A systematic review and meta-analysis of randomized controlled trials, juxtaposing the control of glycemia and blood pressure between large dose empagliflozin and placebo among type 1 diabetes patients

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ABSTRACT

Objectives: While empagliflozin (25 mg) is used to treat type-2 diabetes mellitus patients with optimum renal functioning, its efficacy and safety in type-1 diabetes mellitus (T1DM) is not yet established. Therefore, this study aimed to compare insulin-treated T1DM patients' (with adequate renal functioning) glycemic and blood pressure control between the 25 mg empagliflozin recipients and placebo recipients.

Methods: Parallel-arm randomized controlled trials comparing the effect of daily administered 25 mg empagliflozin tablets in adjunct to insulin treatment with placebo and insulin treatment in T1DM patients with an estimated glomerular filtration rate of 45 mL/min/1.73 m^2 or more were eligible for inclusion. Trials were searched in PubMed, EMBASE, SCOPUS, and CENTRAL with no restriction on date and language. Risk of bias of trials was assessed and mean and standard deviation of glycated hemoglobin (HbA1c, in %), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg) at the end of the trial period were collected, and random-effects meta-analysis was done to estimate the weighted mean difference (WMD). The meta-analysis was done in Stata statistical software. This study was conducted in June 2019.

Results: Three relatively small-sized trials published between 2015 and 2018 were eligible for review and analyses. The trials suffered from unclear risk of performance and detection bias. The HbA1c reduction favored the intervention group (WMD = −0.478, 95% confidence intervals = −0.766–−0.189, $P = 0.001$; I^2 = 0%). The WMD of blood pressure (systolic and diastolic) did not vary between the treatment groups.

Conclusion: Evidence (of moderate quality) suggests that daily administration of empagliflozin 25 mg tablets in adjunct to insulin in T1DM patients with optimum kidney functioning is useful to achieve glycemic control compared to placebo and insulin therapy. However, the effect on blood pressure remained indistinguishable between the compared interventions.

Keywords: Blood glucose, blood pressure, empagliflozin, diabetes mellitus, sodium-glucose transporter 2 inhibitors, type 1

Introduction

Empagliflozin is a sodium-glucose cotransporter (SGLT)-2 inhibitor that decreases the glucose levels in the blood by excreting it through the kidneys.[1] Examples of other SGLT-2 inhibitors are dapagliflozin and canagliflozin.[2]

SGLT-2 (expressed in the S1 segment of the proximal renal tubule) is responsible for almost 90% of the glucose reabsorption by the kidney.[1] SGLT-2 inhibitors were primarily developed for type-2 diabetes mellitus (T2DM) patients and were found to be effective in decreasing glycated hemoglobin (HbA1c, for glycemic control it is regarded as the gold standard test).[1,3-6] These drugs are contemporarily being tested for safety and efficacy in type-1 diabetes mellitus (T1DM) patients in various clinical trials.

The rationale for researching new insulin adjunct therapies like SGLT inhibitors in T1DM patients is presented here. The destruction of insulin-producing beta cells in the pancreas and its

consequent cessation of insulin production causes hyperglycemia in T1DM patients.[7,8] Hyperglycemia plays a chief role in the diabetic complications experienced by these patients.[9] Therefore, T1DM patients depend on the exogenous source of insulin throughout their lifetime.[7,8,10] However, exclusive insulin only treatment does not suit every T1DM patients as it does not mimic endogenous insulin precisely and increases the risk of hypo- or hyperglycemia.[1,11] Besides, its isolated use does not always achieve the optimum glycemic control and might increase the risk of several complications on long-term use.[12,13] Alongside that, the need for multiple daily injections to administer insulin along with the several needle pricks required every day to self-monitor the blood glucose levels can compromise the quality of life of these patients.[13,14] In this background, to decrease the insulin dosage requirement in T1DM patients to reduce its – unwanted consequences and frequency of insulin injection (and the associated need for finger pricking to monitor own blood glucose levels), the research on SGLT inhibitors (like empagliflozin) as possible insulin adjunct therapy is invaluable.

While insulin adjuncts are believed to be helpful in T1DM patients to achieve better glycemic control, there is little evidence in this regard to support it.[12] Therefore, insulin-independent therapy[11] like SGLT inhibitors need to be researched for its suitability in glycemic control among T1DM patients. Finding from the existing double-blinded placebo-controlled trials on SGLT inhibitors such as dapagliflozin and sotagliflozin are promising in this regard as they depict a significant reduction in HbA1c level, total insulin requirement, and body weight.[15,16] These findings are perhaps generalizable as the trials that studied these outcomes were based on relatively large sample size (>800 participants each) with enough statistical power.[15,16] In contrast, the existing prospective double-blind randomized controlled trials[17-19] and single arm trials[9,20,21] that primarily tested the effectiveness of empagliflozin on T1DM patients was based on a fewer number of participants ($n < 80$). Such a small sample size decreases the statistical power and also reduces the chance of generalizability of any nominally significant statistical finding.[22] Therefore, to increase the statistical power of individual trials on empagliflozin (by decreasing the standard error of the weighted average effect size), its important to summarize the findings by meta-analysis,[23] as we have attempted in this paper. This study, thenceforth, explores the role of empagliflozin 25 mg tablets in reducing HbA1c and blood pressure in insulin-treated T1DM patients.

The Intervention

Empagliflozin was approved by the US Food and Drug Administration (FDA) in August 2014 for treating T2DM patients.[2,8] Compared to placebo, in T2DM patients, single dosing of empagliflozin 25 mg tablet increases the total glucose excretion in urine by 18-fold.[2] Whereas, this increase is relatively less with some of the other dosages of empagliflozin (e.g., 11 and 14 folds increase in total glucose excretion in urine for 10 mg and 100 mg dosages of empagliflozin,

respectively).[2] In clinical trials on T2DM patients, 25 mg or 10 mg empagliflozin proved more beneficial in improving HbA1c levels and controlling blood pressure than placebo.[24,25] In T2DM, the FDA recommends daily early morning dosing of empagliflozin with a maximum dosage of 25 mg.[26] These properties of empagliflozin 25 mg in T2DM patients prompted us to investigate its effectiveness in T1DM patients.

However, due to the lack of adequate evidence on efficacy and safety, presently, the FDA does not approve the use of empagliflozin in T1DM patients.[27,28] Early open-label proof of concept trials testing empagliflozin's effect on T1DM patients suggests that the daily administration of 25 mg empagliflozin reduces – the HbA1c, glycemic variability, fasting glucose, and daily insulin dosage requirement.[20,21] Other studies that tested empagliflozin 25 mg on T1DM patients found its role in decreasing arterial stiffness, suggesting its possible future implication in decreasing the risk of cardiovascular complications.[17,29] Compared to the placebo recipients, a randomized double-blinded trial over 28 days found a statistically significant reduction in HbA1c and the weekly average insulin requirement among the 25 mg empagliflozin recipients.[18]

What this review adds?

