

Efficacy and safety of canagliflozin among patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy and safety of canagliflozin in combination therapy among patients with type 2 diabetes mellitus with inadequate glycemic control. **Methods:** Two review authors independently searched for the relevant randomized controlled clinical trials from the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, IndMed, LILACS, and clinical trials registry www.clinicaltrials.gov. Primary outcomes for this review included: change in hemoglobin A1c (HbA1c) levels, fasting plasma glucose (FPG) levels and risk of occurrence of genital mycotic infections at 26 weeks. We combined results using mean difference (MD) for continuous data, and risk ratio (RR) for dichotomous data. **Results:** Of the 124 identified reports, five RCTs with 3565 participants were eligible for the meta-analysis. All included studies had compared canagliflozin 100 mg and 300 mg once daily with placebo or sitagliptin 100 mg once daily. We judged that most of the studies had low risk of bias or unclear risk of bias in five major domains. Canagliflozin 300 mg once daily led to a significant decrease in HbA1c levels (IV Fixed -0.77, 95% CI [-0.90, -0.64] $P < 0.00001$) and FPG levels (IV Fixed -2.08; 95% CI [-2.32, -1.84], $P < 0.00001$), body weight, systolic blood pressure and triglyceride levels after 26 weeks as compared to placebo. There was also a significant difference in the efficacy of canagliflozin 300 mg and sitagliptin 100 mg once daily in favour of canagliflozin. Both doses of canagliflozin led to genital mycotic infections among males and females, urinary tract infections, pollakiuria, polyuria and postural dizziness. **Conclusions:** Canagliflozin significantly decreases HbA1c and FPG levels and body weight as compared to placebo among patients with inadequate glycemic control with an earlier regime of glucose lowering agents. Long term safety studies are required to evaluate the incidence of adverse events.

Key words: Canagliflozin, genital infections, hemoglobin A_{1c}, type 2 diabetes mellitus

INTRODUCTION

The Global Diabetes Atlas 2014 shows that 387 million people have diabetes mellitus and the incidence of type 2 diabetes mellitus (T2DM) is rising across the world.^[1] About 77% of the patients with diabetes live in low and middle

income countries. The Western Pacific area has 138 million patients, which is the maximum in a region over world.^[1] The epidemiologic picture is better in the United States as compared to the world, as there is a steady improvement in the proportion of patients with T2DM achieving the target hemoglobin A_{1c} (HbA_{1c}) levels, blood pressure, and low density lipoprotein (LDL-C) levels in the last 10 years.^[2] Still, 33–49% of patients are not able to achieve adequate glycemic control, blood pressure, and cholesterol control, and just 14% are able to achieve all three targets and a nonsmoking status.^[2]

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Diabetes mellitus is a chronic progressive disease, requiring multipronged continuous care for optimal glycemic control, prevention of acute complications, and decrease in the risk of chronic complications such as retinopathy, neuropathy, nephropathy, and cardiovascular diseases.^[2,3] Currently, a wide variety of treatment modalities targeting different pathologic processes are available. According to the American Diabetes Association (ADA), metformin is the preferred first drug of choice with lifestyle modifications for patients with T2DM.^[4] In addition to metformin, other available glucose-lowering agents include insulin secretagogues (sulfonylureas, meglitinides [repaglinide and nateglinide] glucagon-like peptide-1 [GLP-1] agonist and dipeptidyl peptidase-4 inhibitors); insulin sensitizers (thiazolidinediones); alpha glucosidase inhibitors; and various insulin formulations.^[3,4] The ADA 2015 guidelines recommend the addition of any other treatment regimen to metformin if the glycemic control is not achieved after approximately 3 months of the start of treatment.^[2]

Most importantly, the pharmacotherapy of T2DM should be patient-centered, considering aspects such as efficacy, adverse effects, and cost, at the time of decision.^[2] In addition, both the healthcare professional and the patient prefer and adhere to those regimes which are more patient-centered, more convenient with less adverse effects, and help in achieving adequate glycemic control. The currently available drugs have their own specific uses and adverse effects, thus restricting their use, for example, sulfonylureas are known to cause weight gain, hypoglycemia, and secondary failure; meglitinides also cause secondary failure, hypoglycemia, and are most effective for postprandial hyperglycemia; GLP-1 agonists have to be given subcutaneously and commonly cause nausea and vomiting; thiazolidinediones (pioglitazone and rosiglitazone) may lead to weight gain, edema, congestive heart failure, and increase the risk of cardiovascular diseases.^[3] In this scenario, another drug group has been added to the armamentarium of glucose-lowering agents available for treatment of T2DM. Canagliflozin, a sodium glucose co-transporter (SGLT-2) inhibitor, was approved by the US Food and Drug Administration (US FDA) for use in the management of T2DM.^[5] SGLT2 is mainly responsible for renal glucose reabsorption. Usually, almost all filtered glucose is reabsorbed from the renal tubules till the filtered load exceeds the glucose reabsorptive capacity and then urinary excretion of glucose starts.^[6,7] This level is referred as the renal threshold for glucose (RTG). The RTG level is raised among patients with T2DM. Canagliflozin lowers the threshold level by inhibiting the renal transporters (SGLT2).^[5,8] This results in increased urinary glucose excretion, mild osmotic diuresis, and increased caloric loss with a minimal risk of hypoglycemia through an insulin-independent mechanism.^[5,8]

Canagliflozin and other drugs of the same group, dapagliflozin and empagliflozin, are approved for use as monotherapy or as part of a combination regime for patients with T2DM. The efficacy of canagliflozin has been demonstrated as compared to placebo and active comparators such as sitagliptin, but there are concerns about the adverse events such as genital mycotic infections and urinary tract infections.^[9] We aimed to pool the results of trials studying the efficacy and safety of canagliflozin in combination therapy for a duration of at least 26 weeks.

Objectives

To assess the efficacy and safety of canagliflozin in combination therapy among patients with inadequately controlled T2DM.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Type of participants

Patients with T2DM inadequately controlled with the use of glucose lowering agents, diet, and exercise.

Type of interventions

Treatment with canagliflozin (100 mg or 300 mg once daily) for at least 26 weeks in combination with earlier regimen of oral glucose-lowering agents. The following comparisons were evaluated:

- Canagliflozin 300 mg/day versus placebo after 26 weeks
- Canagliflozin 100 mg/day versus placebo after 26 weeks
- Canagliflozin 300 mg/day versus sitagliptin 100 mg/day after 52 weeks.

Types of outcome measures

Primary outcomes

- Effect on HbA_{1c} levels after 26 weeks
- Effect on fasting plasma glucose (FPG) levels after 26 weeks
- Effect on body weight after 26 weeks.

Secondary outcomes

- Effect on high density lipoprotein (HDL-C) levels after 26 weeks
- Effect on triglyceride levels after 26 weeks
- Effect on LDL-C levels after 26 weeks
- Incidence of adverse events such as urinary tract infections and genital mycotic infections after 52 weeks
- Effect on HbA_{1c}, FPG levels and body weight after 52 weeks.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published and unpublished).

Electronic searches

Two independent (KK and NL) reviewers independently searched the following databases on 09 June 2015 using the search terms mentioned below with no limit of time of publication. Cochrane Central Register of Controlled Trials (CENTRAL) *the Cochrane Library*; MEDLINE; EMBASE, LILACS, and IndMed. We also searched the WHO clinical trial registry platform, ClinicalTrials.gov for ongoing trials. The search terms were “canagliflozin” and “T2DM.”

Searching other resources

We searched Conference Proceedings Citation Index for relevant material.^[10] We contacted researchers/authors of the included studies for data input. We checked the reference lists of existing reviews and all trials identified by the above methods.

Data collection and analysis

Selection of studies

Two authors (KK and NL) independently screened the literature search results and obtained the full reports of all potentially relevant trials. KK and NL independently applied the inclusion criteria to the full reports using an eligibility form and scrutinized publications to ensure each trial was included only once. We resolved any disagreements through discussion with a third author.

Data extraction and management

KK and NL independently extracted data using specifically developed data extraction forms. We had access to the supplementary files of the included studies. We resolved any disagreements through discussion with all of the review authors. We contacted the corresponding publication author in the case of unclear information or missing data. For each outcome, we aimed to extract the number of participants randomized and the number analyzed in each treatment group. For dichotomous outcomes, we recorded the number of participants experiencing the event and the number assessed in each treatment group. For continuous outcomes, we used least mean squares and standard error and then calculated the standard deviation. We included only those clinical trials where the patients were already taking blood glucose-lowering oral agents.

Assessment of risk of bias in included studies

KK and NL independently assessed the risk of bias of each trial using the Cochrane risk of bias form.^[11] We resolved any disagreements by discussion among review authors. Six components were assessed: Generation of the randomization sequence, allocation concealment,

blinding, incomplete outcome data, and selective outcome reporting and other biases (such as the trial stopped early). We categorized our judgments as either “low,” “high,” or “unclear” risk of bias, and described our reasons for doing so. We recorded our judgments and justifications in the risk of bias tables for each included study and generated a risk of bias summary graph and figure.

Measures of treatment effect

We calculated the results using risk ratios (RRs) for dichotomous data and mean difference values for continuous data, and presented these effect estimates with 95% confidence intervals (CIs). We had planned to calculate time-to-event outcomes as safety data, but due to lack of availability of results at 26 weeks, we did not use it for comparison between canagliflozin and placebo. It was used for comparison between canagliflozin and sitagliptin at 52 weeks.

Unit of analysis issues

For dichotomous outcomes, both the sample size and the number of people with events were added across the groups. For continuous outcomes, we combined means and standard deviations using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*.^[12]

Dealing with missing data

The data were analyzed according to the intention-to-treat (ITT) principle (all randomized participants should be analyzed in the groups to which they were originally assigned). Relevant missing data were to be obtained from the respective authors, if feasible. Evaluation of important numerical data such as screened, eligible, and randomized patients as well as ITT and per-protocol (PP) population was carefully performed.

