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REVIEW ARTICLE

Effect of ertugliflozin on glycemic levels, blood pressure and body weight of patients with type 2 diabetes mellitus: a systematic review and meta-analysis

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Abstract

Purpose To conduct a meta-analysis to evaluate the effect of ertugliflozin on long-term hemoglobin A1c (HbA1c), body weight and blood pressure (BP).

Methods Online databases available were searched from their inception to February 2020. Randomized controlled trials (RCTs) comparing ertugliflozin to either placebo or an active control drug were included. Data on four efficacy outcomes were extracted, namely: HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP) and body weight. Continuous outcomes were pooled using a random-effects model and presented as weighted mean differences (WMDs) and corresponding 95% CIs. Additionally, a subgroup analysis was done to compare two doses of ertugliflozin (5 mg and 15 mg). A sensitivity analysis was also performed by eliminating studies using active drugs as controls.

Results From a total of 123 search results, eight studies were included. Compared to the control group, ertugliflozin was associated with a significant decrease in SBP (WMD: −3.64 mmHg, 95% CI [−4.39,-2.90]; $p < 0.001$; $I^2 = 0\%$) and DBP (WMD: −1.13 mmHg, 95% CI [−1.67,-0.60], $p < 0.001$; $I^2 = 0\%$). Similarly, significant reductions in body weight (WMD: −2.35 kg, 95% CI [−2.94,-1.77]; $p < 0.001$; $I^2 = 0\%$) as well as HbA1c (WMD: −0.41%, 95% CI [−0.62,-0.20]; $p < 0.001$; $I^2 = 0\%$) were seen with ertugliflozin. Subgroup analysis demonstrated no significant difference in efficacy between the two doses in any of the four outcomes.

Conclusion Ertugliflozin results in significant reductions in HbA1c, body weight, SBP and DBP, when compared to control. Subgroup analyses suggest that these effects are not dose-dependent.

Keywords Sodium-glucose co-transporter 2 inhibitor · Biomarkers · HbA1c · Steglatro

Introduction

Type-2 diabetes (T2D) has a well-known association with obesity and cardiovascular diseases (CVDs). Obesity-related insulin resistance leads to the development of T2D which, together with obesity, serves as a major risk factor for developing CVDs [1]. Furthermore, CVDs contribute to two-thirds of all the T2D-related deaths [2, 3]. Even though T2D and CVDs are closely linked, most traditional anti-glycemic agents do not reduce cardiovascular events [4]. However, newer oral anti-diabetics have shown efficacy in reducing CVDs in the diabetic population. These include dipeptidyl peptidase-4 (DPP-4) inhibitors especially linagliptin, sodium glucose co-transporter (SGLT)-2 inhibitors and glucagon-like peptide (GLP)-1 agonists [5, 6]. These drugs have opened up new horizons for endocrinologists and cardiologists to control the development of CVDs in T2D patients.

SGLT-2 inhibitors such as dapagliflozin, empagliflozin and canagliflozin have shown efficacy in reducing major adverse cardiovascular events (MACE), especially the incidence

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of hospitalization due to heart failure [7–9]. This reduction in cardiovascular events has been attributed to the glucosuria-associated caloric loss and osmotic diuresis which also help lower body weight and blood pressure (BP) [7].

Although canagliflozin, empagliflozin and dapagliflozin have been known to effectively reduce blood pressure and body weight [10, 11], it is unknown whether this is a class effect of SGLT-2 inhibitors [12]. Ertugliflozin, a new and highly selective SGLT-2 inhibitor has proven to be safe and efficacious as a glucose-lowering agent [13]. However, its effects on BP and body weight remain unclear as most trials conducted on the drug are small in size and heterogenous in their methodology. Therefore, we performed a focused systematic review and meta-analysis to evaluate the effect of ertugliflozin on long-term hemoglobin $A1_c$ ($HbA1_c$), body weight and BP by pooling results from all available clinical trials of ertugliflozin. Additionally, we sought to perform a subgroup analysis to assess if the effects of ertugliflozin varied with dosage.

Materials and methods

Protocol This meta-analysis conforms to the PRISMA guidelines [14]. The search, data extraction and quality assessment were conducted independently by two reviewers (MZ and AA), and a third (MSU) was consulted to resolve discrepancies.

Information sources Three electronic databases (Cochrane, MEDLINE, and PubMed) were searched for published randomized clinical trials (RCTs) from their inception to February 2020. Clinicaltrials.gov was searched for any RCTs that had not yet been published but had reported their results online. Similarly, we sought Google Scholar for any abstracts published in the past year, the full-texts of which had not been published yet.

