56.2 (10.8)	32.5 (5.7)	5.22 (5.55)	90 (59.2)
			Placebo		153	8.11 (0.92)	10.0 (2.5)	94.2 (25.2)	56.1 (10.9)	33.3 (6.8)	4.63 (4.52)	82 (53.6)

AHAS, antihyperglycemic agents; BMI, body mass index; HbA1c, glycated hemoglobin; MET, metformin; NR, not reported; St, sitagliptin. †Data are mean ± standard deviation or median (range). ‡Date that both ertugliflozin (ertu) 5 mg group and ertu15 mg group are mean ± standard deviation or number (percentage).

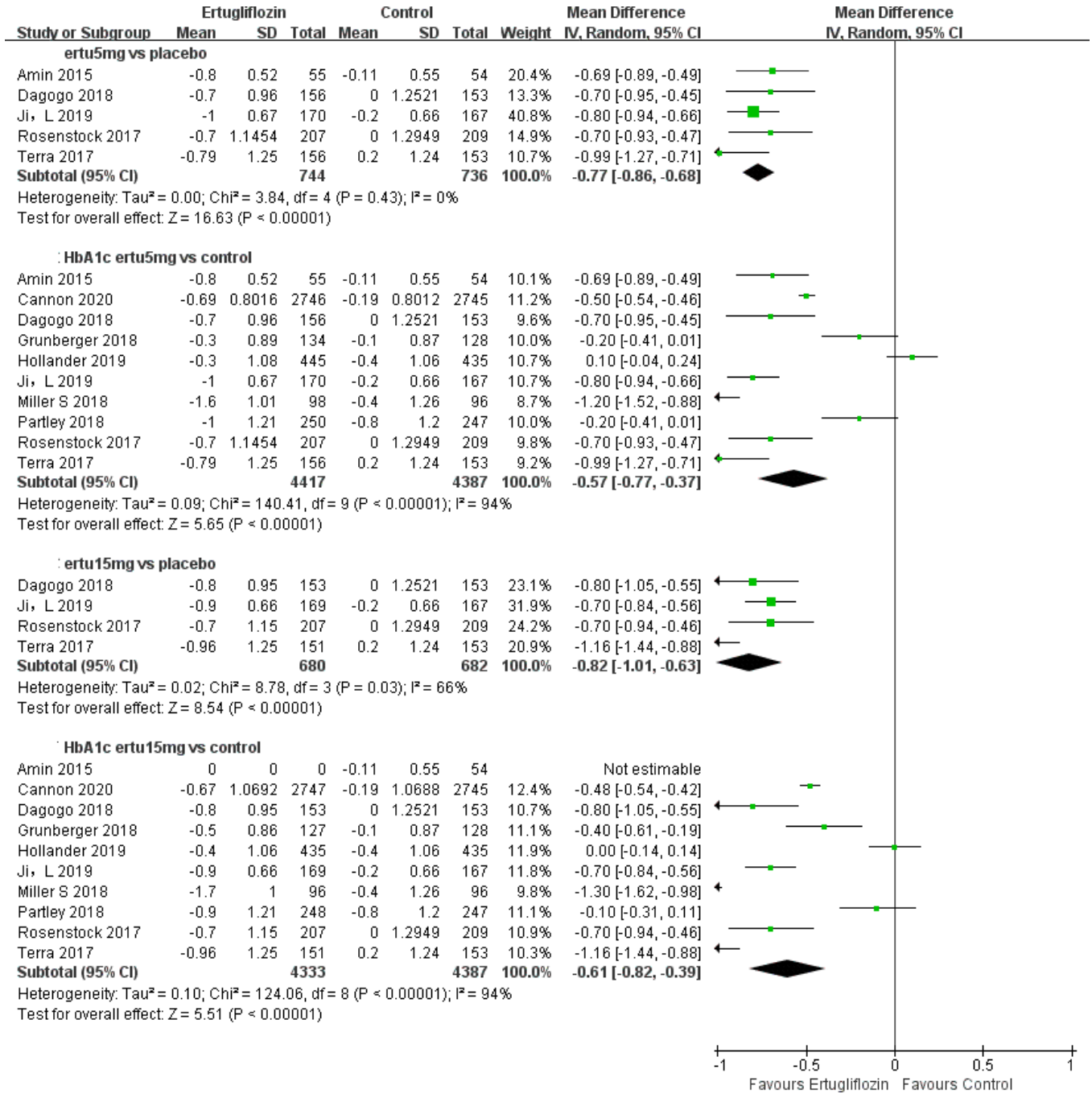

Figure 3 | Forest plots of overall effect size of glycated hemoglobin (HbA1c) and subgroup meta-analysis of different doses. Results from inverse-variance (IV) random effects comparing ertugliflozin 5 mg or ertugliflozin 15 mg once daily with control or placebo. CI, confidence interval; ertu, ertugliflozin; SD, standard deviation.