Assessment of heterogeneity

The statistical heterogeneity was analyzed by looking at the forest plots for overlapping CIs, applying the χ^2 test ($P < 0.10$ considered statistically significant) and the I^2 statistic (I^2 value $< 50\%$ used to denote moderate levels of heterogeneity).

Data synthesis

We analyzed the data using review manager (RevMan) 5.3 of Cochrane collaboration. For the quantitative analysis, we used the fixed-effect meta-analysis.^[12] Random effect model was used, when significant heterogeneity was present. We used the fixed effect model for calculating the change in HbA_{1c} levels, FPG levels and body weight in canagliflozin 300 mg, and placebo arms after 26 weeks. The statistical analysis was performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions*. Where heterogeneity was very high such that meta-analysis was not appropriate, we displayed the results in tables but did not combine the results.

RESULTS

Description of studies

Results of the search

We conducted the literature search up to 09 June 2015 and identified 124 references [Figure 1]. This initial search of randomized, controlled trials led to 22 results (from MEDLINE), 38 from Cochrane central, 24 from EMBASE, 38 from LILACS, and 2 from other sources. After excluding the duplicate reports, 55 reports were screened and then 26 were excluded. Then 29 studies were evaluated for eligibility. Five clinical studies were included for meta-analysis.

Included studies

Five clinical studies enrolling 3565 patients were included in the quantitative analysis [Table 1 - characteristics of included studies].

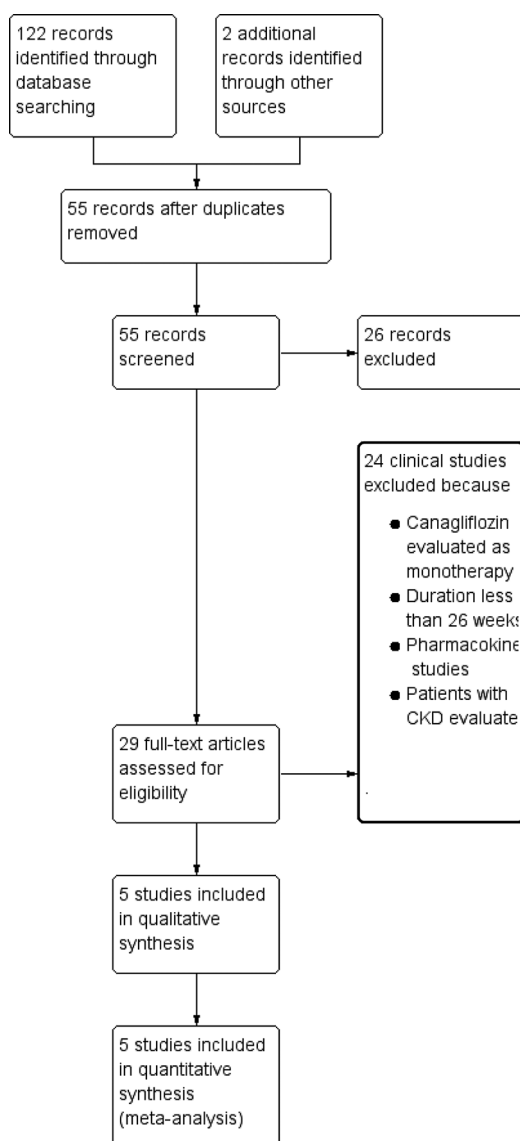


Figure 1: Study flow diagram

Design

These were randomized, double-blind clinical trials. All the trials had multinational design.

Intervention

All studies had compared canagliflozin with placebo. In three studies, there were three arms of the studies, that is, canagliflozin 100 mg and 300 mg once daily and placebo arms for the first 26 weeks in the first phase. In the following second phase (26–52 weeks), patients of placebo arm were administered sitagliptin 100 mg once a day and evaluated at the end of the study.^[13-15] Lavallo-Gonzalez *et al.* had taken another arm of sitagliptin 100 mg once daily and Schernthaner *et al.* had only two arms of canagliflozin 300 mg once daily and sitagliptin 100 mg once a day.^[16,17] All these studies had evaluated efficacy as primary (effect on HbA_{1c} levels after 26 weeks) and secondary end points (FPG levels, body weight after 26 weeks, and HbA_{1c} levels after 52 weeks) and monitored the safety and tolerability at 26 and 52 week interval.

Excluded studies

The reasons for exclusion of the studies are mentioned in table. Most of RCTs have evaluated the efficacy and tolerability of canagliflozin as monotherapy and some have assessed its efficacy among patients with chronic renal failure [Table 2].^[18-41]

Risk of bias in the included studies

Overall, the included studies suggested low risk of bias as these studies generally had a randomized controlled, double-blind design, typically employing an ITT analysis [Figure 2]. Inter-rater agreement for the key quality indicators such as randomization, concealment of allocation, and blinding was complete with no full publication necessary to be discussed by a third author. Figure 3 shows a summary of the judgments of the risk of bias for each domain in each of the included trials.

The included studies had allocation concealment thus avoiding the risk of bias. All studies employed a double-blind design. Most publications reported an ITT analysis using the last observation carried forward method to impute missing values. No publication indicated selective outcome reporting.

Effect of interventions

See summary of findings for the main comparison.

Canagliflozin 300 mg once a day versus placebo

We evaluated the effect of canagliflozin 300 mg once daily as compared to placebo on HbA_{1c} and FPG levels after 26 weeks. Four trials had reported the mean

Table 1: Characteristics of included studies

Bode <i>et al.</i>	
Methods	Design: Randomized controlled trial
Participants	Number of participants: 716; Mean age: 63.6±6.2 Gender: 396 (55.5%) M; 318 (44.5%) F Duration of symptoms Inclusion criteria: Men and women with T2DM, aged 55 to 80 years, who had inadequate glycemic control (HbA _{1c} levels ≥7.0% to ≤10.0%) on no blood glucose-lowering agent, or on a stable regimen of glucose-lowering agent (s) as monotherapy or combination therapy (including metformin, sulfonylurea, DPP-IV inhibitor, α-glucosidase inhibitor, GLP-1 agonist, or insulin [for ≥12 weeks prior to screening] or pioglitazone [for ≤6 months prior to screening]) used in accordance with local prescribing information. Eligible subjects were required to have a body mass index (BMI) between 20 and 40 kg/m ² , FPG level <270 mg/dL at week 2 (start of the single-blind, placebo run-in period), and fasting finger stick blood glucose level ≥110 mg/dL (6.1 mmol/L) and <270 mg/dL (15.0 mmol/L) at baseline Exclusion criteria: History of type 1 diabetes mellitus; repeated FPG level ≥270 mg/dL (15.0 mmol/L) during the pretreatment phase; history of myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening; history of New York Heart Association Class III-IV cardiac disease; uncontrolled hypertension; or estimated glomerular filtration rate <50 mL/min/1.73 m ² . Subjects on background metformin therapy were excluded if they had serum creatinine levels ≥1.4 mg/dL (124 μmol/L) for men and ≥1.3 mg/dL (115 μmol/L) for women or any contraindication to the use of metformin (including low eGFR) based on the label for the country of the investigational site
Interventions	Group 1: PBO group (237) Group 2 :CANA 100mg (241) Group 3:CANA 300mg (236)
Outcomes	Primary efficacy endpoint (at week 26) Change in HbA _{1c} levels from baseline to week 26 Secondary endpoints evaluated at week 26 included the Change in FPG levels Change in systolic blood pressure Change in baseline body weight Change in fasting high density lipoprotein cholesterol levels Change in fasting triglyceride levels Proportion of subjects reaching HbA _{1c} levels <7% Incidence of genital mycotic infections Incidence of urinary tract infections
Risk of bias table	
Bias	Authors judgement Support for judgement
Random sequence generation (selection bias)	Low risk Randomization was balanced across treatment groups using permuted blocks of 6 subjects per block and stratified based on the T-score of the lumbar spine (-1.5 or <-1.5; assessment of bone density to be reported separately) and whether subjects were taking pioglitazone
Allocation concealment (selection bias)	Low risk HbA _{1c} and FPG levels were masked to the study centers unless these values met prespecified glycemic criteria for the initiation of rescue medication or after glycemic rescue medication was started
Blinding of participants and personnel (performance bias)	Low risk All subjects, investigators, and local sponsor personnel remained blinded to treatment assignment until the final database lock
Blinding of outcome assessment (detection bias)	Low risk Investigators and local sponsor personnel remained blinded to treatment assignment until the final database lock
Incomplete outcome data (attrition bias)	Low risk The number of withdrawals was similar in all the groups. All the included patients were analyzed for results
Selective reporting (reporting bias)	Low risk No selective reporting found
Other bias	Unclear risk No clear interpretation of any other bias
Forst <i>et al.</i>	
Methods	Design: Randomized controlled trial
Participants	Number of participants: 344; Mean age: 57.4±10.0 Gender 216 (63.2%) M, 126 (36.8%) F Duration of symptoms Inclusion criteria: Men and women aged ≥18 and ≤80 years with T2DM; FPG <15 mmol/l (270 mg/dl) at week -2, and fasting finger stick glucose ≥6.1 mmol/l (110 mg/dl) and <15 mmol/l (270 mg/dl) on day 1. Patients on protocol-specified doses of metformin (≥2000 mg/day) and pioglitazone (30 or 45 mg/day) with HbA _{1c} ≥7.0% to ≤10.5% at screening directly entered the placebo run-in period Exclusion criteria: Repeated FPG and/or fasting self monitored blood glucose ≥15.0 mmol/l (270 mg/dl) during the pretreatment phase; history of type 1 diabetes, cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months prior to screening, or uncontrolled hypertension; ongoing eating disorder or 5% change in body weight within 12 weeks; and eGFR <55 ml/min/1.73m ² or serum creatinine ≥124 μmol/l for men and ≥115 μmol/l for women

Contd...