Search strategy The keywords searched were: Ertugliflozin OR Steglatro OR 5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triol OR PF 04971729 OR PF-04971729 OR PF04971729. Both the generic and trade names of ertugliflozin were used for the search. All studies retrieved through this search string were checked for unintentionally missed RCTs in their reference section.

Eligibility criteria and study selection The main outcomes of interest were changes in glycemic levels, body weight and blood pressure. The secondary aim of our study was to assess whether the extent of changes in these parameters was related to the dose of ertugliflozin administered. The inclusion criteria set prior to the search was: (a) Participants: Adult (>18 years) patients with T2D; (b) Study design: Published and unpublished RCTs on ertugliflozin with a minimum follow-up duration of 26 weeks; (c) Compared intervention groups: those receiving ertugliflozin compared with those receiving control or placebo; (d) A change in at least one of the three outcomes assessed; namely $HbA1_c$, body weight and BP. Some of the studies included patient groups receiving background therapy. In these studies, patients were screened before the start of the trial to determine their baseline values. EndNote was used to remove duplicate studies. The remaining articles were manually screened on the basis of title and abstract first, after which the full-text was read to assess relevance. During full-text screening, articles were excluded based on the following criteria: (1) No results reported; (2) None of the desired outcomes were assessed; (3) Different study design, e.g. observational. The detailed Prisma flow chart for the number of articles screened/excluded/included is included in the supplementary file as **Fig. S1**. If more than one source of trial data for the same study population was found, the one with the longer follow-up duration was included.

Risk of Bias assessment The Cochrane Collaboration Risk of Bias tool was used to assess each RCT for the risk for the detection bias, performance bias, selection bias, reporting bias, and attrition bias. Based on these criteria, the methodology of each RCT was categorized as high risk, low risk or unclear risk [15]. Subsequently, the findings were matched and any discrepancies in opinion were resolved by discussion. Trials found to be at high risk of bias were to be excluded from the analysis. The **Supplemental Table 1** shows each component of the risk of bias assessment.

Data collection and analysis All statistical analyses were done using Review Manager V.5.3. The outcomes that were extracted from the selected trials were: (a) $HbA1_c$; (b) Body weight; (c) Systolic Blood Pressure (SBP) and (d) Diastolic Blood Pressure (DBP). The data were presented as mean differences between the two groups and corresponding standard deviations. They were pooled using a random-effects model to derive the weighted mean differences (WMD) and corresponding 95% confidence intervals (CIs). Division of the population was made into two sub-groups based on doses of the drug administered. Higgins I^2 statistics was used to evaluate the heterogeneity across the studies and an I^2 value of 75% or more was considered significant [16]. Two trials, namely eValuation of ERTuliflozin effIcacy and Safety (VERTIS) SU [17] and eValuation of ERTugliflozin effIcacy and Safety (VERTIS) FACTORIAL [18] used active drugs as controls rather than placebo, and thus were excluded during sensitivity analysis to assess any significant changes in the results. Publication bias was assessed using eggers regression test. A p value <0.05 was considered significant for all results.

Results

Figure S1 highlights the detailed literature search. We included a total of 8 RCTs in the final analysis. These RCTs randomized 4702 T2D patients; with 3142 in the intervention group administered with 5 mg (1587) and 15 mg (1555) doses of ertugliflozin, and 1560 in the control group. All articles meeting the inclusion criteria were in English language. Table 1 shows the baseline characteristics of the studies included. No evidence of publication bias was found ($P = 0.67$). **Supplementary Table 1** shows the quality assessment of studies**.** The quality assessment concluded that three RCTs had moderate risk of bias, while the remaining five had low risk of bias. Since no RCTs had a high risk of bias, none were removed from the analysis. The included RCTs were methodologically sound, suggesting that the included studies contributed minimum bias to our pooled findings.

Ertugliflozin was associated with a significant decrease in SBP compared with controls (WMD: −3.64 mmHg, 95% CI [−4.39, −2.90]; $p < 0.001$; $I^2 = 0\%$) (Fig. 1). This effect was significant with both the 5 mg dose (WMD: −3.83 mmHg, 95% CI [−4.76, −2.90]; $p < 0.001$; $I^2 = 0\%$), and 15 mg dose (WMD: −3.31 mmHg, 95% CI [−4.56, −2.06]; $p < 0.001$; $I^2 = 36\%$), however, the difference between these two doses was not significant (p interaction = 0.51) (**Fig. S2**). Similarly, there was a significant decrease in DBP with the use of ertugliflozin (WMD: −1.13 mmHg, 95% CI [−1.67, −0.60]; $p < 0.001$; $I^2 = 0\%$) (Fig. 1). The decrease was significant in both the 5 mg (WMD: −1.22 mmHg, 95% CI [−1.82, −0.62]; $p < 0.001$; $I^2 = 5\%$) and 15 mg (WMD: −0.79 mmHg, 95% CI [−1.97, 0.39]; $p = 0.19$; $I^2 = 76\%$) subgroups. The difference between the doses was however, insignificant (p interaction = 0.52) (**Fig. S3**).

