Int J Clin Exp Med 2016;9(5):7807-7817
www.ijcem.com /ISSN:1940-5901/IJCEM0018493

Original Article

Therapeutic effect of canagliflozin on type 2 diabetes mellitus: a systematic review and meta-analysis

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Received October 25, 2015; Accepted March 24, 2016; Epub May 15, 2016; Published May 30, 2016

Abstract: Background and Objective: In order to assess the efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, on treatment of type 2 diabetes mellitus (T2DM), we perform this systematic review and meta-analysis. Methods: Randomized controlled trials were identified by searching databases from the period 1960 to 2015, as well as from the reference sections of retrieved articles. Results from individual studies were synthetically combined using Cochrane Collaboration's Review Manager 5.2 software. Results: A total of 7 randomized controlled trials were included in our meta-analysis, involving 4,606 participants. Five trials compared canagliflozin with placebo, one trial compared canagliflozin with sitagliptin, and the other one compared canagliflozin with glimepiride. Five included trials were categorized as low risk and two were moderate. A significant number of subjects achieved HbA1c < 7.0% in canagliflozin groups compared with placebo group. Apart from the genitourinary tract infections, canagliflozin was well tolerated. There was a trend to increase both high and low density lipoprotein cholesterols, but decrease triglycerides in canagliflozin groups compared with control groups. Conclusions: Canagliflozin seems to significantly improve short-term outcomes in participants with T2DM but long-term follow-up data are required.

Keywords: Canagliflozin, type 2 diabetes mellitus, systematic review, meta-analysis, randomized controlled trial

Introduction

According to the International Diabetes Federation (IDF) latest statistics, in 2013 the world has 382 million adults with diabetes and the number is expected to reach 592 million by 2035. Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease resulting from defects in insulin secretion and insulin action, which lead to hyperglycemia, deterioration in β-cell function (βCF), subsequent insulin secretion failure and finally clinical diabetes [1-3]. Metformin, the standard and preferred first-line pharmacological drug for T2DM, provides effective control [4]. However, some patients who could not tolerate metformin due to contraindications have to choose other medicines such as sulphonylureas, a-glucosidase inhibitors, thiazolidinediones, incretins and insulin, most of which lead to weight gain and increase the risk of hypoglycemia. A recent statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) suggests that therapy should be individualized and tailored to the specific needs of each patient [4]. In view of this, new AHAs which can provide glycemic control, minimal hypoglycemia and beneficial effects on weight are required.

Canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, is in development for the treatment of patients with T2DM [5-8]. The SGLT-2 is a protein located in the proximal tubule of the kidney, which is responsible for renal glucose reabsorption [9]. The SGLT2 inhibitor lowers the renal threshold for glucose (RTG) and increases urinary glucose excretion (UGE), resulting in improving glycemic control, mild osmotic diuresis and weight loss [10]. Therefore, canagliflozin with the novel mechanism independent from insulin, might offer new oral treatment options to treat patients with T2DM as a monotherapy or combination treatments. In March 2013, the Food and Drug Administration (FDA) approved canagliflozin for utilization in patients with T2DM [11, 12]. Therefore, the aim of this review was to assess

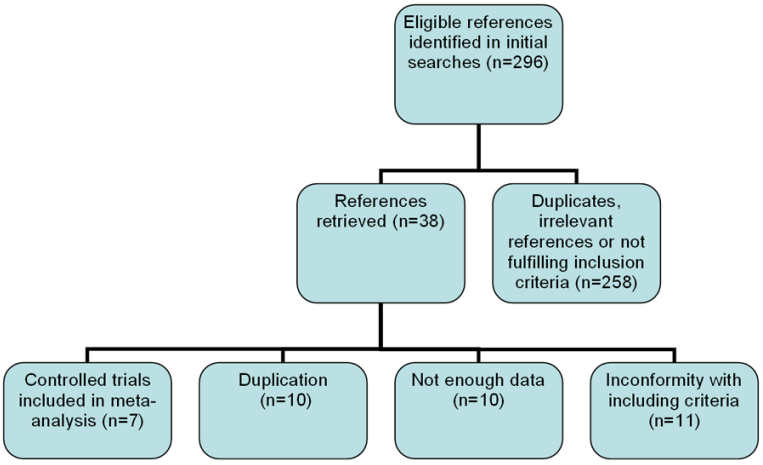

Figure 1. Flow chart of the trial selection process.

the efficacy and safety of canagliflozin at different doses in the treatment of T2DM, compared with placebo or other antidiabetic agents, either as monotherapy or add-on treatment.