Symptomatic hypoglycemia

The incidence of symptomatic hypoglycemia that is an event with clinical symptoms reported by the investigator as hypoglycemia (biochemical documentation not required) did not differ between ertugliflozin and a comparator (for 5 mg ertugliflozin, RR 0.97, 95% CI 0.56–1.68, I^2 = 83%; for 15 mg ertugliflozin, RR 0.91, 95% CI 0.56–1.49, I^2 = 80%; Figure S8). To explore the heterogeneity, we carried out a sensitivity analysis (Figures S9a and S9b). After excluding the patients compared with glimepiride[14], the heterogeneity decreased to a great extent (for 5 mg ertugliflozin, RR 0.98, 95% CI 0.91–1.07, I^2 = 0%; for 15 mg ertugliflozin, RR 0.97, 95% CI 0.75–1.25,

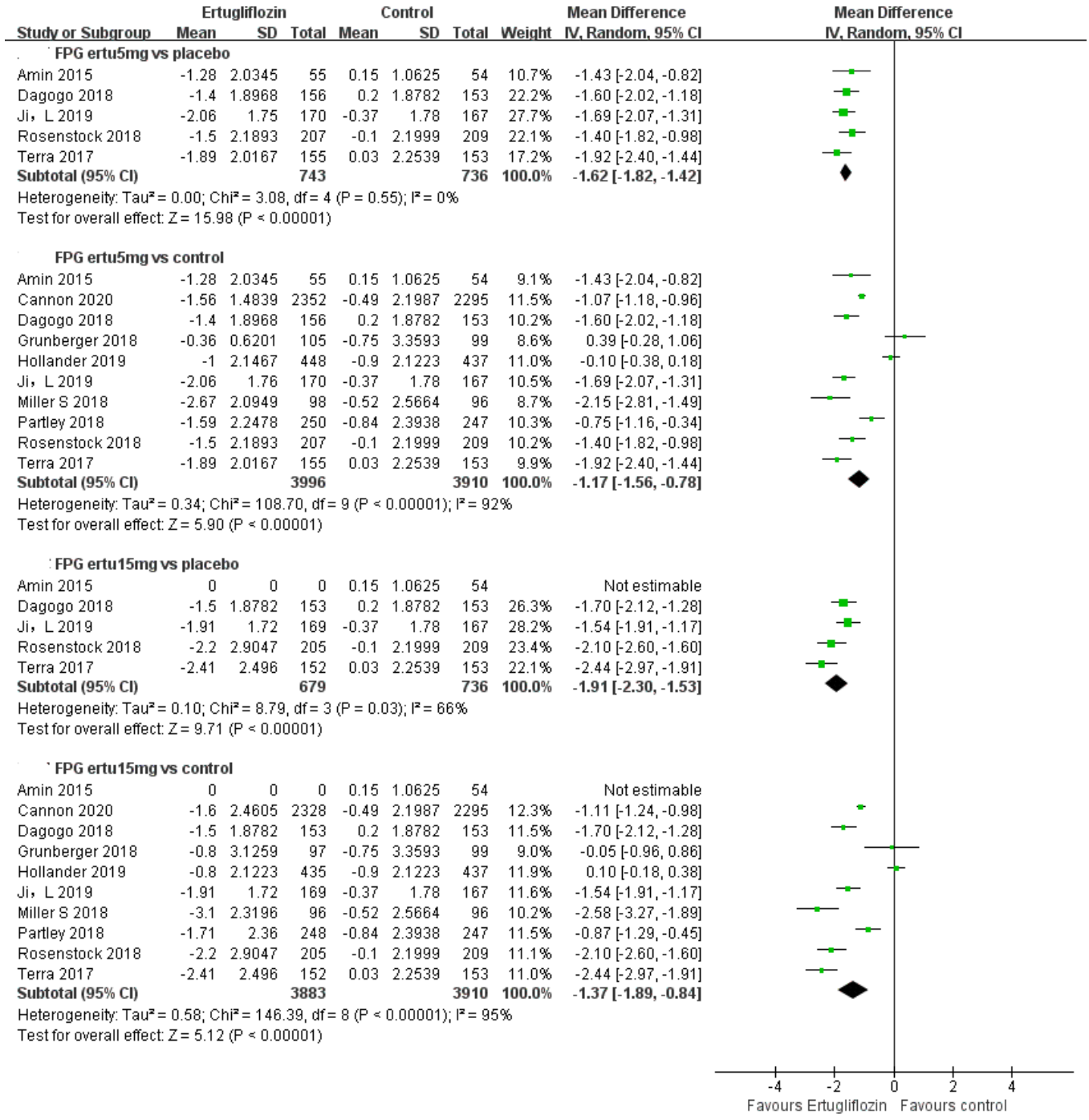

Figure 4 | Forest plots of overall effect size of fasting plasma glucose (FPG) and subgroup meta-analysis of different dose. Results from inverse-variance (IV) random-effects comparing ertugliflozin 5 mg or ertugliflozin 15 mg once daily with control or placebo. CI, confidence interval; ertu, ertugliflozin; SD, standard deviation.

I^2 = 19%; Figure S10). Ertugliflozin compared with glimepiride reduced the risk of symptomatic hypoglycemia (for 5 mg ertugliflozin, RR 0.17, 95% CI 0.11–0.28; for 15 mg ertugliflozin, RR 0.29, 95% CI 0.20–0.43).

DISSCUSSION

In the present study, we carried out a meta-analysis to compare the effectiveness and safety of ertugliflozin with a comparator, used either as monotherapy or add-on therapy. Ertugliflozin is