Interventions	Group 1: Placebo group (115) Group 2 : CANA 100mg (113) Group 3: CANA 300mg (114)
Outcomes	Primary efficacy endpoint (at week 26) Change in HbA _{1c} levels from baseline to week 26 Secondary endpoints evaluated at week 26 included the Change in FPG levels Change in systolic BP Change in baseline body weight Change in fasting HDL-C levels Change in fasting triglyceride levels Proportion of subjects reaching HbA _{1c} levels <7% Incidence of genital mycotic infections Incidence of urinary tract infections

Risk of bias table

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was balanced using permuted blocks of six patients per block and stratified according to: (i) whether a patient entered the AHA adjustment period and (ii) dose of pioglitazone at randomization
Allocation concealment (selection bias)	Low risk	Allocation was concealed from the investigators
Blinding of participants and personnel (performance bias)	Low risk	After randomization, HbA _{1c} and FPG values were masked to the study centers unless they met pre-specified glycemic rescue criteria
Blinding of outcome assessment (detection bias)	Low risk	After completion of the core treatment period, the database was locked and the study was unblinded by the sponsor for regulatory filing. Patients and study centre and local sponsor personnel remained blinded throughout the extension period
Incomplete outcome data (attrition bias)	Low risk	Efficacy data were analyzed according to randomized treatment assignment using the last observation carried forward approach to impute missing data; for patients who received glycemic rescue therapy, the last post-baseline value prior to initiation of rescue was used for analysis
Selective reporting (reporting bias)	Low risk	No evidence of any reporting bias
Other bias	Unclear risk	No clear interpretation of any other bias

Lavalle-Gonzalez *et al.*

Methods	Design: Randomized controlled trial
Participants	Number of participants: 1284; Mean age: 55.4±9.4 Gender: 605 (47.1%) M; 679 (52.9%) F Inclusion criteria: Men and women with type 2 diabetes, aged ≥18 and ≤80 years, who had inadequate glycemic control (HbA _{1c} ≥7.0% and ≤10.5%) and who were on stable metformin therapy for ≥8 weeks and had FPG <15 mmol/l at week -2 and fasting finger stick glucose ≥6.1 mmol/l and <15 mmol/l on day 1 Exclusion criteria: Repeated FPG and/or SMBG ≥15.0 mmol/l during the pretreatment phase; history of type 1 diabetes, cardiovascular disease (including myocardial infarction, unstable angina, re-vascularisation procedure or cerebrovascular accident) in the 3 months before screening or uncontrolled hypertension; treatment with a PPAR γ agonist, insulin, another SGLT2 inhibitor or any other glucose lowering agent (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 weeks before screening; or estimated glomerular filtration rate <55 ml/min/1.73m ² or serum creatinine ≥124 μmol/l (men) or ≥115 μmol/l (women)
Interventions	Placebo group (n=183) SITA 100mg (n=366) CANA 100mg (n=368) CANA 300mg (n=367)
Outcomes	Primary efficacy endpoint (at week 26) Change in HbA _{1c} levels from baseline to week 26 Secondary endpoints evaluated at week 26 included the Change in FPG levels Change in systolic blood pressure Change in baseline body weight Change in fasting HDL-C levels Change in fasting triglyceride levels Proportion of subjects reaching HbA _{1c} levels <7% Incidence of genital mycotic infections Incidence of urinary tract infections

Risk of bias (Lavalle-Gonzalez *et al.*)

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was balanced using permuted blocks of seven and stratified by whether a participant was on metformin monotherapy or metformin plus sulfonylurea at screening
Allocation concealment (selection bias)	Low risk	Allocation was concealed from the investigators

Contd...

Blinding of participants and personnel (performance bias)	Low risk	After randomization, HbA _{1c} and FPG values were masked to the study centers unless they met glycemic rescue criteria
Blinding of outcome assessment (detection bias)		After completion of period I, the database was locked and the study was unblinded by the sponsor for regulatory filing; the participants and the study centre and local sponsor personnel remained blinded throughout period II
Incomplete outcome data (attrition bias)	Low risk	Efficacy data were analyzed according to randomized treatment assignment using the LOCF approach to impute missing data; for patients who received glycemic rescue therapy, the last post-baseline value prior to initiation of rescue was used for analysis
Selective reporting (reporting bias)	Low risk	No evidence of any reporting bias
Other bias	Unclear risk	No clear interpretation of any other bias

Schernthaler 2013

Methods	Design: Randomized controlled trial	
Participants	Number of participants: 756; Mean age : 56.7±9.5 Gender: 422 (55.9%) M, 333 (44.1%) F Inclusion criteria: Men and women 18 years of age or older with T2DM using stable metformin and sulfonylurea therapy. Subjects at screening already using the combination of metformin and sulfonylurea with both agents at maximally or near-maximally effective doses (metformin ≥2,000 mg/day [or ≥1,500 mg/day if unable to tolerate a higher dose]; sulfonylurea at half-maximal labeled dose or more), who had HbA _{1c} ≥7.0% (53 mmol/mol) and ≤10.5% (91 mmol/mol) Exclusion criteria: Repeated FPG or fasting self-monitored blood glucose measurements ≥16.7 mmol/L (300 mg/dL), or both, during the pretreatment phase; history of type 1 diabetes, cardiovascular disease, or uncontrolled hypertension; treatment with either a PPAR γ agonist, ongoing insulin therapy, another SGLT2 inhibitor, or any other glucose lowering agent (other than metformin and a sulfonylurea) within 12 weeks before screening; or eGFR <55 mL/min/1.73 m ² ; or serum creatinine ≥124 mmol/L (men) and ≥115 mmol/L (women)	
Interventions	Canagliflozin 300 mg once daily (<i>n</i> =378) Sitagliptin 100 mg once daily (<i>n</i> =378) Added to the earlier regime of metformin and a sulfonyurea agent	
Outcomes	Primary efficacy endpoint (at week 52) Change in HbA _{1c} levels from baseline to week 52 Secondary endpoints evaluated at week 26 included the Change in FPG levels Change in systolic blood pressure Change in baseline body weight Change in fasting HDL-C levels Change in fasting triglyceride levels Proportion of subjects reaching HbA _{1c} levels <7% Incidence of genital mycotic infections Incidence of urinary tract infections	

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Subjects were randomly assigned to.....underwent the frequently sampled mixed-meal tolerance test."
Allocation concealment (selection bias)	Low risk	Quote "After randomization, HbA _{1c} and FPG values and all glucose levels from the FSMMTT....and the final database was locked."
Blinding of participants and personnel (performance bias)	Low risk	Quote "Subjects, investigators, and local sponsor personnel remainedand the final database was locked."
Blinding of outcome assessment (detection bias)		Local sponsor personnel were blinded
Incomplete outcome data (attrition bias)	Low risk	Reasons for attrition have been provided. Intent to treat analysis was followed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified.

Wilding *et al.* 2013

Methods	Design: Randomized controlled trial	
Participants	Number of participants: 469; Mean age : 56.8±9.3 Gender: 239 (51%) M; 230 (49%) F Duration of symptoms Inclusion criteria: Men and women aged 18-80 years with T2DM who had inadequate glycemic control (HbA _{1c} ≥7.0% to ≤10.5%) on metformin plus sulphonylurea, with both agents at maximally or near-maximally effective doses Exclusion criteria: History of diabetic ketoacidosis or type 1 DM, repeated FPG ≥15.0 mmol/l during the pre-treatment phase, history of ≥1 severe hypoglycemia episode within 6 months before screening, eGFR <55 ml/min/1.73 m ² or serum creatinine ≥124 mmol/l for men and ≥115 mol/l for women, uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg), or taking any glucose lowering agent other than metformin plus sulphonylurea within 12 weeks prior to screening	

Contd...

Interventions	Placebo (<i>n</i> =156) CANA 100 mg (<i>n</i> =157) CANA 300 mg (<i>n</i> =156)
Outcomes	Primary efficacy endpoint (at week 26) Change in HbA _{1c} levels from baseline to week 26 Secondary endpoints evaluated at week 26 and 52 included the Change in FPG levels Change in systolic blood pressure Change in baseline body weight Change in fasting HDL-C levels Change in fasting triglyceride levels proportion of subjects reaching HbA _{1c} levels <7% Incidence of genital mycotic infections Incidence of urinary tract infections

Risk of bias (Wilding *et al.* 2013)

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization was balanced using permuted blocks ...in the frequently-sampled mixed-meal tolerance test."
Allocation concealment (selection bias)	Low risk	Quote "To maintain blinding after randomization, HbA _{1c} and FPG values were masked to....after glycemic rescue therapy was started."
Blinding of participants and personnel (performance bias)	Low risk	Quote "After completion of the core treatment period, the database was locked....blinded throughout the extension period."
Blinding of outcome assessment (detection bias)	Low risk	The local sponsor personnel remained blinded throughout the extension period
Incomplete outcome data (attrition bias)	Low risk	Efficacy data were analyzed according to randomized treatment with the LOCF approach used to impute missing values
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No other bias identified

DPP: Dipeptidyl peptidase 4; GLP: Glucagon-like peptide 1; BMI: Body mass index; FPG: Fasting plasma glucose; eGFR: Estimated glomerular filtration rate; PBO: Placebo; CANA: Canagliflozin; SBP: Systolic blood pressure; HDL-C: High density lipoprotein cholesterol; SMBG: Self monitored blood glucose; LOCF: Last observation carried forward; BP: Blood pressure; FS-MMTT: Frequently sampled mixed-meal tolerance test

change as compared to baseline. There was a significant mean difference in HbA_{1c} levels (IV Fixed - 0.77, 95% CI [-0.90, -0.64], *P* < 0.00001) [Analysis 1.1, Figure 4] and FPG levels (IV Fixed - 2.08; 95% CI [-2.32, -1.84], *P* < 0.00001) in the canagliflozin arm as compared to placebo [Analysis 1.2, Figure 5]. Similarly, there was a significant mean difference in effect on body weight [Analysis 1.3, Figure 6], systolic blood pressure [Analysis 1.4, Figure 7], HDL-C [Analysis 1.5, Figure 8], and triglyceride levels [Analysis 1.6, Figure 9] favoring canagliflozin 300 mg once a day as compared to placebo. The clinical studies had shown a numerical increase in LDL-C levels and this increase significantly favors placebo over canagliflozin [Analysis 1.7, Figure 10].