Methods

Data sources and search strategies

Eligible studies were identified by searching databases from the period 1960 to 2015, including Embase, Cochrane Central Register of Controlled Trails, PubMed, Web of Science and Clinical Trials Registry Platform as well as from the reference sections of retrieved articles. The search terms included "canagliflozin", "diabetes", "diabetes mellitus", and "randomized controlled clinical trials". These terms were adjusted to fit the requirements for each database.

Study selection criteria

Studies meeting the following criteria were included in our systematic review and meta-analysis: 1. Randomized controlled clinical trials in any language examined the efficacy or safety of canagliflozin on T2DM; 2. Participants were adults (over 18 years of age) with T2DM fulfilling ADA or WHO criteria. The diagnosis should be made by using the standard criteria valid at beginning of the trial; 3. Canagliflozin should be given orally for at least 12 weeks; 4. Studies evaluated any of the following endpoint were screened, including glycolated hemoglobin A1c (HbA1c), body weight change from baseline, low density lipoprotein-cholesterol (LDL-C) change, high density lipoprotein-cholesterol (HDL-C) change, triglyceride change, blood pressure change, βCF change, adverse events, all-cause mortality, diabetes related mortality, diabetes related morbidity, cardiovascular morbidity and cancer risk.

Data extraction and management

Two authors extracted data independently. Data extracted from the included trials were filled in a predesigned data collection form and were input into Review Manager 5.2 software. Disagreements were resolved by consulting to a third review author.

Data synthesis and analysis

Meta-analysis was performed using Review Manager 5.2 software. Dichotomous data were analyzed by using the risk ratio (RR) computed using the Mantel Haenszel Method (fixed or random models). Continuous outcomes measured on the same scale were expressed as a mean value and standard deviation (SD) and were analyzed by using weighted mean difference (WMD). Heterogeneity was explored by I^2 test. According to the Cochrane review guidelines, if severe heterogeneity was present at $I^2 \geq 50\%$, the random-effect model was used to combine the results, otherwise, the fixed-effect model was used. Subgroup analysis were planned to be performed if necessary. Sensitivity analyses were conducted by omitting each study sequentially, to evaluated the quality and consistency of the results. We planned to assess risk of bias in all included studies using the Cochrane Collaboration's tool.

Results

Included studies

A flow chart for identification and selection of included studies is presented in **Figure 1**. Our search retrieved 296 records. After review of titles and abstracts and removal of duplicates across databases, 38 records were identified for further evaluation. Then, 31 records [5,