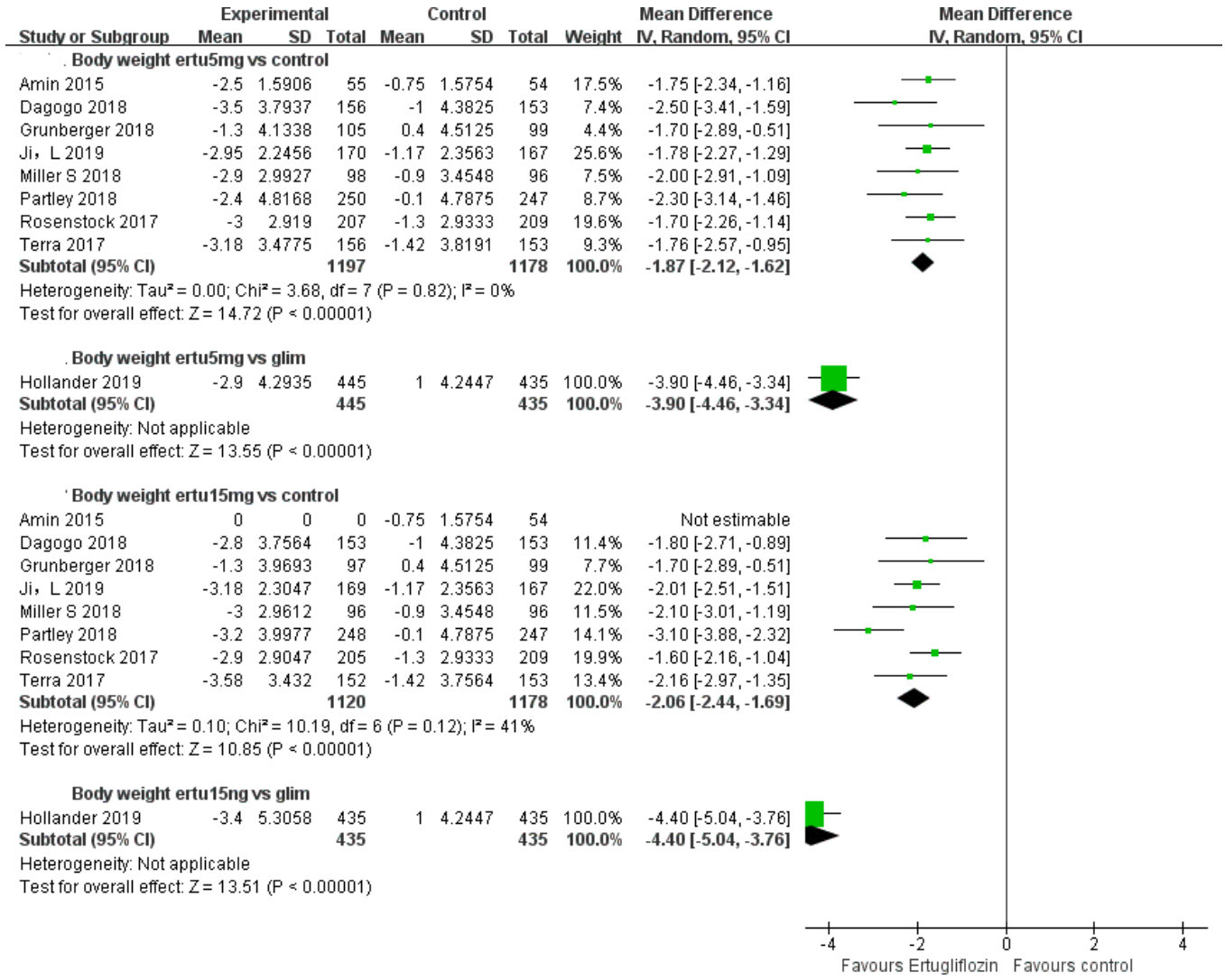

Figure 5 | Forest plots of overall effect size of bodyweight, and subgroup meta-analysis of different indexes of measure and dose. Results from inverse-variance (IV) random effects comparing ertugliflozin 5 mg or ertugliflozin 15 mg once daily with control and glimepiride. CI, confidence interval; ertu, ertugliflozin; glim, glimepiride; SD, standard deviation.

a kind of oral SGLT2 inhibitor[26] presently under evaluation for marketing authorization in the USA and Europe[7,8]. In our meta-analysis, treatment with ertugliflozin compared with a placebo was found to be effective in reducing HbA1c, FPG and bodyweight, and achieving the target of HbA1c <7%.

In line with discoveries from previous meta-analyses, the present results suggested that ertugliflozin is consistent with other SGLT2 inhibitors, including canagliflozin[27], dapagliflozin[9] and empagliflozin[28]. However, there are few reviews on ertugliflozin for type 2 diabetes, the purpose of the present study was to systemically assess the effectiveness and safety of different doses of ertugliflozin for patients with type 2 diabetes. Ertugliflozin vastly reduced the HbA1c levels relative to a placebo, which matched up with the results reported in previous meta-analyses. Both doses of 5 mg and 15 mg once per day ertugliflozin are beneficial to the management of blood glucose and bodyweight. A dose-dependent improvement was seen for HbA1c, FPG and bodyweight.

In five included trials that compared ertugliflozin monotherapy with a placebo[16,18,20,23,24], ertugliflozin brought about a significantly enormous reduction in HbA1c and FPG than all included trials. Ertugliflozin monotherapy compared with a placebo also showed the statistical superiority to other comparators in achieving the target of HbA1c <7%. The results showed good glycemic control over the previous 2–3 months. The present results showed that ertugliflozin contributed to a meaningful clinical weight reduction in patients with type 2 diabetes, except for the trial that compared ertugliflozin with

glimepiride[14]. Weight loss with ertugliflozin was clinically significant, especially in the setting of obese patients.