A significant reduction in body weight was seen with the use of ertugliflozin when compared with controls (WMD: −2.35 kg, 95% CI [−2.94, −1.77]; $p < 0.001$; $I^2 = 0\%$) (Fig. 1). This effect was significant in both the 5 mg subgroup (WMD: −2.32 kg, 95% CI [−3.13, −1.51]; $p < 0.001$; $I^2 = 88\%$) and 15 mg subgroup (WMD: −2.39 kg, 95% CI [−3.24, −1.54]; $p < 0.001$; $I^2 = 89\%$) compared with controls. No significant difference between the doses was seen (p interaction = 0.91) (**Fig. S4**). Likewise, a significant decrease in $HbA1_c$ values was also seen in the ertugliflozin arm (WMD: −0.41%, 95% CI [−0.62, −0.20]; $p < 0.001$; $I^2 = 0\%$) (Fig. 1). The decrease was significant following both the 5 mg dose (WMD: −0.37%, 95% CI [−0.70, −0.04]; $p = 0.03$; $I^2 = 93\%$) and 15 mg dose (WMD: −0.44% [−0.72, −0.16]; $p = 0.002$; $I^2 = 91\%$) and no significant difference between the two doses was seen (p interaction = 0.75) (**Fig. S5**). The results of the sensitivity analysis showed consistency with the results of the overall analysis (**Fig. S6**).

Table 1 Baseline characteristics of included studies

Author, year	Ertugliflozin dose (with other OHA if applicable)	Control	(n)	Mean age in years	Study design	$HbA1_c$ in %	Body weight, Kgs ± SD	% of Male sex	Follow-up (weeks)	SBP in mmHg ± SD	DBP in mmHg± SD
Ji, 2019	5 mg; 15 mg	PLA	506	56.5 ± 9.1	Multileft	8.1 ± 0.9	70.3 ± 11.5	55.5	26	ND	ND
Hollander, 2019	5 mg; 15 mg	Glim	1315	58.2 ± 9.6	Multileft	7.8 ± 0.6	86.9 ± 19.6	48.8	52; 104	ND	ND
Dagogo, 2017	5 mg; 15 mg	PLA	464	59.1 ± 9.0	Multileft	8.0 ± 0.9	86.9 ± 19.6	56.9	26; 52	131.3 ± 13.0	78.6 ± 7.4
Aronson, 2017	5 mg; 15 mg	PLA/Met	461	56.4 ± 11.0	Multileft	8.2 ± 1.0	92.9 ± 23	56.6	26; 52	130 ± 13.9	78.5 ± 7.9
Gallo, 2019	5 mg; 15 mg	PLA/Glim	621	56.6 ± 8.8	Multileft	8.12 ± 0.90	84.9 ± 16.9	46.4	26; 52; 104	130.1 ± 13.8	78.0 ± 7.8
Grunberger, 2018	5 mg; 15 mg	PLA	468	67.3 ± 8.6	Multileft	8.2 ± 0.9	88.5 ± 19.8	49.5	26; 52	ND	ND
Miller, 2018	5 mg; 15 mg (each with S100)	PLA	291	55.6 ± 10.0	Multileft	8.9 ± 0.9	92.3 ± 21.3	57.4	26	129.1 ± 13	77.6 ± 7.6
Pratley, 2018	5 mg; 15 mg (each with S100)	SIT (S100)	1233	55.1 ± 10.1	Multileft	8.6 ± 1.0	88.7 ± 21.46	53.9	26; 52	129.2 ± 12.62	ND

OHA, Oral hypoglycemic agents; *(n)*, Total number of participants; *SBP*, Systolic blood pressure; *PLA*, placebo; *Glim*, glimepiride; *Met*, metformin; *SIT*, sitagliptin; *S100*, sitagliptin (100 mg); *SD*, standard deviation; *ND*, not determined