Table 1. Summary characteristics of included studies

First author (Year)	Intervention group					Control group					Follow-up
	Sample size (M/F)	Age (Year) (mean ± SD)	Disease duration (Year) (mean ± SD)	A1C (%)	Treatment protocol	Sample size (M/F)	Age (Year) (mean ± SD)	Disease duration (Year) (mean ± SD)	A1C (%)	Treatment protocol	
Rosenstock 2012	64 (34/30)	53.3±8.5	5.6±5.0	8.00±0.99	CANA 50 mg QD	65 (31/34)	53.3±7.8	6.4±5.0	7.75±0.83	PBO	12 weeks
	64 (36/28)	51.7±8.0	6.1±4.7	7.83±0.96	CANA 100 mg QD	65 (38/27)	51.7±8.1	6.0±4.9	7.75±0.93	SITA 100 mg QD	
	65 (33/32)	52.9±9.6	6.4±5.7	7.61±0.80	CANA 200 mg QD						
	64 (36/28)	52.3±6.9	5.9±5.2	7.69±1.02	CANA 300 mg QD						
	64 (28/36)	55.2±7.1	5.8±4.6	7.73±0.89	CANA 300 mg BID (Add-on to metformin)						
Yale 2013	90 (58/32)	69.5±8.2	15.6±7.4	7.9±0.9	CANA 100 mg QD	90 (57/33)	68.2±8.4	16.4±10.1	8.0±0.9	PBO	26 weeks
	89 (48/41)	67.9±8.2	17.0±7.8	8.0±0.8	CANA 300 mg QD (With or not with other AHA)						
Inagaki 2013	82 (50/32)	57.4±10.8	Unclear	8.13±0.78	CANA 50 mg QD	65 (31/34)	57.7±11.0	unclear	7.99±0.77	PBO	12 weeks
	74 (52/22)	57.7±10.5		8.05±0.86	CANA 100 mg QD						
	76 (49/27)	57.0±10.7		8.11±0.88	CANA 200 mg QD						
	75 (55/20)	57.1±10.1		8.17±0.81	CANA 300 mg QD						
Bode 2013	241 (124/117)	64.3±6.5	12.3±7.8	7.8±0.8	CANA 100 mg QD	237 (143/94)	63.2±6.2	11.4±7.3	7.8±0.8	PBO	26 weeks
	236 (129/107)	63.4±6.0	11.3±7.2	7.7±0.8	CANA 300 mg QD (With or not with other AHA)						
Stenlof 2013	195 (81/114)	55.1±10.8	4.5±4.4	8.1±1.0	CANA 100 mg QD	192 (88/104)	55.7±10.9	4.2±4.1	8.0±1.0	PBO	26 weeks
	197 (89/108)	55.3±10.2	4.3±4.7	8.0±1.0	CANA 300 mg QD						
Schernthaner 2013	377 (207/170)	56.6±9.6	9.4±6.1	8.1±0.9	CANA 300 mg QD (Add-on to metformin and sulfonylurea)	378 (215/163)	56.7±9.3	9.7±6.3	8.1±0.9	SITA 100 mg QD	52 weeks
Cefalu 2013	483 (252/231)	56.4±9.5	6.5±5.5	7.8±0.8	CANA 100 mg QD	482 (263/219)	56.3±9.0	6.6±5.0	7.8±0.8	Glimepride	52 weeks
	485 (241/244)	55.8±9.2	6.7±5.5	7.8±0.8	CANA 300 mg QD (Add-on to metformin)						

M, male; F, female; SD, standard deviation; QD, four times a day; BID, twice a day; CANA, canagliflozin; PBO, placebo; SITA, sitagliptin.

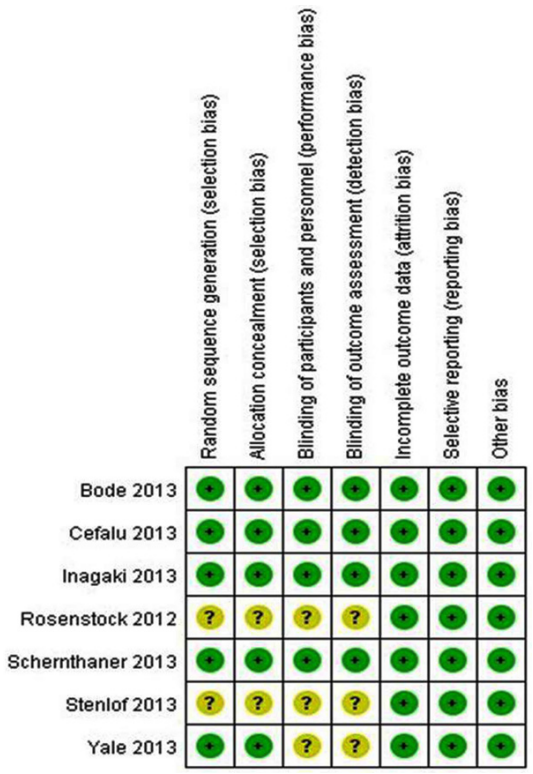

Figure 2. Summary of the risk of bias assessment results of the included studies.

13-42] were excluded for duplication, inconformity with including criteria, or no data available. Therefore, 7 studies [43-49] were retained for our meta-analysis. Of the 7 included studies, most trials are sponsored by pharmaceutical companies. A total of 4,606 patients took part in the trials. The median trial duration was 6 months (range from 3 to 24 months). Canagliflozin was administered orally in all studies. Most doses were between 100-300 mg/d (range from 50 mg QD to 300 mg BID). All included studies were published in English. Further details for included studies were available in **Table 1**.

Risk of bias in included studies

The risks of bias of included trials were summarized in **Figure 2**. Five included trials were categorized as low risk [43-45, 47, 49] and two were moderate [46, 48].