The existing evidence shows various detrimental drug reactions, such as foot amputation, cancer, diabetic ketoacidosis and UTI, as well as MGI. Therefore, in addition to improved glycemic efficacy and weight reduction, there were some adverse events, including GMI, UTI and symptomatic hypoglycemia. Glimepiride, a kind of sulfonylurea, usually brings about hypoglycemia on account of improving insulin secretion and sensitivity, and β-cell function[25]. Apart from the result that ertugliflozin with respect to glimepiride reduced the risk of symptomatic hypoglycemia, ertugliflozin did not increase the risk of symptomatic hypoglycemia compared with comparators, as SGLT2 inhibitors reduce hyperglycemia independent of β-cell function and insulin resistance. Furthermore, the incidence of GMI was higher in patients treated with ertugliflozin than with comparators, particularly in male patients. Ertugliflozin increasing the risks of GMIs might be related to an increase in urinary glucose excretion, which promote the growth of bacterial reproduction[29]. However, the patients treated with ertugliflozin did not increased the risk of UTI compared with comparators. In the trial of patients with type 2 diabetes and atherosclerotic cardiovascular disease, there were 444 deaths among 5,499 patients due to cardiovascular disease or heart failure, and hospitalization for worsening heart failure. In the study of remaining RCTs, there were 17 deaths across the ertugliflozin groups. Four of the 10 fatal events in the ertugliflozin group were connected with cardiovascular death. One was connected with multiple organ dysfunction syndrome, two were related to infections (pneumonia and septic shock), one was related to depression and one was related to chronic obstructive pulmonary disease. One patient in the ertugliflozin group died of an ischemic stroke on day 318. There were seven deaths from other serious adverse events. A total of four deaths occurred in the control groups. Ketoacidosis similarly was treated as a safety concern for the SGLT2 inhibitor class during the observations of the ertugliflozin clinical studies. Ketoacidosis was reported in few patient populations in the present analysis. It is worth noting that the incidence of bladder cancer and breast cancer increased with dapagliflozin[30,31], which was not found with ertugliflozin. Meanwhile, this conclusion should be confirmed in larger and clinical follow-up trials.