This review adds the most recent evidence on the role of empagliflozin (25 mg) in adjunct to insulin on glycemic and blood pressure control in T1DM patients. Yamada et al. recently conducted a meta-analysis on the efficacy and safety of SGLT2 inhibitor therapy with placebo or other antidiabetic medication in T1DM patients.[11] However, in their study, the data primarily sourced from trials testing drugs other than empagliflozin (only one trial tested empagliflozin) such as sotagliflozin, dapagliflozin, and canagliflozin. Therefore, in comparison to their study, this study informs specifically about empagliflozin (of a particular dosage, i.e., 25 mg) in T1DM patients with an optimum estimated glomerular filtration rate (eGFR) (i.e., 45 mL/min/1.73 m² or more) and includes a more recent search of the literature (until June 2019). This study aims to synthesize the existing evidence about the achievable glycemic and blood pressure control in insulin-treated T1DM patients (with optimal kidney functioning) by comparing these between 25 mg empagliflozin tablet recipients and those treated with placebo.

Methods

Design of the study

This systematic review and meta-analysis adhere to the PRISMA[30] reporting guideline. A pre-published protocol is unavailable for this review.

Inclusion and exclusion criteria

Treatment population
Eighteen years or older T1DM patients on insulin therapy were eligible for recruitment. The study participants should

have eGFR 45 mL/min/1.73 m^2 or more. The eGFR cutoff was set because an optimum renal functioning is desirable before starting patients on empagliflozin tablet (empagliflozin is not recommended in those with eGFR <45 mL/min/1.73 m^2).[26] We accepted the diagnosis of T1DM as made by the trialists. Trials on T2DM patients and gestational diabetes patients were excluded from the study.

Intervention and treatment groups

Trials were eligible for inclusion when they compared the following treatments in T1DM patients – daily 25 mg empagliflozin tablet in adjunct to insulin therapy versus placebo and insulin therapy. Insulin dosages, regimen, and route of administration were accepted as per the trialists.

Study design

We included parallel-arm randomized controlled trials (RCT) only.

Outcome

Our outcomes of interests were HbA1c (in %), systolic blood pressure (SBP; in mmHg), and diastolic blood pressure (DBP; in mmHg) in both treatment groups at the end of the trial period.

Studies were excluded from this review if they had a study design other than that mentioned above (such as observational study or cross-over study or single-arm trial) and if the participants received any other diabetes diagnosis besides T1DM (e.g. T2DM, and gestational diabetes). In addition, unpublished literature such as conference abstracts was not included in the study.

Information sources

We searched for trials in the following databases – PubMed, EMBASE, SCOPUS, and CENTRAL. Our search was not restricted to any date or language. The last date of our search was June 7, 2019. In addition, we searched for trials in the reference section of the articles we read the full text.

Search

We used the following search terms for searching title and abstracts of the following databases – Empagliflozin AND type 1 OR type-1 OR "type 1" AND Diabetes AND trial. We used the filter "clinical trial" instead of the word "trial" for databases like PubMed, where such a filter was available. Additional search terms "insulin-dependent diabetes mellitus," "SGLT," "SGLT," and "SGLT2-inhibitors" were used to conduct supplementary searches in internet search engines.

Study selection

Using the PRISMA flow diagram,[30] we selected the trials. We skimmed through the title and abstract of the papers produced by the database search and shortlisted papers that seemed to match our eligibility criteria or when a decision about inclusion or exclusion of a trial was not possible by reading the title and abstract alone.

Data collection process

For data collection, we used a pre-piloted form constructed for the purpose. The first author performed the data collection initially and the second author cross-checked it for accuracy.

The first author independently collected the data using a pre-piloted form. These were successively checked by the coauthor for accuracy (data were not collected in duplicate by the coauthor). We contacted the authors of the reviewed trials for data that were not clearly evident by reading their publications.

Data items

We primarily collected the following data – study description (first author's last name, year of publication and country where the trial was conducted), population, intervention, comparison groups, outcomes, study design, baseline demographic information, and miscellaneous information about participant consent, ethical clearance, and trial registration number.

Risk of bias in individual studies

We assessed the risk of bias of the trials using the tool depicted for this purpose in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011).[31] We checked trials for bias in the following domains – selection bias, performance bias, attrition bias, reporting bias, and miscellaneous sources of bias.[31] Selection bias was assessed in two ways. First, by determining if an appropriate randomization method was used to generate a random sequence. Second, by determining if the allocation of the participants to different intervention groups was concealed from researchers and participants appropriately (e.g., using sequentially enumerated, opaque, and sealed envelopes). The evaluation of performance bias depended on how the trial personnel and participants remained blinded to the intervention received by each of the treatment groups during the trial. The blinding information of the outcome assessor to the intervention received by the participants was used to assess the detection bias. The judgment of the attrition bias was contingent on the missingness of the outcome data. The reporting bias was evaluated based on whether the results were reported selectively for significant outcomes only or for all outcomes as per the pre-stated intentions expressed by the trialists. Any other type of bias, besides the above, was used to determine the miscellaneous bias. The questions of bias under each of these domains were answered as either low risk of bias, high risk of bias, or unclear risk of bias (when it did not fit either low or high risk of bias).[31]

While assessing the risk of bias when our opinion did not match, we resolved the issue by discussion. In addition, we used Review Manager (RevMan) software to represent the risk

of bias diagrammatically by constructing a risk of bias graph and risk of bias summary.[31,32]

Summary measures

We pooled data only from trials that do not have a high risk of bias. We determined the mean differences of HbA1c, SBP, and DBP between the treatment groups at follow-up (at the end of the trial period). We primarily contacted the authors for standard deviations (SD) of the means at follow-up when it was not directly reported in the paper or a standard error was not available for conversion to SD. In case of non-response from the trialists, we substituted the baseline SD as the follow-up SD.[31]

Meta-analysis

We used random-effect (RE) model meta-analysis as the study population was diverse in origin and was conducted by trialists in different nations independently (which would unlikely make the study population functionally equivalent).[33] We combined the mean differences between the treatment groups by determining the weighted mean differences (WMD) for HbA1c (in %), SBP (in mmHg), and DBP (in mmHg) since

these outcomes were measured in same units across all trials. We reported the summary estimates along with their p-values and 95% confidence intervals (CI). We used Cochrane's Q (along with its P-value) and I^2 statistics to report the heterogeneity across the trials. We designated heterogeneity as low, moderate, and high based on I^2 values of 25%, 50%, and 75% respectively.[34] For a visual overview of the summary effects, we included forest plots with our results. $P < 0.05$ was used to determine statistical significance. All analyses were done using Stata statistical software (StataCorp, College Station, Texas, USA).