Effects of interventions

Glycolated hemoglobin A1c: Canagliflozin 100 mg versus placebo trials [43, 45, 48, 49] demonstrated substantial heterogeneity (I^2 = 55%). After elimination of the study [45] in Japanese patients only, heterogeneity decreased to an I^2 of 0%. A significant number of subjects in canagliflozin 100 mg group [43, 48, 49] achieved HbA1c < 7.0% compared with placebo group. Pooled risk ratios (RR) was 1.84 (95% CI: 1.53-2.21) (**Figure 3A**).

Canagliflozin 300 mg versus placebo trials [43, 45, 48, 49] also showed substantial heterogeneity. Elimination of Inagaki 2013 [45] (Japanese patients only) resulted in an I^2 of 49% and the pooled RR was 2.38 (95% CI: 2.00-2.83) (**Figure 3B**).

Adverse events: Overall adverse events did not differ significantly for canagliflozin 100 mg or 300 mg compared to placebo. RR were 1.06 (95% CI: 0.97-1.16) and 1.08 (95% CI: 1.00-1.17) respectively (**Figure 4**). No significant heterogeneity was found among these trials. For the incidence of serious adverse effects, no significant difference was found in either individual trial data or pooled analysis results.

Rates of genitourinary tract infections were higher in canagliflozin groups than in controls (**Figure 5A**), sitagliptin, or glimepiride groups, but we found no significant difference of urinary tract infection among these groups (**Figure 5B**).

All trials reported hypoglycemic episodes. No significant statistical differences in RRs of hypoglycemic episodes were found for canagliflozin compared with placebo or sitagliptin group. While compared with glimepiride, canagliflozin significantly lowered hypoglycemic episodes risk (OR = 0.16, 95% CI: 0.11-0.24). Incidence of severe hypoglycemia was rare in all trials and was seen primarily in participants receiving a sulfonylurea as the allocation or background treatment.

Body weight (change from baseline): Body weight change from baseline was assessed in all trials, but just two trials [43, 44] provided the data of SDs.

In the trial of Bode 2013 [43], both canagliflozin doses significantly reduced body weight compared with controls. WMD were -2.50 (95% CI: -2.78 to -2.22) for canagliflozin 100 mg and -3.20 (95% CI: -3.56 to -2.84) for 300 mg respectively. Cefalu 2013 [44] compared canagliflozin 100 mg and 300 mg with glimepride.

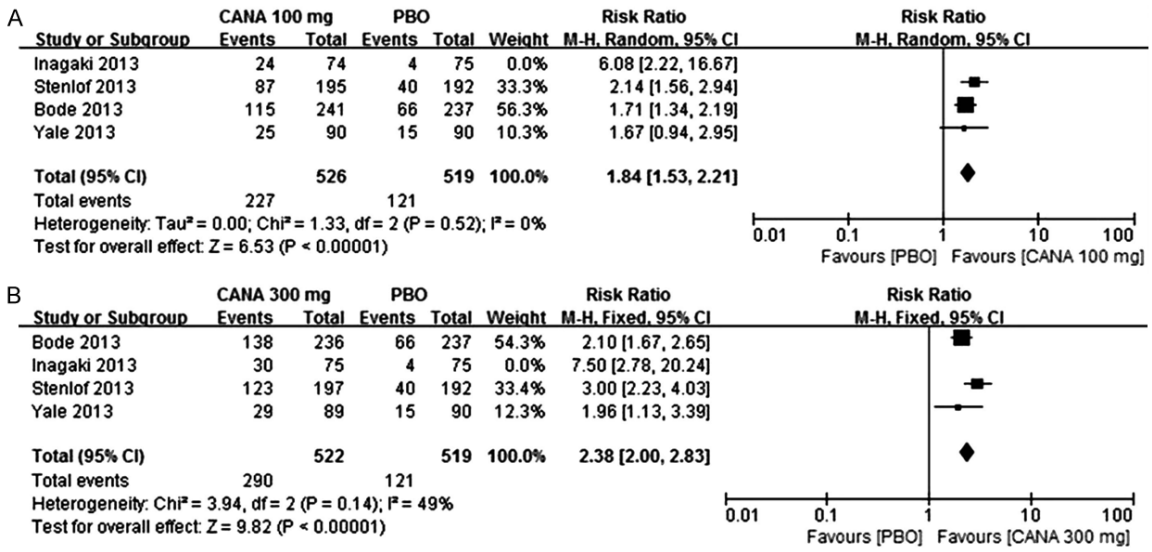

Figure 3. Forest plots of HbA1c. A: CANA 100 mg vs. PBO, B: CANA 300 mg vs. PBO.