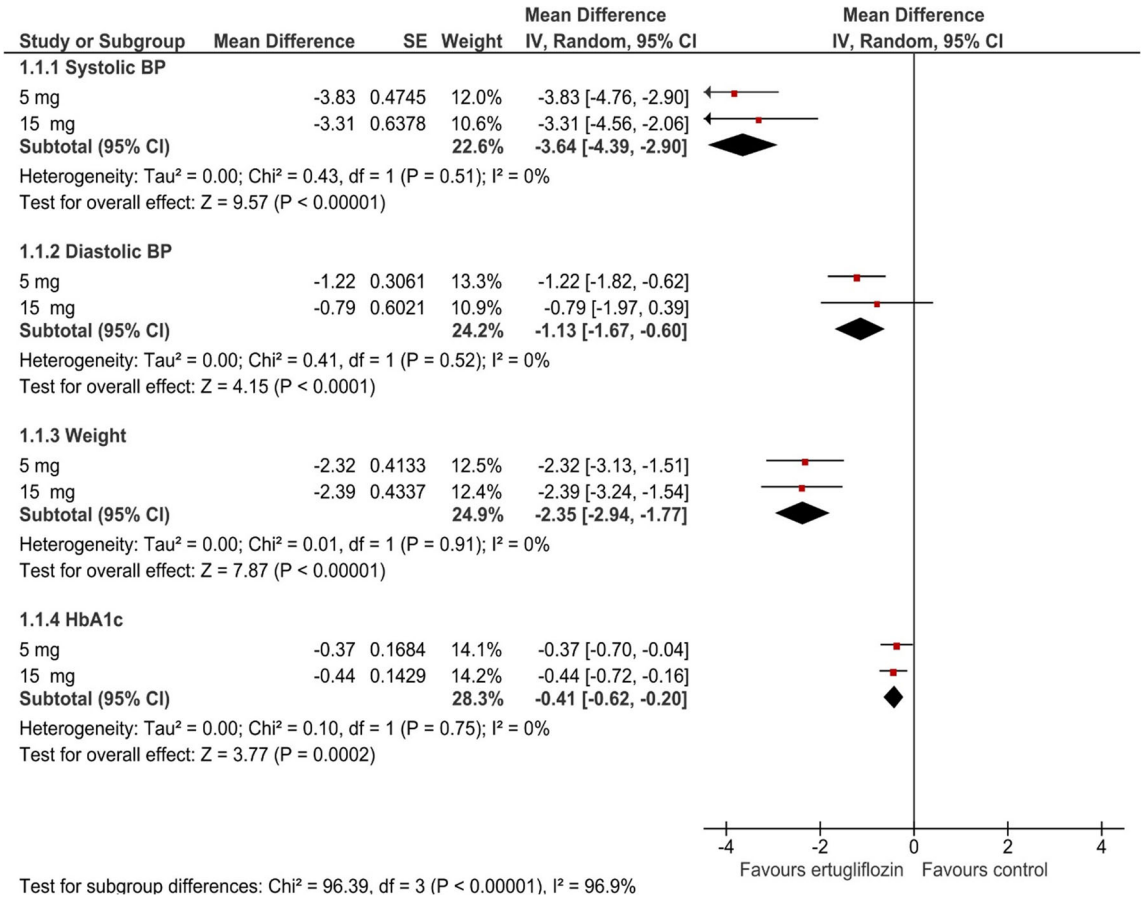

Fig. 1 Forest plot demonstrating the effect of ertugliflozin on body weight, $HbA1_c$ and blood pressure; overall and with each dosing regimen (5 mg vs. 15 mg). SE: standard error; CI: confidence interval; IV: inverse variance

Discussion

This meta-analysis of 4702 T2D patients indicates the efficacy of ertugliflozin in controlling cardiovascular risk factors assessed by the decrease in body weight, $HbA1_c$ and BP. A few SGLT-2 inhibitors have long been known for their effects on these outcomes [19, 20]. In a meta-analysis by Mazidi M, et al. [10], SGLT-2 inhibitors including dapagliflozin, empagliflozin and canagliflozin were shown to be effective in improving HbA1c (pooled estimate: −2.48%), reducing body weight (pooled estimate: −1.88 kg) and managing SBP and DBP (WMD: −2.46 mmHg and − 1.46 mmHg respectively). A recent meta-analysis by Khan MS, et al. [11] reported similar results with canagliflozin; body weight (WMD: -3.32%), SBP (WMD: −4.40 mmHg) and DBP (WMD: −1.68 mmHg). However, these analyses are limited by the inclusion of specific, not all SGLT-2 inhibitors. This is the first systematic review done to gauge the beneficial effects of the newly developed SGLT-2 inhibitor, ertugliflozin. Significant improvement in all the parameters assessed was seen, with no significant difference between the two doses administered showing that ertugliflozin's efficacy is dose-independent and is rather a classic drug effect.