Risk of bias across studies and additional analysis

We assessed publication bias visually using funnel plots and contour enhanced funnel plots, and statistically using Egger's test. Moreover, for the RE models, we also determined the predictive intervals for future studies. Finally, we did a sensitivity analysis for all outcomes using a fixed-effect (FE) model meta-analysis. To do so, we assumed that all of the included trials were functionally identical, and our goal was to determine the common effect size for the trial population only (rather than looking for external validity).[33]
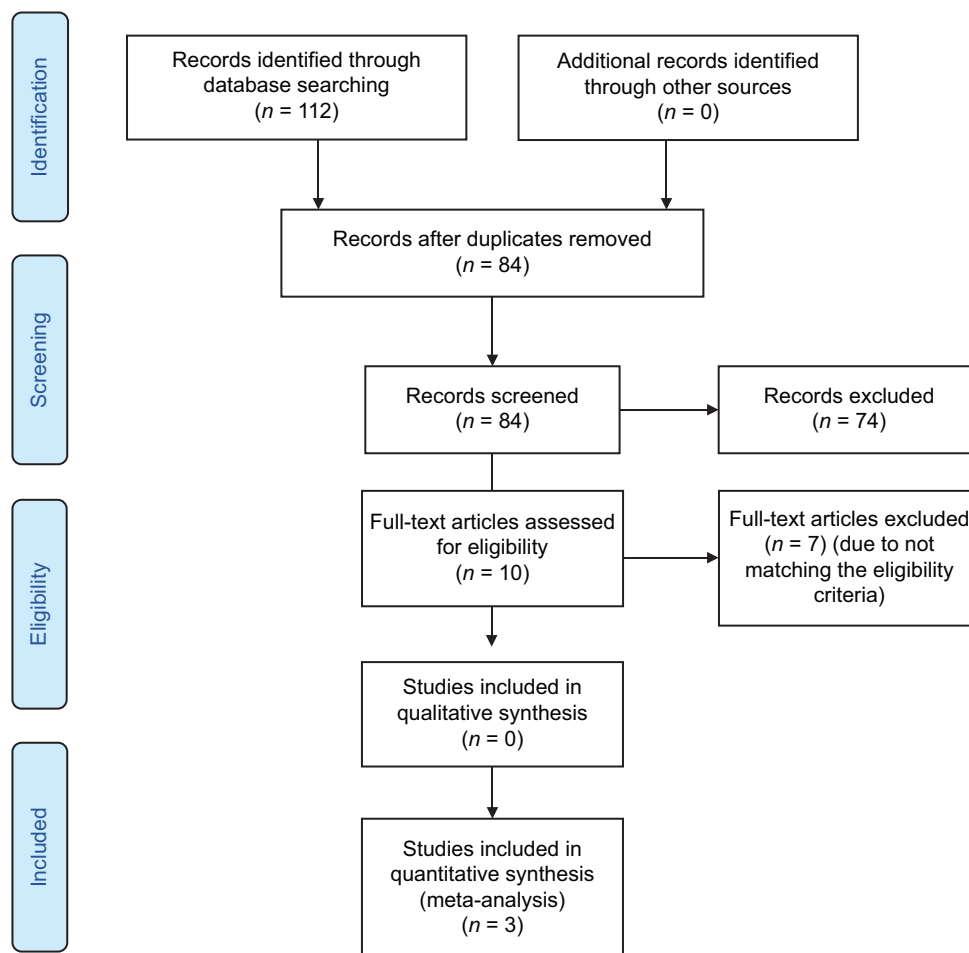

Figure 1: PRISMA 2009 flow diagram (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal. pmed1000097)

Results

Study selection

The database search yielded 112 search results (71 Scopus, 26 CENTRAL, nine PubMed, and six EMBASE). After excluding the duplicate papers, we read the title and abstracts of 84 articles and subsequently shortlisted ten papers for full-text review. Finally, only three trials, matching the eligibility criteria of our study, were included for systematic review and meta-analyses [Figure 1].

Study characteristics

The eligible trials were published between 2015 and 2018 and were conducted in the following nations – Slovenia, Austria, Germany, and Japan (18–20). The salient features of the trials are tabulated in Table 1.

Population

The total number of participants enrolled for randomization was 163.[17-19] The mean age of participants in the empagliflozin group and placebo group was between 41–47 years and

Table 1: Summary table for included trials

Study	Components	Features
Shimada *et al.*, 2018, Japan[19]	Study design	Trial description: Parallel-group, randomized, multicentric, phase 2 trial Country where the trial was conducted: Japan Ethical clearance: Obtained Participant consent: Obtained Funding information: Provided Clinical trial registration: NCT02702011

	Population	Number of participants: 48 (47 completed the 4 weeks trial)
		Empagliflozin 25 mg arm: *n*=12
		Empagliflozin 10 mg arm: *n*=12
		Empagliflozin 2.5 mg arm: *n*=13
		Placebo arm: *n*=11
		Baseline features of Empagliflozin group:
		  Mean (SD) age: 46.6 (10.8)
		  Mean (SD) duration (years) since T1DM: 20.8 (13.5)
		  Daily mean (SD) basal insulin dose (U/kg): 0.27 (0.09)
		  Daily mean (SD) bolus insulin dose (U/kg): 0.39 (0.13)
		  Mean (SD) HbA1c in %: 7.89 (0.91)
		  Mean (SD) eGFR in mL/min/1.73 m^2: 88.8 (14.1)
		  Mean (SD) FPG in mg/dL: 147.8 (79.2)
		  Mean (SD) UGE in g/24 h: 14.9 (14.5)
		Baseline features of placebo group:
		  Mean (SD) age: 43.9 (11.7)
		  Mean (SD) duration (years) since T1DM: 14.8 (10.0)
		  Daily mean (SD) basal insulin dose (U/kg): 0.30 (0.17)
		  Daily mean (SD) bolus insulin dose (U/kg): 0.40 (0.20)
		  Mean (SD) HbA1c in %: 8.23 (0.47)
		  Mean (SD) eGFR in mL/min/1.73 m^2: 95.1 (16.5)
		  Mean (SD) FPG in mg/dL: 194.0 (55.8)
		  Mean (SD) UGE in g/24 h: 15.2 (13.3)
		Inclusion criteria: T1DM patients aged 20–65 years on multiple insulin injections per day, HbA1c 7.5–10%, fasting C-peptide<0.6 ng/ml with BMI 18.5–35 kg/m^2, eGFR 60–150 ml/min/1.73 m^2, who were able to manage their blood glucose monitoring, carbohydrate counting, and insulin dosages
		Exclusion criteria: Maturity-onset diabetes of young, T2DM, history of - chronic pancreatitis or pancreatic surgery, acute coronary syndrome, stroke, transient ischemic attack, liver disease, severe hypoglycemia, treatment with antihyperglycemic medication other than insulin or anti-obesity drugs causing unstable body with 3 months before screening, DKA with in past 3 months of screening or between screening and randomization