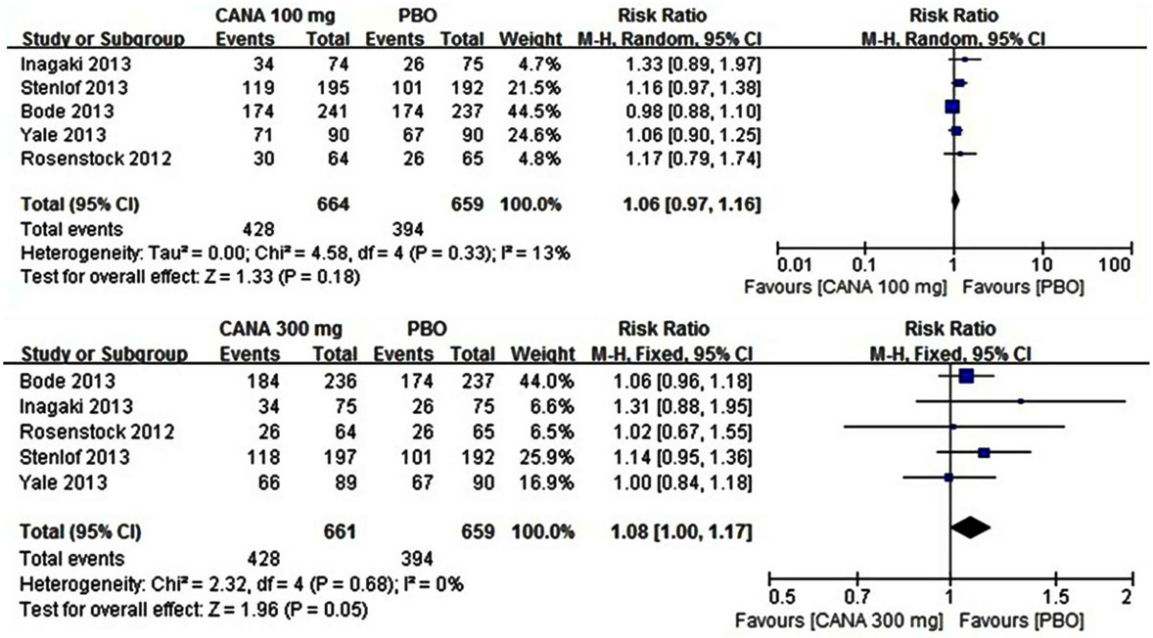

Figure 4. Forest plots of overall frequency of adverse events.

Significant reduction of body weight was found in both groups. WMD were -4.40 (95% CI: -4.95 to -3.85) and -4.70 (95% CI: -5.25 to -4.15) respectively.

Lipid profile: All trials assessed LDL-C level, HDL-C level and triglyceride level. However, data in Rosenstock 2012 [46] were not available. Significant improvement of HDL-C was found in trials [43, 45, 48, 49] comparing canagliflozin 100 mg with placebo. WMD was 2.49 (95% CI: 1.52-3.47). A decrease in triglycerides and an increase in LDL-C were seen in these four trials [43, 45, 48, 49]. WMD were -11.12 (95% CI: -20.32 to -1.95) and 3.85 (95% CI: 0.70 to 7.00) respectively. No significant heterogeneity was found between these trials (**Figure 6**).

Blood pressure: Canagliflozin 50 mg, 100 mg, 200 mg, 300 mg and 300 mg BID were associated with a reduction in systolic blood pressure