Specialized studies on patients with type 2 diabetes and atherosclerotic disease have reported the effect of cardiac damage on the antihyperglycemic efficacy and tolerability of individual SGLT2 inhibitors[32–34]. Findings suggested that treatment with empagliflozin might benefit patients with type 2 diabetes and atherosclerotic cardiovascular disease irrespective of a history of myocardial infarction or stroke. In patients with atherosclerotic disease, dapagliflozin did not lead to a significantly lower incidence of major adverse cardiovascular events, but it did generate a lower incidence of cardiovascular death and hospitalization. In the same way, canagliflozin reduced the cardiovascular outcome. In the end, patients treated with ertugliflozin were not shown to be non-inferior to a placebo in regard to major adverse cardiovascular events. However, given the differences in pharmacokinetics, pharmacodynamics, and efficacy and safety profiles within the SGLT2 inhibitors class, the cardioprotective effects of specific SGLT2 inhibitors can be different. These findings showed that ertugliflozin might be conducive to treating patients with progressive of cardiac function.

We should acknowledge some limitations of our meta-analysis. First, it is worth noting that only one glimepiride-controlled RCT and one sitagliptin-controlled RCT were brought into this study, and an increasing number of trials with active agents will contribute to judge the relative therapeutic effect of ertugliflozin. Therefore, more evidence is necessary to judge the comparative efficacy of ertugliflozin against other active agents. Furthermore, the majority of included trials ranged in duration from 12 to 52 weeks, and only one trial's duration was 104 weeks, so the long-term effects of this treatment are unknown. To date, there are no trials assessing the relative efficacy and safety between SGLT2 inhibitors. In addition, all of the included studies were in English, which might result in language bias. There was evident statistical heterogeneity in the analysis of efficacy indicators, which might be caused by the inclusion of some dedicated trials. In the dedicated trials patients with stage 3 chronic kidney disease (estimated glomerular filtration rate ≥30–60 mL/min/1.73 m^2) and atherosclerotic cardiovascular disease, respectively, were included.

In summary, as an add-on drug to other hypoglycemic drugs, both daily doses of ertugliflozin (5 mg or 15 mg) have a useful impact on blood glucose control and bodyweight in patients with type 2 diabetes. Additionally, it is connected with an increased occurrence and development of GMI. However, treatment with ertugliflozin 5 mg or 15 mg once daily did not increased the risk of UTI and symptomatic hypoglycemia. Considering the limitations of the present study, the long-term safety profile of ertugliflozin remains to elucidated from large clinical trials.

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DISCLOSURE

The authors declare no conflict of interest.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Funnel plot of urinary tract infections (UTIs).

Figure S2 | Forest plots of overall effect size of achieving the target of glycated hemoglobin (HbA1c) <7% and subgroup meta-analysis of different doses.

Figure S3 | Forest plots of overall effect size of bodyweight, and subgroup meta-analysis of different doses.

Figure S4a | Sensitivity analysis of bodyweight (ertugliflozin 5 mg).

Figure S4b | Sensitivity analysis of bodyweight (ertugliflozin 15 mg).

Figure S5 | Forest plots of overall effect size of genital mycotic infections (GMIs) and subgroup meta-analysis of different doses.

Figure S6 | Forest plots of overall effect size of genital mycotic infections (GMIs) and subgroup meta-analysis of different sexes.

Figure S7 | Forest plots of overall effect size of urinary tract infections (UTIs) and subgroup meta-analysis of different doses.

Figure S8 | Forest plots of overall effect size of symptomatic hypoglycemia and subgroup meta-analysis of different doses.

Figure S9a | Sensitivity analysis of symptomatic hypoglycemia (ertugliflozin 5 mg).

Figure S9b | Sensitivity analysis of symptomatic hypoglycemia (ertugliflozin 15 mg).

Figure S10 | Forest plots of overall effect size of symptomatic hypoglycemia and subgroup meta-analysis of different indexes of measure and dose.