The incidence of adverse effects in the two arms could not be compared quantitatively as the clinical studies except Bode *et al.*, have not described this information at 26 weeks. The number of adverse effects has been listed in Table 3 for comparison.

Canagliflozin 100 mg once a day versus placebo

On evaluation of the above-mentioned four clinical studies, there was a significant mean difference in decrease in HbA_{1c} (IV, Fixed - 0.58 [-0.61, -0.55], *P* < 0.0001) [Analysis 2.1, Figure 11] and FPG levels [IV, Fixed -1.35 95% CI [-1.50, -1.19], *P* < 0.0001) [Analysis 2.2, Figure 12]

in favor of canagliflozin. The mean difference was also significant for effect on body weight [Analysis 2.3, Figure 13], systolic blood pressure [Analysis 2.4, Figure 14], and HDL-C levels [Analysis 2.5, Figure 15] and nonsignificant for triglyceride levels [Analysis 2.6, Figure 16] in favor of canagliflozin 100 mg as compared to placebo. Similar to canagliflozin 300 mg dose, even 100 mg once a day also led to increase in LDL-C levels and the comparison was in favor of placebo [Analysis 2.7, Figure 17]. As mentioned earlier, the incidence of adverse events could not be compared at 26 weeks.

Canagliflozin 300 mg once daily versus sitagliptin 100 mg once daily

We compared the effect of canagliflozin 300 mg once daily and sitagliptin 100 mg once daily when added to an earlier regime of anti-hyperglycemic agents in two clinical studies.^[16,17] The duration of the clinical studies was 52 weeks. There was a significant mean difference in the effect on HbA_{1c} levels (IV, Fixed - 0.16, 95% CI [-0.29,-0.02], *P* = 0.02) [Analysis 3.1, Figure 18]. There was also a significant mean difference in FPG levels (IV, Fixed - 1.03, 95% CI [-1.29, -0.76], *P* < 0.0001) [Analysis 3.2, Figure 19] and body weight (IV, Fixed - 2.49, 95% CI [-3.00, -1.97], *P* < 0.0001) [Analysis 3.3, Figure 20]. There was a significant difference in decrease in systolic BP [Analysis 3.4, Figure 21] and increase in HDL-C levels [Analysis 3.5, Figure 22] in

favor of canagliflozin, but a nonsignificant difference in decrease in triglyceride levels [Analysis 3.6, Figure 23]. Both canagliflozin and sitagliptin groups had witnessed a numerical increase in LDL-C levels in the clinical studies, but the comparative mean difference in favor of sitagliptin was not significant [Analysis 3.7, Figure 24].

Incidence of adverse effects

There was a nonsignificant difference between the two groups with respect to occurrence of adverse effects (RR: 0.98, 95% CI: 0.92, 1.05, $P = 0.57$) [Analysis 3.8, Figure 25]. In addition, the occurrence of osmotic diuretic-related adverse effects and volume depletion-related adverse events was not significantly different between the two groups [Analysis 3.9, Figure 26]. The risk of development of genital mycotic infections was higher with canagliflozin among both males (MH, Fixed 11.96, 95% CI [2.84–50.41], $P = 0.0007$) and females (MH, Fixed 3.99, 95%

CI [2.15–7.40], $P < 0.0001$) [Analysis 3.10, Figure 27] as compared to sitagliptin.

DISCUSSION

Summary of main results

Five good quality randomized studies comparing two different doses of canagliflozin with placebo or sitagliptin among patients inadequately controlled with oral anti-hyperglycemic agents over 26 weeks were included for quantitative analysis.^[13-17] The results show that both the doses of canagliflozin (100 mg/day and as 300 mg/day) when used in combination with other oral anti-hyperglycemic agents led to a significant decrease in HbA_{1c} levels, FPG levels, and body weight as compared to placebo over a period of 26 weeks. In addition, canagliflozin significantly decreased the systolic blood pressure, mean triglyceride levels, and increased HDL-C levels as compared to placebo. No quantitative analysis was done for the incidence of adverse effects at 26 weeks because of the unavailability of the results.^[14-16] In all the included studies, there was a numerical increase in LDL-C levels, which was nonsignificant in favor of placebo and sitagliptin upon analysis. Comparison of canagliflozin 300 mg once daily and sitagliptin 100 mg once daily shows a significant difference in the decrease of HbA_{1c} levels, FPG levels, and body weight in favor of canagliflozin at 52 weeks.^[16,17] The incidence of total adverse effects and selected adverse effects such as urinary tract infections, osmotic diuresis related, and volume-related adverse effects were nonsignificantly different between the two groups. However, the incidence of genital mycotic infections among both males and females was significantly more in the canagliflozin arm as compared to sitagliptin. Although the included clinical studies, that is, Bode *et al.*, Forst *et al.*, and Wilding *et al.* had reported the efficacy and safety results at 52 weeks as well, we did not include these results, as the patients of the placebo arm had been shifted to a comparator group at 26 weeks and then followed up for next 26 weeks.^[13-16] Thus, the comparator drug administered for the later 26 weeks could not be compared with canagliflozin given for 52 weeks. With reference to the comparison of canagliflozin and sitagliptin, there is a need to have more long-term studies for conclusive results.

The need of new glucose-lowering agents is based on multiple factors. First, T2DM is a chronic disease that often requires combination therapy with glucose-lowering agents as the disease progresses. Second, improved glycemic control is associated with significantly decreased rates of microvascular and neuropathic complications.^[2,42] Intensive

Table 2: Characteristics of excluded studies

Study Id	Reason for exclusion
Cefalu 2013	No placebo arm and this was the only study comparing canagliflozin with glimepride
Devineni 2012	Duration of study was 28 days
Devineni 2013	Single and multiple dose pharmacokinetics study
Gonzalez-Galvez 2014	Monotherapy and conference proceedings and details could not be collected
Inagaki 2013	Canagliflozin monotherapy was compared with placebo for 12 weeks
Inagaki 2014a	Canagliflozin monotherapy was compared with placebo for 24 weeks
Inagaki 2014 b	Outcome was pharmacokinetic evaluation of canagliflozin among patients with renal impairment
Langslet 2014	Pooled analysis for glycemic control
Neal 2013	Rational and design explained of CANVAS study
Nicolle 2012	Duration of study was 12 weeks
Nicolle 2014	Pooled analysis for incidence of urinary tract infections
Nyirjesy 2012	Duration of study was 12 weeks
Nyirjesy 2014	Pooled analysis of phase 3 studies; outcome was genital mycotic infections
Polidori 2013	Analysis of a novel method to calculate renal threshold for glucose excretion (RT (G))
Qiu 2014	Duration of study was 18 weeks
Rosenstock 2012	Dose ranging study with duration of 12 weeks
Sha 2011	Ascending single oral-dose phase 1 study
Sinclair 2014	Patients >65 years of age; pooled analysis
Stenlof 2013	Canagliflozin monotherapy was compared with placebo
Stenlof 2014	Canagliflozin monotherapy was compared with placebo; outcome was evaluated at 52 weeks
Stein 2014	Single dose study
Triana 2014	Outcomes were weight-related quality of life and satisfaction with physical health and emotional health, using data from a previously reported study
Yale 2013	Included patients had type 2 diabetes mellitus and stage 3 chronic kidney disease
Yale 2014	Included patients had type 2 diabetes mellitus and stage 3 chronic kidney disease; duration was 52 weeks

Table 3: Adverse events observed in the included studies

Patients (n)	Bode et al. (at 26 weeks)			Forst et al. (at 52 weeks)			Wilding et al. (52 weeks)			Lavalle et al. (52 weeks)			
	CANA 100 mg (n=241)	CANA 300 mg (n=236)	PBO (n=237)	CANA 100 mg (n=113)	CANA 300 mg (n=114)	PBO/SITA (n=115)	CANA 100 mg (n=157)	CANA 300 mg (n=156)	PBO (n=156)	CANA 100 mg (n=316)	CANA 300 mg (n=321)	PBO/SITA (n=153)	SITA 100 mg (n=313)
Any AE	174	184	174	79	87	88	64	72	53	138	119	63	134
AEs leading to discontinuation	5	17	10	2	5	7	2	3	2	0	1	1	8
AEs related to study drug	64	79	66	22	33	27	11	21	4	29	16	7	28
Serious AEs	10	8	12	8	7	6	3	2	6	3	4	3	10
Deaths	0	0	0	0	0	0	0	0	0	0	0	0	1
Selected AEs													
UTI	14	19	12	6	9	9	4	5	4	12	6	10	12
Genital mycotic infections													
Males	4	8	0	3	3	0	1	3	0	3	1	0	0
Females	18	12	2	6	11	3	4	2	0	8	1	1	2
Osmotic diuresis related AEs	10	16	5	11	11	1	1	1	0	0	2	0	0
Volume depletion AEs	4	4	1	9	5	4	1	3	1	1	2	0	0
Hypoglycemic episodes							28	34	10				
Severe episodes							0	1	0				

AE: Adverse event; CANA: Canagliflozin; PBO: Placebo; SITA: Sitagliptin

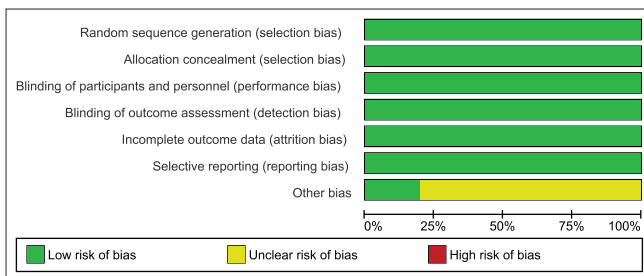


Figure 2: Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies

early management of T2DM patients may also reduce the long-term cardiovascular disease rates (both fatal and nonfatal myocardial infarction and sudden death).^[2] Third, many of the available glucose-lowering agents have adverse effects such as weight gain and increased risk of hypoglycemia. Finally, it will be advantageous if the glucose-lowering agents can simultaneously have beneficial effects on body weight, blood pressure, and lipid profile, that is, triglyceride, LDL-C, and HDL-C levels. Another reason is that more patients with T1DM and T2DM are living into older age and there is lack of clinical evidence for their management.^[2] Hence, it is vital to have efficacious and safe drugs for the management of T2DM.