	Intervention	Empagliflozin group: 25 mg empagliflozin orally daily in the morning along with insulin treatment Placebo group: Daily placebo drug daily in the morning along with insulin treatment Intervention duration: 4 weeks
	Outcome of interest	On day 28, the decrease (−0.20%; 95% confidence intervals: −0.49% to 0.08%; *P*=0.1620) in HbA1c in the 25 mg empagliflozin receiving group was not statistically significantly different from the placebo group. Small reduction in SBP and DBP was noted in the 10 mg empagliflozin group
Pieber *et al.*, 2015, Austria and Germany[18]	Study design	Randomized, multicentric, double-blind, placebo-controlled, parallel group, phase 2 trial Country where the trial was conducted: One center at Germany and one in Austria Ethical clearance: Obtained Participant consent: Obtained Funding information: Provided Clinical trial registration: NCT01969747

(Contd...)

Table 1: (*Continued*)

Study	Components	Features

	Population	Number of participants: n=75
		Empagliflozin 25 mg arm: n=18
		Empagliflozin 10 mg arm: n=19
		Empagliflozin 2.5 mg arm: n=19
		Placebo arm: n=19
		Baseline features of Empagliflozin group
		   Mean (SD) age: 41.9 (9.7) years
		   Mean (SD) duration (years) of T1DM: 23.7 (14.5)
		   Daily mean (SD) basal insulin dose (U/kg): 0.32 (0.13)
		   Daily mean (SD) bolus insulin dose (U/kg): 0.33 (0.14)
		   Mean (SD) HbA1c in %: 8.15 (0.54)
		   Mean (SD) eGFR in mL/min/1.73 m^2: 99.0 (13.9)
		   Mean (SD) FPG in mg/dL: 9.8 (2.8)
		   Mean (SD) UGE in g/24 h: 13.4 (11.2)
		Baseline features of placebo group
		   Mean (SD) age: 40.5 (10.6) years
		   Mean (SD) duration (years) since T1DM: 20.5 (12.8)
		   Daily mean (SD) basal insulin dose (U/kg): 0.33 (0.12)
		   Daily mean (SD) bolus insulin dose (U/kg): 0.33 (0.16)
		   Mean (SD) HbA1c in %: 8.18 (0.67)
		   Mean (SD) eGFR in mL/min/1.73 m^2: 101.4 (14.5)
		   Mean (SD) FPG in mg/dL: 9.2 (3.7)
		   Mean (SD) UGE in g/24 h: 20.3 (17.4)
		Inclusion criteria: T1DM patients aged between 18 and 65 years, BMI between 18.5 and 35 kg/m^2, HbA1c between 7.5 and 10.5%, eGFR between 60 and 150 ml/min/1.73 m^2, C-peptide<1.5 ng/ml, on multiple insulin injections (bolus and basal) per day for 12 months or more, overall daily insulin needs 1.5 U/kg or less, stable insulin administration for 12 weeks or more
		Exclusion criteria: Sudden onset symptomatic UTI or infection of genitals, long-term or recurrent (thrice or more per year) cystitis, hypoglycemia needing emergency treatment or inpatient care in the previous 3 months before screening, two or more hypoglycemic episodes in 3 months before screening, no awareness about hypoglycemia (based on researcher's acumen), DKA requiring emergency treatment or hospitalization within previous 12 months before screening, Brittle diabetes (based on researcher's acumen), high level of alanine transaminase, aspartate transaminase or alkaline phosphatase at screening, bodyweight fluctuation in previous 3 months of screening due to surgery, aggressive diet or drugs to curb obesity, intake of any research drug in past 30 days of taking the trial drug

	Intervention	Empagliflozin group: Received 25mg empagliflozin for 28 days in addition to insulin Placebo group: Placebo for 28 days in addition to insulin In addition, all patients received diet and exercise counseling and SMBG recommendations Intervention duration: 4 weeks
	Outcome of interest	On day 28, the decrease (−0.49%; 95% confidence intervals: −0.75% to−0.22%; P<0.001) in HbA1c in the 25 mg empagliflozin receiving group was statistically significantly different from the placebo group SBP and DBP change from baseline on day 28 was not statistically significantly different between the compared intervention groups of interest
Lunder *et al.*, 2018, Slovenia[17]	Study design	Trial description: Prospective, single centered, double-blinded randomized controlled trials Country where the trial was conducted: Slovenia Ethical clearance: Obtained Participant consent: Obtained Funding information: Provided Clinical trial registration: NCT03639545

	Population	Number of participants: n=40
		Empagliflozin 25 mg arm: n=10
		Empagliflozin 25 mg/metformin 2000 mg arm: n=10
		Metformin 2000 mg arm: n=10
		Placebo arm: n=10
		Baseline features of Empagliflozin group
		   Mean (SE) age: 46.0 (2.3) years
		   Mean (SE) duration (years) since T1DM: 22.5 (3.7)
		   Daily mean (SD) basal insulin dose (U/kg): NA
		   Daily mean (SD) bolus insulin dose (U/kg): NA
		   Mean (SE) HbA1c in %: 7.8
		   Mean (SD) eGFR in mL/min/1.73 m^2: NA
		   Mean (SD) FPG in mg/dL: NA
		   Mean (SD) UGE in g/24 h: NA
		Baseline features of placebo group
		   Mean (SE) age: 43.1 (2.1) years
		   Mean (SE) duration (years) since T1DM: 22.2 (3.8)

(*Contd...*)

Table 1: (*Continued*)

Study	Components	Features
	Population	Daily mean (SD) basal insulin dose (U/kg): NA Daily mean (SD) bolus insulin dose (U/kg): NA Mean (SE) HbA1c in %: 7.8 Mean (SD) eGFR in mL/min/1.73 m²: NA Mean (SD) FPG in mg/dL: NA Mean (SD) UGE in g/24 h: NA Inclusion criteria: T1DM patients age between 30 and 65 years Exclusion criteria: Advanced heart disease, eGFR<60 ml/min/1.73 m², liver failure, benign prostate hyperplasia, prostate cancer, frequent UTI, BMI<23 kg/m²
	Intervention	Empagliflozin group: Daily 25 mg empagliflozin with insulin (either as intensive therapy or insulin pump therapy) Comparison group: Placebo with insulin (either as intensive therapy or insulin pump therapy) Intervention duration: 12 weeks
	Outcome of interest	After 12 weeks of intervention, the authors reported the within-group comparison of HbA1c, SBP, and DBP; however, none of these outcomes were statistically significantly different for any of the intervention groups of interest. In the empagliflozin 25 mg group and the placebo group, the HbA1c dropped by 0.4% and 0.1%, respectively