Since the approval for the use of ertugliflozin in the management of T2D [21], a series of trials were conducted to assess its safety and efficacy in different scenarios and help modify guidelines on its use. The purpose was to compare the responses of ertugliflozin both as mono and add-on therapy [17, 18, 22–27].

Ertugliflozin was found to effectively maintain target $HbA1_c$ levels as low as <7.0% [7]. Combining it with sitagliptin augmented this effect and provided better long-term outcomes compared to those achieved by each drug on its own [18]. This hypoglycemic effect is best explained by its well-established glucose-lowering mechanism. Ertugliflozin, being an SGLT-2 inhibitor, inhibits the resorption of glucose in the proximal kidney tubules and increases its excretion in the urine. Since it functions independently of β-cell function and insulin secretion, its efficacy is not influenced by the progressive dysfunction of β-cells seen in T2D and lasts long-term. SGLT-2 inhibitors also have a positive effect on body weight and BP. The caloric loss due to glucosuria and resulting osmotic diuresis help lower body weight and BP [7], which together with its effects on glycemic levels and insulin sensitivity, lower the overall risk of the development of CVDs. This effect on non-glycemic factors was reported in

all VERTIS studies. The use of ertugliflozin caused significant reduction in body weight irrespective of the baseline values as seen from the comparison between VERTIS Asia trial [22] conducted on Asian population having body weight and BMI lower than the western population included in VERTIS MET study [26]. Our meta-analysis found that this effect on body weight is independent of dosage. Similar results with BP modification were seen. The results with these non-glycemic endpoints were also consolidated by the combination therapy of ertugliflozin and sitagliptin which had its effects even in patients inadequately controlled by background metformin [18]. Possible effects of metformin on outcomes with combination therapy were disregarded in VERTIS SITA [27].

In a sensitivity analysis among patients receiving control therapy with other antidiabetics, we excluded VERTIS SU [17] and VERTIS FACTORIAL [18] which compared ertugliflozin (5 mg and 15 mg) with glimepiride and sitagliptin, respectively. It failed to report any significant differences for efficacy outcomes. The possible reason being that the efficacy of ertugliflozin is not limited by the progressive β-cell dysfunction-seen with insulin secretagogues like sitagliptin/glimepiride- because of its direct glucose lowering mechanism.

Strengths and limitations

This well-powered meta-analysis provides early insight as to the benefit of ertugliflozin therapy in T2DM patients with CVDs. Our analysis suggests that using a 15 mg dose (rather than a 5 mg dose) may provide no additional reduction in blood pressure and BMI; however, this result was based on a study-level subgroup analysis, and our study does not replace the need for head-to-head trials comparing doses.

Conclusions

In conclusion, ertugliflozin may be a good alternative to other SGLT-2 inhibitors as it appears to follow the same pattern of efficacy in the improvement of $HbA1_c$, body weight, SBP and DBP in T2D cases [10, 11]. Some individual studies also suggest that ertugliflozin may be more efficacious in reducing HbA1c than dapagliflozin and empagliflozin, further supporting its clinical use [28, 29]. Unlike other drugs in SGLT-2 inhibitor class [30–32], we found no significant difference in outcomes between the two doses administered (5 mg and 15 mg). These findings warrant further research, to explain the lack of a dose-related effect.

Authors' contributions

1. Maryam Zaman: Conception and design; data acquisition, interpretation and analysis; revision and final approval of the manuscript.
2. Roha Saeed Memon: Conception and design; data interpretation and analysis; drafting and final approval of the manuscript.
3. Arooba Amjad: Data interpretation and analysis; revision and final approval of the manuscript.
4. Tehlil Rizwan: Data interpretation and analysis; revision and final approval of the manuscript.
5. Jai Kumar: Data analysis; revision and final approval of the manuscript.
6. Ibtehaj-ul-Haque: Data acquisition; revision and final approval of the manuscript.
7. Syed Saad Ali: Data acquisition; revision and final approval of the manuscript.
8. Lin Li: Data interpretation and analysis; final approval of the manuscript.
9. Muhammad Shariq Usman: Data interpretation and analysis; revision and final approval of the manuscript.

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Data availability All data used for this study is present within the manuscript and supplementary material.

Compliance with ethical standards

Conflict of interest Authors MZ, RSM, AA, TR, JK, IUQ, SSA, LL, MSU declare that they have no conflicts of interest.

Ethical approval No approval from the ethical review board was required as this is an analysis of publicly available data.

Code availability RevMan 5.3.

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