Canagliflozin and other SGLT2 inhibitors, the latest drugs to be added to the pool of glucose-lowering agents, have the advantage of an insulin-independent mechanism of action, while on the downside; these drugs have been associated with some adverse effects. US FDA has given a warning regarding the risk of increased incidence of keto-acidosis with canagliflozin.^[43] This safety issue is being investigated

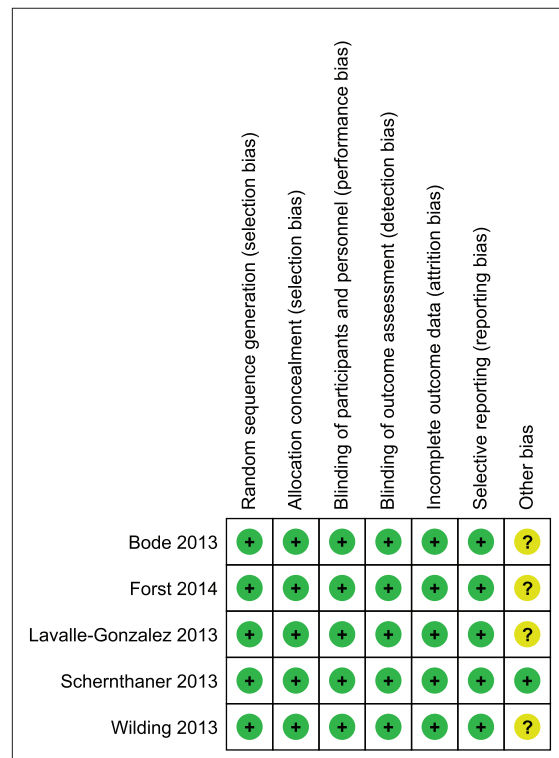


Figure 3: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study

by the drug authorities and in future, a modification in drug prescribing may be required. Furthermore, there is a need to evaluate the incidence of genital mycotic infections and the increase in LDL-C levels. Long-term randomized and observational safety studies comparing canagliflozin with available glucose-lowering agents can help in assessing the incidence of adverse effects.

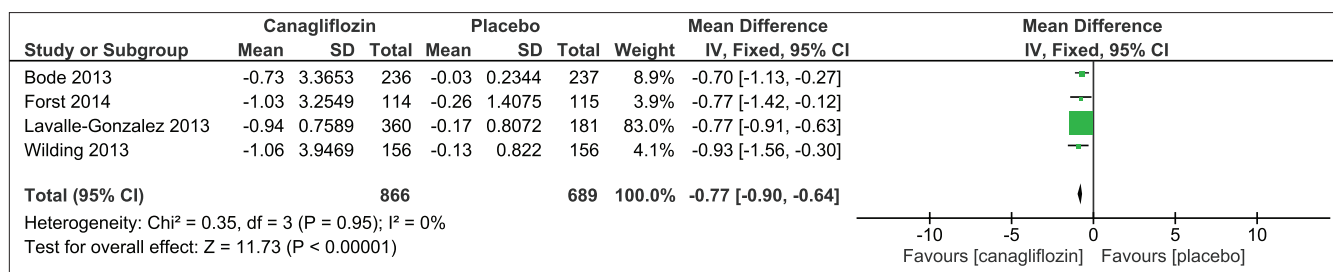


Figure 4: Forest plot of comparison: 1 canagliflozin 300 mg once daily versus placebo after 26 weeks, outcome: 1.1 effect on hemoglobin A_{1c} levels

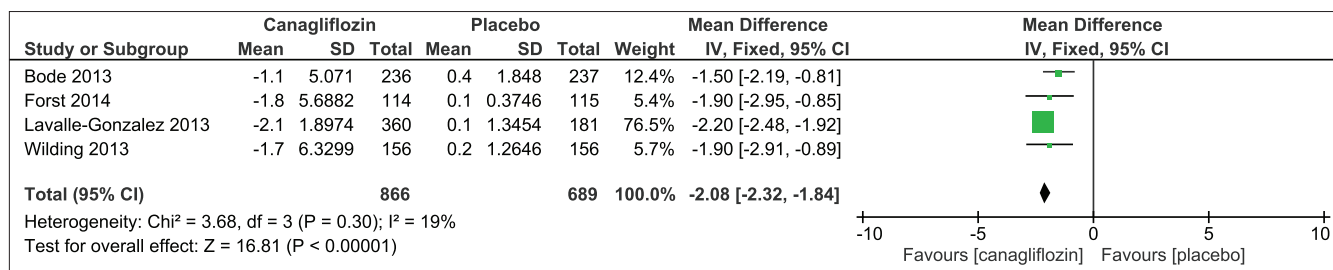


Figure 5: Forest plot of comparison: 1 canagliflozin 300 mg once daily versus placebo after 26 weeks, outcome: 1.2 effect on fasting plasma glucose levels

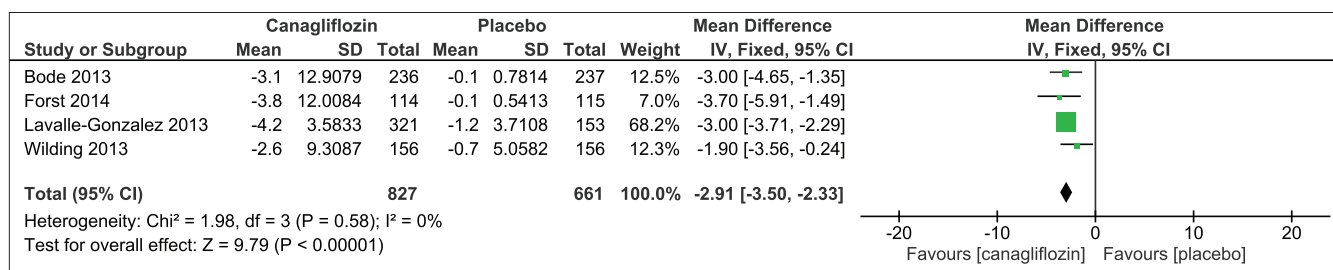


Figure 6: Forest plot of comparison: 1 canagliflozin 300 mg once daily versus placebo after 26 weeks, outcome: 1.3 effect on body weight

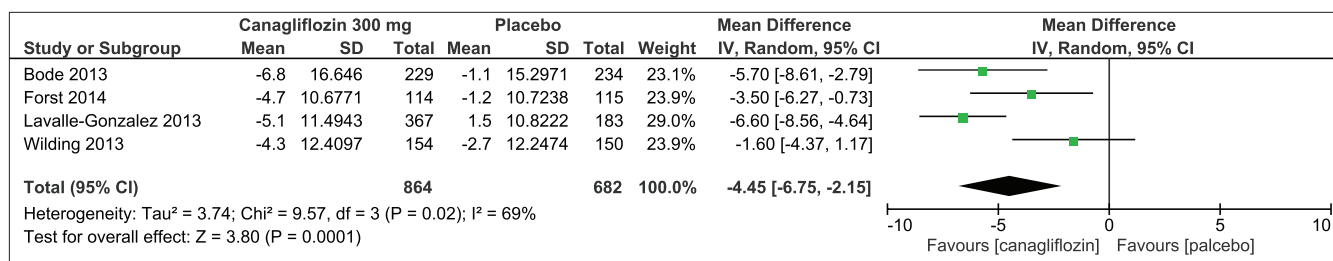


Figure 7: Forest plot of comparison: 1 canagliflozin 300 mg once daily versus placebo after 26 weeks, outcome: 1.4 effect on systolic blood pressure

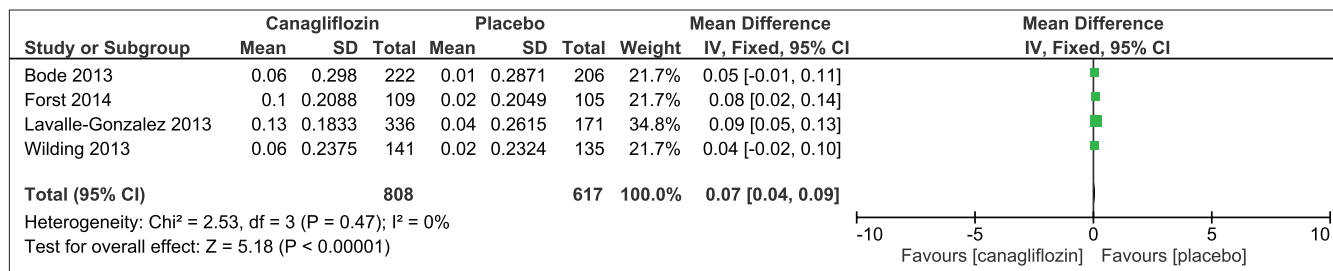


Figure 8: Forest plot of comparison: 1 canagliflozin 300 mg once daily versus placebo after 26 weeks, outcome: 1.5 effect on high-density lipoprotein-C levels