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, HbA1c: Glycated hemoglobin, eGFR: Estimated glomerular filtration rate, NA: Not available, T1DM: Type-1 diabetes mellitus, DKA: Diabetic ketoacidosis

40–44 years, respectively.[17-19] Among the intervention groups, the average duration of T1DM varied between 15 and 24 years.[17-19] In one trial, participants in the treatment groups were only males.[17]

Intervention

The duration of the trials was 4 weeks in two trials[18,19] and 12 weeks in one.[17] The treatment group across all trials received 25 mg empagliflozin tablet every day in adjunct to insulin treatment, whereas, the placebo group received a placebo along with insulin therapy.[17-19]

Design

The trial from Slovenia[17] was single centered, whereas, the other two[18,19] were multicentric. All trials were a parallel arm, randomized placebo-controlled trials.[17-19]

Outcomes

At the end of the trial period, all RCTs reported the mean HbA1c (in %), SBP (in mmHg), and DBP (in mmHg).

Risk of bias within studies

In two of the trials,[17,19] the risk of selection bias was unclear due to the lack of clear mention of the procedure of randomization[17] and how participant allocation was concealed from the researchers.[17,19] While the risk of performance bias and detection bias was unclear across all trials (due no apparent mention of how the participants, the interventionists, and the outcome assessors were blinded), the risk of attrition bias and reporting bias was low in all of the trials.[17-19] The risk of bias assessment is detailed in Table 2 and pictorially represented in Figures 2 and 3.

Results of individual studies

After 4 weeks trial period, Shimada *et al*.[19] found no statistically significant difference between adjusted mean change between empagliflozin 25 mg (and insulin) treated
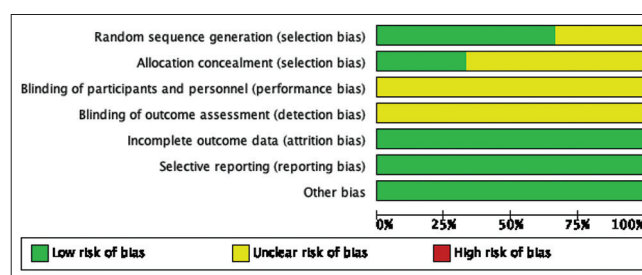

Figure 2: Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies

group and placebo (and insulin) treated group ($P = 0.1620$). In contrast, this difference was significantly different in Pieber *et al*.[18] study ($p < 0.001$). Pre-post within-group change in HbA1c was not statistically significant different between the intervention groups of interest in Lunder *et al*. study.[17] Minimal changes in SBP and DBP were observed through all trials at the endpoint.[17-19] The follow-up values for the outcome of interest are tabulated in Table 3. In two trials, we substituted the baseline SD as follow-up SD, as we could not obtain the latter from the trialists.[18,19] For Lunder *et al*. study, we calculated the follow-up SD for the treatment groups from the follow-up SE using the methodology mentioned Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011).[31]

Findings of Meta-analysis

Here, we mention the results of meta-analyses using the RE model (Figures 4-6, top-left diagrams). Glycemic control favored daily empagliflozin 25 mg tablet consuming group in adjunct to insulin (WMD = -0.478, 95% CI = -0.766–-0.189, $P = 0.001$; $I^2 = 0\%$, Cochrane's Q = 0.40, P-value of Cochrane's Q = 0.818). SBP (WMD = -0.843, 95% CI = -6.465–4.780, $P = 0.769$; $I^2 = 0\%$, Cochrane's Q = 0.05, P-value of Cochrane's Q = 0.975), and DBP (WMD = -0.831, 95% CI = -7.148–5.486, $P = 0.797$; $I^2 = 58.2\%$, Cochrane's

Table 2: Risk of bias assessment

Study*	Domain	Author's judgment	Support for judgment
Lunder et al., 2018[17]	Random sequence generation (selection bias)	Unclear	Quote: "The patients were equally randomized into three treatment groups that received the treatment in addition to insulin." Author's comment: Not clear how the random component of the sequence generation was accomplished
	Allocation concealment (selection bias)	Unclear	Author's comment: No clear mention of how the participant allocation to different groups was blinded from the researchers and participants
	Blinding of participants and personnel (performance bias) Outcome: HbA1c, SBP, DBP	Unclear	Quote: "In this 12-week, prospective, double-blind randomized clinical study ………" Author's comment: Not clear how participants and personnel were blinded about the measured outcomes
	Blinding of outcome assessment (detection bias) Outcome: HbA1c, SBP, DBP	Unclear	Quote: "Glycated hemoglobin (HbA1c) was assessed using the VITRO 5.1FS chemistry system ………" Author's comment: It is unclear how the outcome assessors were blinded about the measured outcomes
	Incomplete outcome data (attrition bias)	Low	Author's comment: Outcome data of interest were reported for all those randomized into the treatment and placebo group.
	Selective reporting (reporting bias)	Low	Author's comment: The authors mentioned outcome data of interest for both treatment groups.
	Other bias	Low	Author's comment: The study seems to be free from other sources of bias
Pieber et al. 2015[18]	Random sequence generation (selection bias)	Low	Quote: "Randomization was undertaken using a third-party interactive voice and web response system and was stratified by site." Author's comment: The random sequence generation process likely to be unbiased due to the use of advanced technology (third-party interactive voice and web response system).
	Allocation concealment (selection bias)	Low	Quote: "Randomization was undertaken using a third-party interactive voice and web response system and was stratified by site" Author's comment: Involvement of a third party to randomize likely decreased the risk of allocation concealment bias.
	Blinding of participants and personnel (performance bias)	Unclear	Author's comment: It is not clear how participants, personnel, and outcome assessors were blinded
	Blinding of outcome assessment (detection bias)	Unclear	
	Incomplete outcome data (attrition bias)	Low risk	Quote: "No patients prematurely discontinued from the study."
	Selective reporting (reporting bias)	Low risk	Author's comment: Outcome of interest were mostly reported
	Other bias	Low risk	Author's comment: The study seems to be free from other sources of bias
Shimada et al., 2018[19]	Random sequence generation (selection bias)	Low risk	Quote: "Randomization followed a permuted block design and was used by a pseudo-random number generator and supplied seed number." Author's comment: The use of pseudo-random number generators is likely to decrease bias related to random sequence generation.
	Allocation concealment (selection bias)	Unclear risk	Quote: "Participants, investigators, and study personnel remained blinded to the randomized treatment assignments until database lock." Author's comment: Although the trialists mention that participants, investigators, and study personnel were kept blinded until the end of the trial, it does not clearly state the mechanism used to achieve it.
	Blinding of participants and personnel (performance bias)	Unclear risk	
	Blinding of outcome assessment (detection bias)	Unclear risk	
	Incomplete outcome data (attrition bias)	Low risk	Author's comment: All participants randomized to 25 mg empagliflozin group and placebo followed until the end of the trial period
	Selective reporting (reporting bias)	Low risk	Author's comment: Authors mostly reported the outcomes of interest
	Other bias	Low risk	Author's comment: The study seems to be free from other sources of bias

*first author's last name, year

Q = 4.78, *P*-value of Cochrane's Q = 0.091) measurements did not differ between the intervention groups at follow-up. We observed moderate heterogeneity only for the summary estimates of DBP.