As we included clinical studies evaluating canagliflozin in combination therapy, we could not analyze the status

of canagliflozin in monotherapy. Quantitative analysis of canagliflozin monotherapy has also shown that canagliflozin

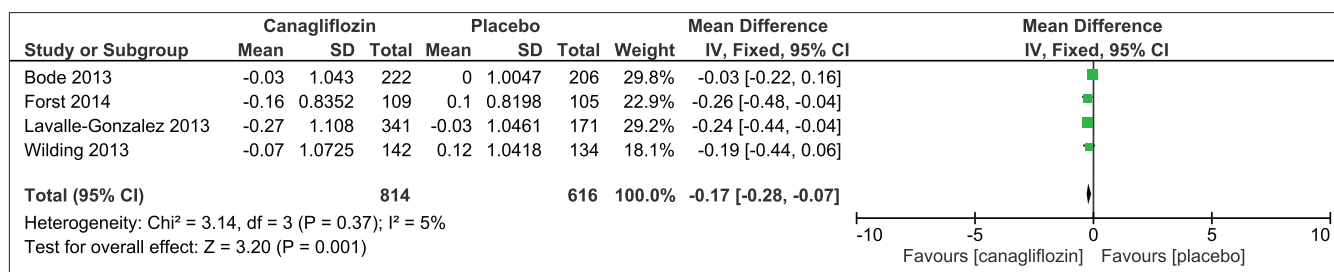


Figure 9: Forest plot of comparison: 1 canagliflozin 300 mg once daily versus placebo after 26 weeks, outcome: 1.6 effect on triglyceride levels

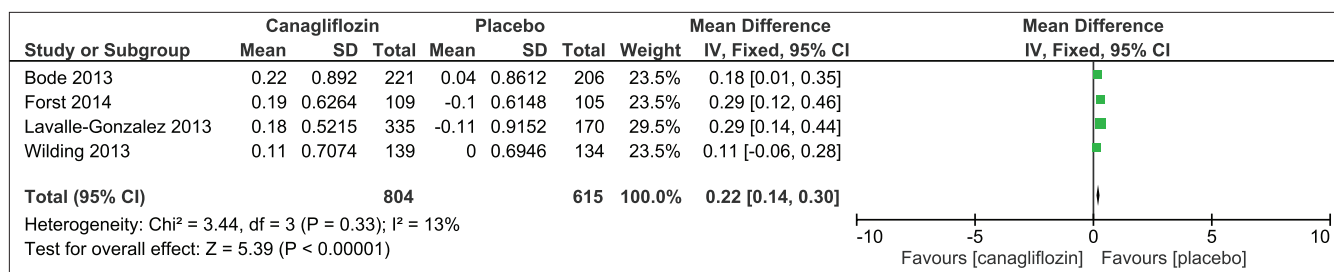


Figure 10: Forest plot of comparison: 1 canagliflozin 300 mg once daily versus placebo after 26 weeks, outcome: 1.7 effect on low-density lipoprotein-C levels

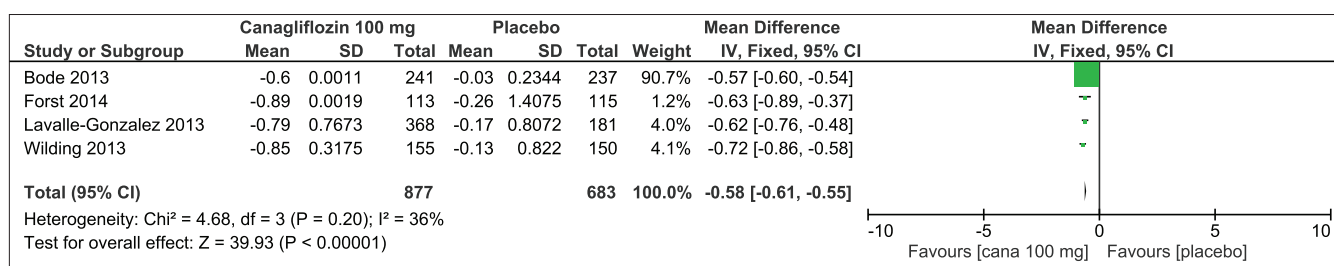


Figure 11: Forest plot of comparison: 2 canagliflozin 100 mg once daily versus placebo after 26 weeks, outcome: 2.1 effect on hemoglobin A_{1c} levels

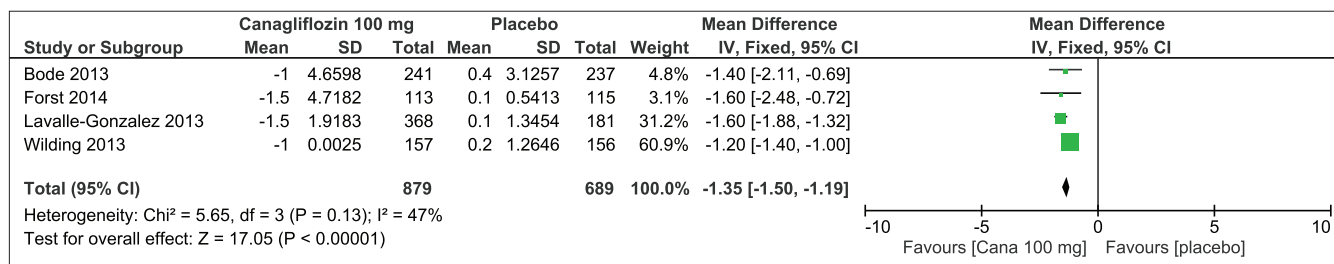


Figure 12: Forest plot of comparison: 2 canagliflozin 100 mg once daily versus placebo after 26 weeks, outcome: 2.2 effect on fasting plasma glucose levels

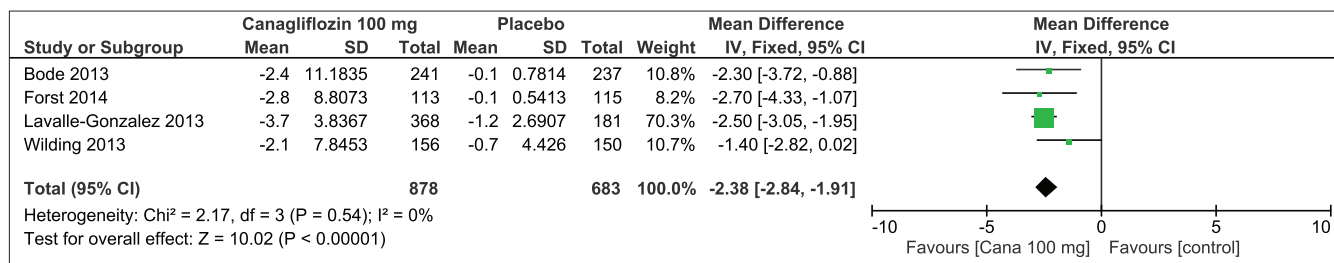


Figure 13: Forest plot of comparison: 2 canagliflozin 100 mg once daily versus placebo after 26 weeks, outcome: 2.3 effect on body weight

is significantly more efficacious than placebo in decreasing HbA_{1c}, FPG, and body weight.^[44,45] Canagliflozin has also been shown to be efficacious and safe among patients with

T2DM and chronic kidney disease. There was a significant decrease in HbA_{1c} levels, body weight, and blood pressure over 52 weeks.^[41]

Strengths and weaknesses of the review

One of the important strengths of the review includes the assessment of efficacy and safety of canagliflozin in combination therapy in two different doses with

placebo and a comparator, sitagliptin. We have searched the databases till June 2015, thus trying to include all the possible data related to canagliflozin. This review consists of published data only. Upon completion of a thorough

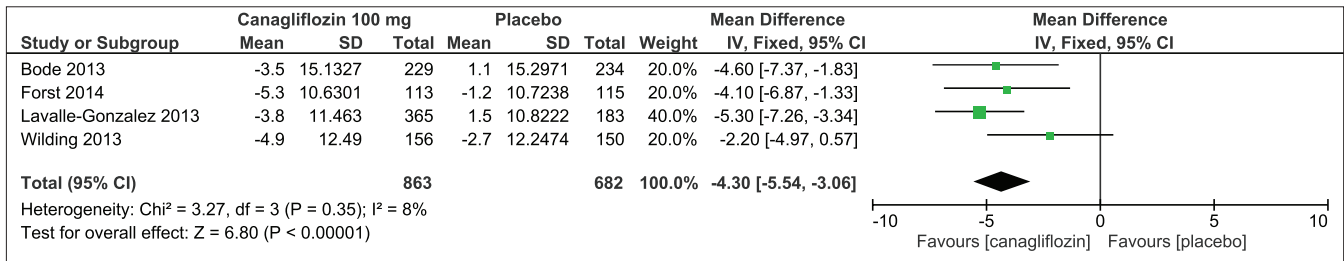


Figure 14: Forest plot of comparison: 2 canagliflozin 100 mg once daily versus placebo after 26 weeks, outcome: 2.4 effect on systolic blood pressure