Risk of bias across studies

For publication bias, we constructed funnel and contour enhanced funnel plots that suggested some asymmetry visually (Figures 4-6, bottom left and bottom right diagrams).

Nevertheless, on using Egger's regression test, no statistically significant symmetry was detected for HbA1c ($P = 0.596$), SBP ($P = 0.733$), or DBP ($P = 0.894$). However, we could not rule out publication bias with certainty as the number of trials available was too few.

Additional analysis

We did sensitivity analysis using FE model for all meta-analyses; however, the findings did not change (Figures 4-6, top-right diagrams). For HbA1c, the predictive interval (−2.35–1.39) (Figure 4, top-right diagram) crossed the line of null effect suggesting that in a future study, the placebo with insulin therapy may prove more effective than empagliflozin 25 mg in adjunct to insulin.

Discussion

Summary of evidence

We found three eligible trials (out of the 112 database search results) conducted in Slovenia, Austria, Germany, and Japan between 2015 and 2018. In total, the trials randomized 163 participants into different treatment groups. Across all trials, the risk of detection bias and performance bias was unclear, and the risk of attrition bias and reporting bias was low. Compared to the comparison group, the intervention group favored glycemic control both in RE and FE model meta-analyses. This finding was not affected by heterogeneity, and the risk of publication bias was relatively low. The follow-up SBP and DBP did not differ due to the different modes of treatment.

Quality of evidence

We used the GRADE approach (by GRADE Working Group (2004)[35] to grade the evidence for HbA1c. We downgraded the trials by one level and graded as moderate quality

Figure 3: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study

Table 3: Simple summary of data at follow-up for HbA1c, SBP, and DBP

Outcome: HbA1c						
Study (first author's last name, year)	Empagliflozin (25mg) group			Placebo group		
	Sample size (n)	Mean (in %)	SD (in %)	Sample size (n)	Mean (in %)	SD (in %)
Lunder, 2018	10	7.4	0.32*	10	7.7	0.95*
Pieber, 2015	18	7.48	0.54#	19	8	0.67#
Shimada, 2018	12	7.48	0.91#	11	8.02	0.47#
Outcome: Systolic blood pressure						
Study (first author's last name, year)	Empagliflozin (25 mg) group			Placebo group		
	Sample size (n)	Mean (mmHg)	SD (mmHg)	Sample size (n)	Mean (mmHg)	SD (mmHg)
Lunder, 2018	10	127.2	9.17*	10	127.4	9.17*
Pieber, 2015	18	125.6	13.4#	19	127.2	15.4#
Shimada, 2018	12	119.2	18.2#	11	120.3	18#
Outcome: Diastolic blood pressure						
Study (first author's last name, year)	Empagliflozin (25 mg) group			Placebo group		
	Sample size (n)	Mean (mmHg)	SD (mmHg)	Sample size (n)	Mean (mmHg)	SD (mmHg)
Lunder, 2018	10	81.9	7.59*	10	77	7.59*
Pieber, 2015	18	74.4	7.8#	19	79	9.4#
Shimada, 2018	12	71.3	13.6#	11	74.2	9.7#

*calculated using the follow-up standard error of mean. #baseline SD substituted. DBP: Diastolic blood pressure, SBP: Systolic blood pressure, HbA1c: Glycated hemoglobin
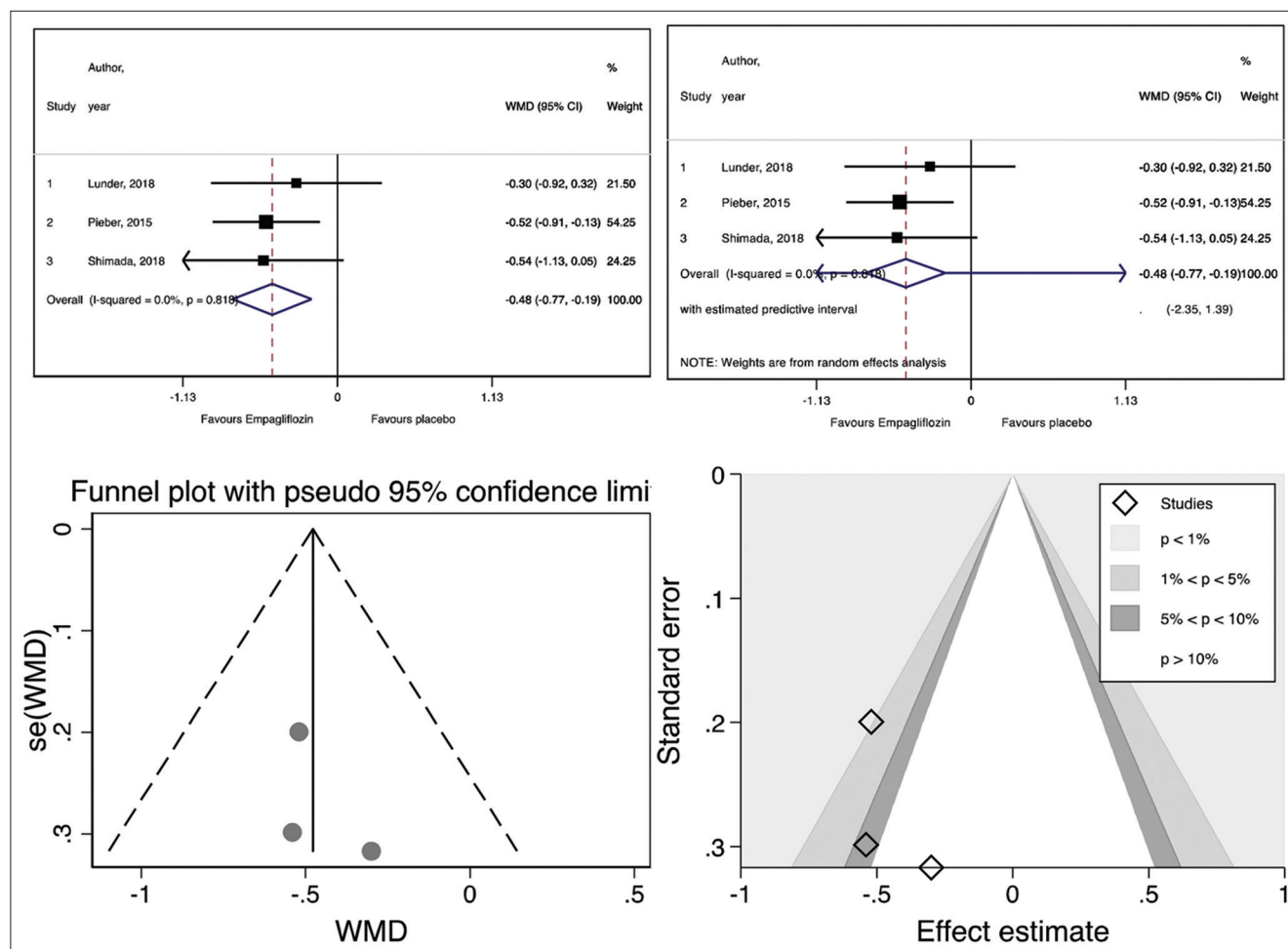
Figure 4: Forest plot of comparison (top-left: Fixed-effect model, top-right: Random effect model): 25 mg empagliflozin in adjunct to insulin versus placebo with insulin, outcome: Glycated hemoglobin (HbA1c). Bottom-left: Funnel plot for outcome HbA1c. Bottom-right: Contour enhanced funnel plot for outcome HbA1c