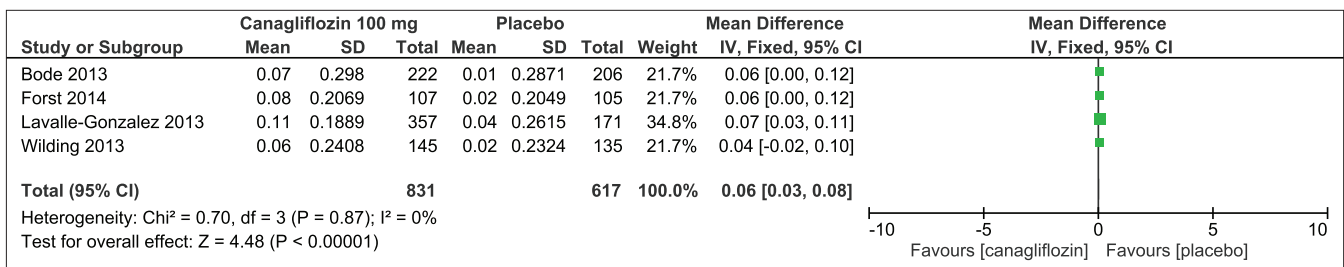


Figure 15: Forest plot of comparison: 2 canagliflozin 100 mg once daily versus placebo after 26 weeks, outcome: 2.5 effect on high-density lipoprotein-C levels

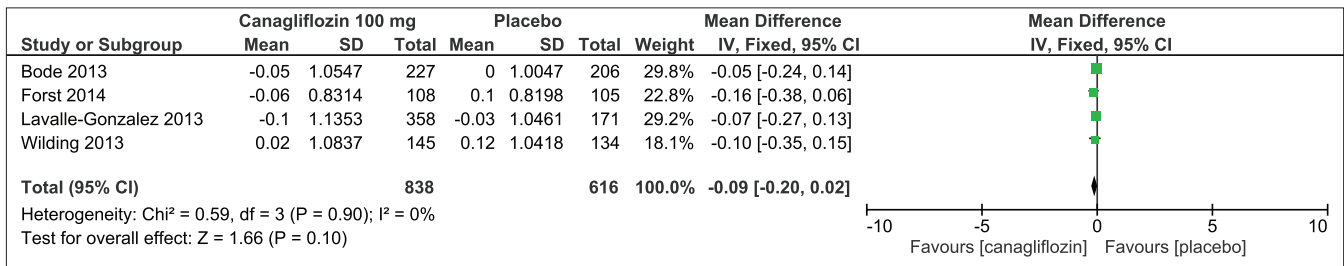


Figure 16: Forest plot of comparison: 2 canagliflozin 100 mg once daily versus placebo after 26 weeks, outcome: 2.6 effect on triglyceride levels

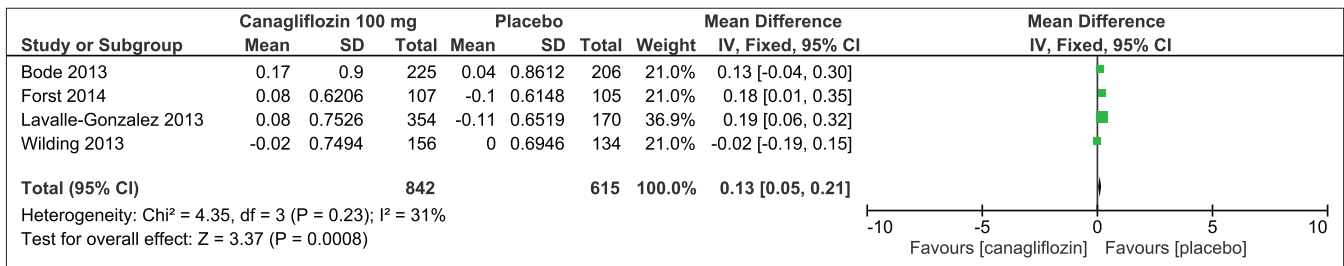


Figure 17: Forest plot of comparison: 2 canagliflozin 100 mg once daily versus placebo after 26 weeks, outcome: 2.7 effect on low-density lipoprotein-C levels

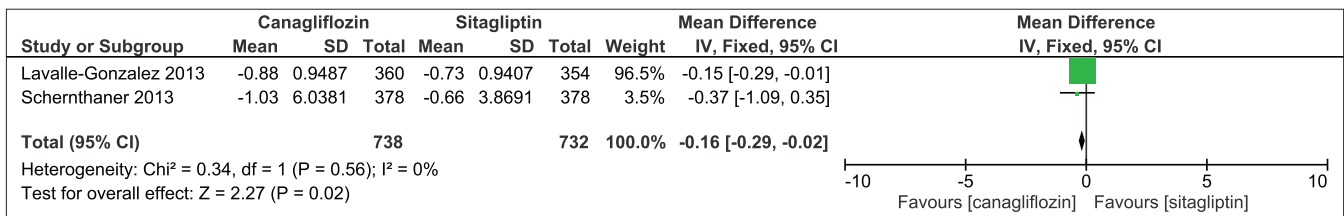


Figure 18: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.1 effect on hemoglobin A_{1c} levels

search of all major databases with no language restrictions, we believe that all relevant studies were identified. Two review authors assessed the trials for inclusion in the review and the risk of bias, and a third review author adjudicated whether there was any discrepancy. Most of the reviews have evaluated canagliflozin in monotherapy

and for shorter duration of administration, that is, 12–18 weeks.

One weakness of the review includes the nonavailability of safety data from the included studies at 26 weeks for quantitative analysis. Information about the incidence of

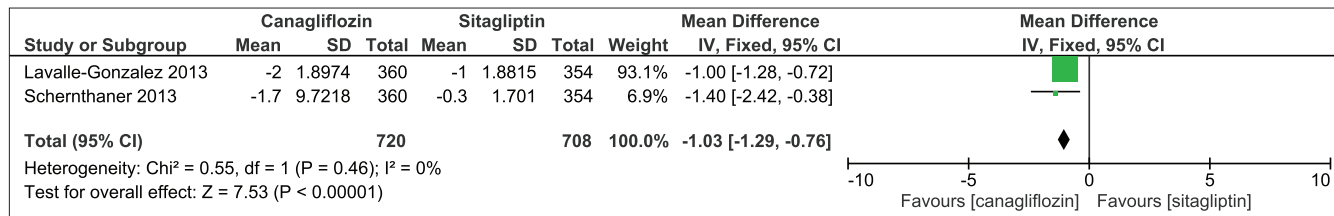


Figure 19: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.2 effect of fasting plasma glucose levels

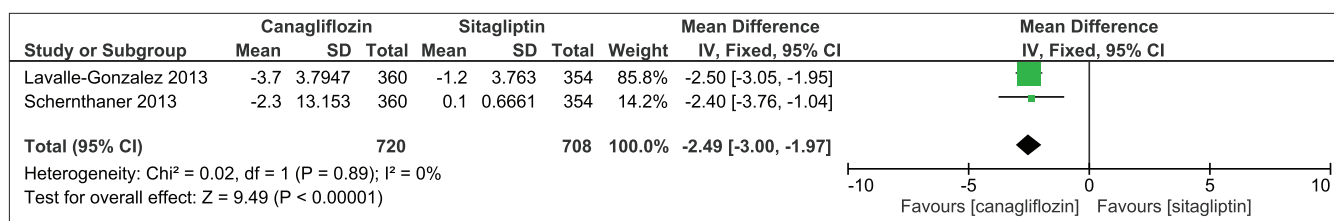


Figure 20: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.3 effect on body weight

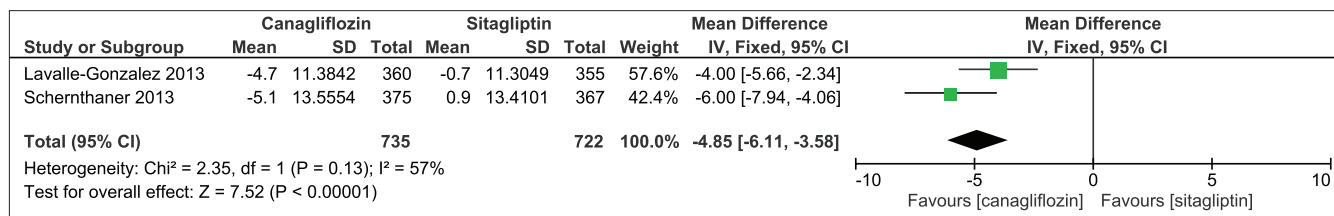


Figure 21: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.4 effect on systolic blood pressure

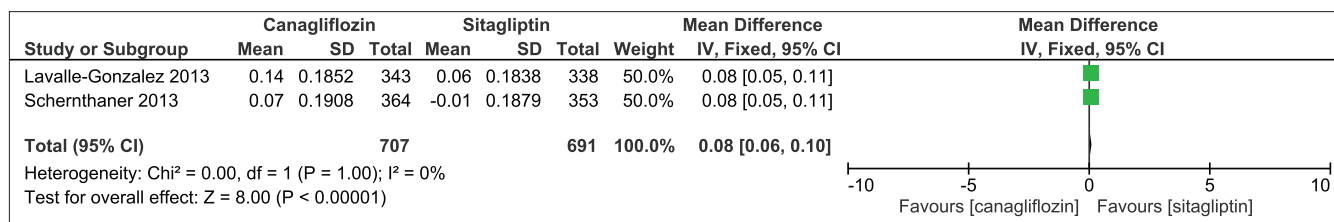


Figure 22: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.5 effect on high-density lipoprotein-C levels

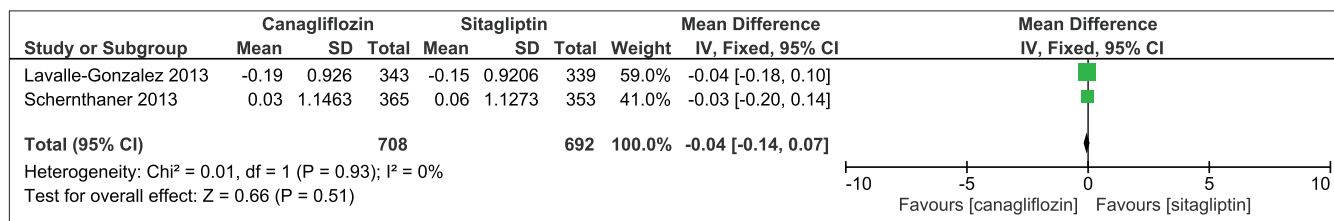


Figure 23: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.6 effect on triglyceride levels