evidence. The reason for downgrading was the unclear risk of selection bias, detection bias, and performance bias among the trials.[17-19]

Implication of this review for different people

At the current time, there is no clear consensus about the efficacy of daily intake of empagliflozin 25 mg tablets in adjunct to insulin for glycemic control in T1DM patients with optimum renal functioning. In this milieu, our study may serve as a preliminary source of synthesized evidence for researchers and health-care professionals. In addition, future trialists may find this evidence helpful to construct and report trials with much more scientific rigor. Finally, T1DM patients may also find our research informative in knowing where the existing evidence lies in this context.

Comparison to what is already known

Currently, there is a paucity of studies comparing the effect of daily empagliflozin 25 mg tablets in adjunct to insulin with placebo and insulin in T1DM patients with optimal

kidney functioning. We found one meta-analysis by Yamada et al.[11] that compared HbA1c and SBP change in T1DM patients treated with SGLT2 inhibitors with insulin compared to placebo. Like ours, the Yamada et al. study[11] also found a statistically significant reduction in HbA1c after adding SGLT2 inhibitors to insulin (compared to placebo). However, while we did not find any difference in follow-up SBP between the treatment groups, the Yamada et al. study[11] found a statistically significant decline in SBP the SGLT2 inhibitor group compared to the placebo group. This is perhaps because Yamada et al. included only one empagliflozin related trial (in meta-analysis) to estimate the effect on SBP and primarily sourced the data from other SGLT inhibitors such as dapagliflozin and sotagliflozin.[11,36] Whereas, we pooled data from empagliflozin specific trials.

Strengths of this review

Our review has the following strengths. First, this study is perhaps one of the preliminary papers comparing the treatment effect of daily 25 mg empagliflozin tablet administration (along
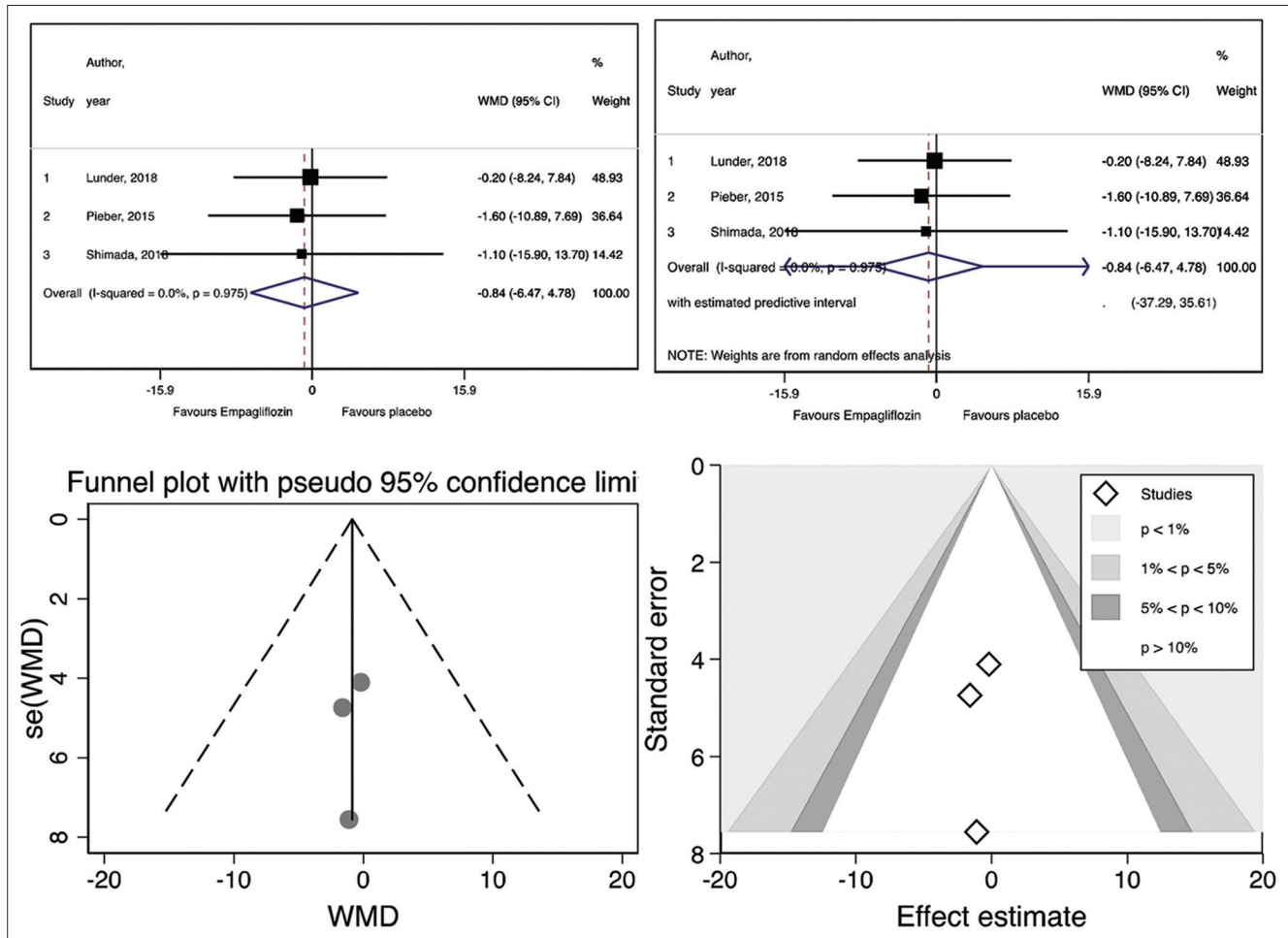
Figure 5: Forest plot of comparison (top-left: Fixed-effect model, top-right: Random effect model): 25 mg empagliflozin in adjunct to insulin versus placebo with insulin, outcome: Systolic blood pressure (SBP). Bottom-left: Funnel plot for outcome SBP. Bottom-right: Contour enhanced funnel plot for outcome SBP