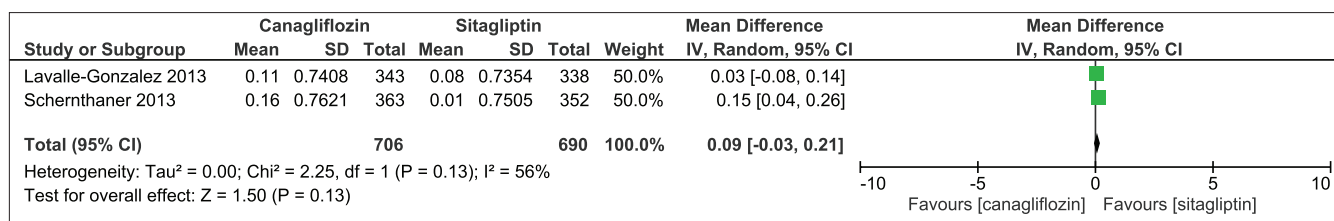


Figure 24: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.7 effect on low-density lipoprotein-C levels

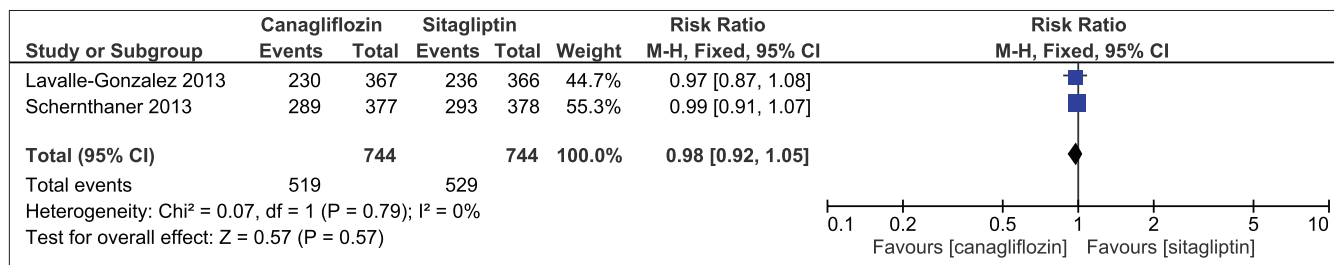


Figure 25: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.8 adverse events

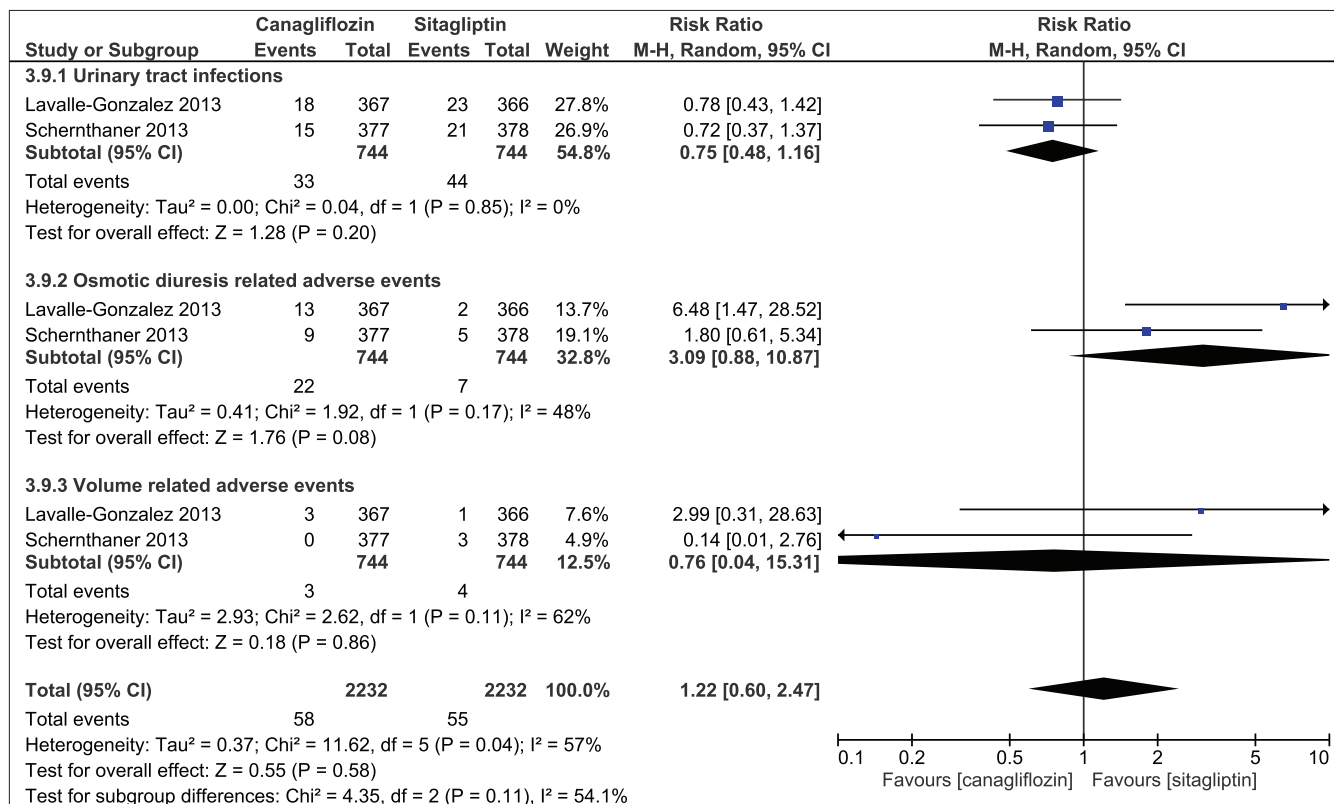


Figure 26: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.9 selected adverse events

adverse effects in comparison to placebo at 26 weeks was available from Bode *et al.*, only.^[13] Rest of the studies had mentioned the safety profile at 52 weeks, which could not be compared as in these studies the initial placebo arm had been shifted to a comparator group at 26 weeks.^[14-16] Hence, this arm could not be compared with canagliflozin arms.

CONCLUSION

Canagliflozin (100 mg and 300 mg once daily) significantly decreases HbA_{1c} levels, FPG levels, body weight, systolic blood pressure, and triglyceride levels, and simultaneously also increases HDL-C levels when used in combination

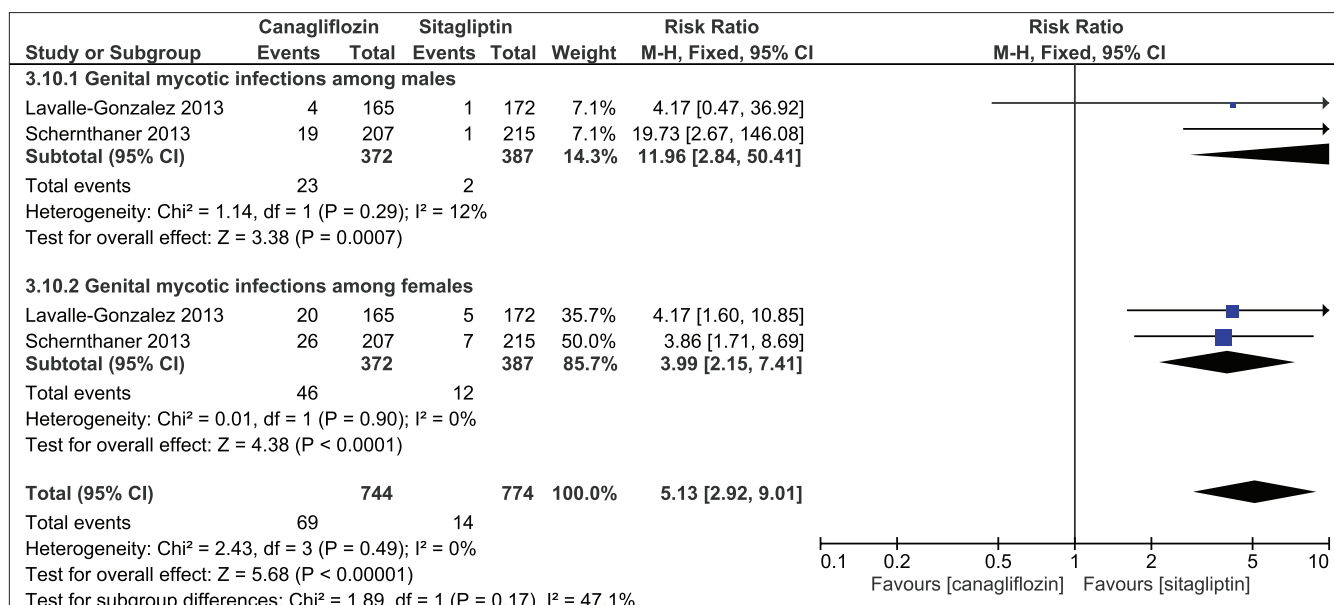


Figure 27: Forest plot of comparison: 3 canagliflozin 300 once daily versus sitagliptin 100 mg after 52 weeks, outcome: 3.10 genital mycotic infections

therapy among patients with inadequate glycemic control as compared to placebo. In view of increasing concern about the safety profile of canagliflozin, there is a need of long-term studies of canagliflozin as compared to the available glucose-lowering agents.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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