with insulin therapy) with a combination of placebo and insulin therapy in T1DM patients with optimum renal functioning. Second, as the database search was not limited to any date or language our review is likely to be more complete in terms of searching the eligible trials. Third, as the data were pooled from RCTs, the evidence is likely to be of superior quality (since RCTs are considered as the highest level of epidemiological evidence). Finally, the trials were primarily multicentric[18,19] (except that by Lunder *et al.*).[17] Compared to single-center trials, multicenter trials are at lesser risk of overestimating the treatment effect and selective reporting.[37]

Limitations

This review suffers from the following limitations.

At the study level
The trials had one common weak point – the sample size of the intervention groups compared in this paper was relatively (too) small, hence increasing the risk of being underpowered trials.

At outcome level
The trials suffered from unclear risk of selection bias, detection bias, and performance bias (as mentioned above).

At review level
The studies included were only parallel arm RCTs. Henceforth, we could not include data from other types of trials (such as single-arm trials and crossover trials) or studies (such as good-quality observational studies). Next, due to limited resources, we could not search some of the other popular databases such as Web of Science. Furthermore, the substitution of SDs due to the unavailability of endpoint SDs may also introduce bias in the findings of our study. Finally, the availability of a fewer number of trials also limited the generalizability of our findings.

Conclusion

This study compared the effects of empagliflozin 25 mg tablets with placebo on glycemia and blood pressure in insulin-treated T1DM patients with optimum renal functioning
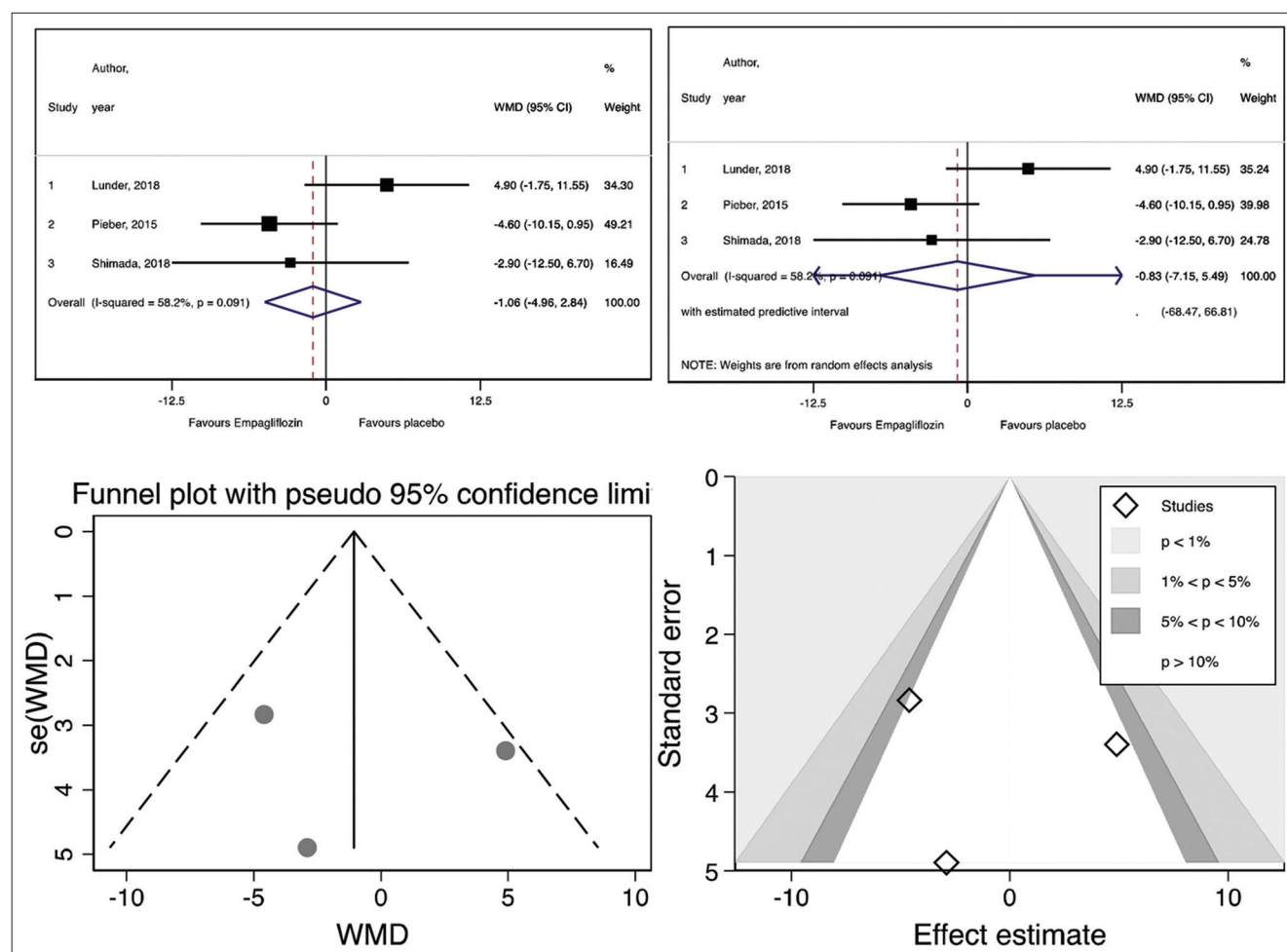
Figure 6: Forest plot of comparison (top-left: Fixed-effect model, top-right: Random effect model): 25 mg empagliflozin in adjunct to insulin versus placebo with insulin, outcome: DBP. Bottom-left: Funnel plot for outcome DBP. Bottom-right: Contour enhanced funnel plot for outcome DBP

(eGFR 45 mL/min/1.73 m² or more). We found moderate quality evidence suggesting that treatment with daily 25 mg empagliflozin in these patients is likely to achieve better glycemic control than treatment with placebo and insulin. However, the systolic and DBP did not differ between the compared intervention groups. For a definitive conclusion in this context, large trials with low risk of bias are required.

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Conflicts of Interest

None declared.

Statement of Ethics

Since no human subjects were involved in this systematic review, an ethical approval was not required.

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