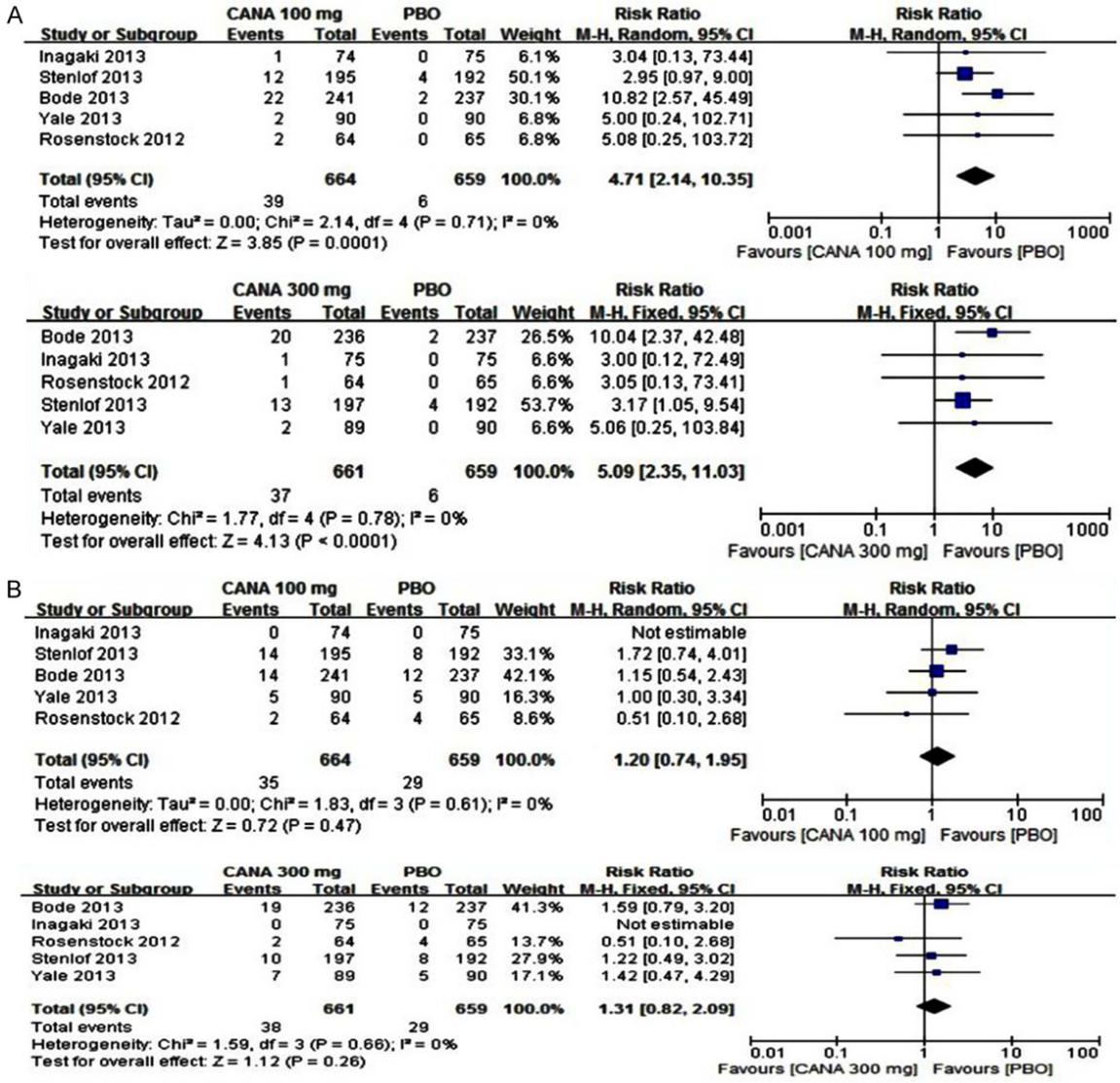

Figure 5. Forest plots of the safety outcomes. A: Genitourinary tract infections, B: Urinary tract infection.

compared with placebo. WMD were -2.86 (95% CI: -5.52 to -0.19), -4.02 (95% CI: -5.37 to -2.66), -5.59 (95% CI: -8.28 to -2.89), -6.20 (95% CI: -7.57 to -4.82) and -2.30 (95% CI: -6.32 to 1.72), respectively. However, considerable heterogeneity was found among studies. Systolic blood pressure reduction was significantly different between canagliflozin and glimepride group, but no significant difference was found when canagliflozin was compared with sitagliptin.

Diastolic blood pressure was also modestly reduced by canagliflozin treatment when compared with placebo or glimepride. However, the pooled result of diastolic blood pressure showed no significant difference between canagliflozin groups and sitagliptin groups. No significant heterogeneity was found between trials except for canagliflozin 200 mg versus placebo trial which included only two trials [45, 46].

Mortality: No significant difference was found between intervention groups and controls. The reasons of deaths were not explained in original trails.

Sensitivity analysis

In view of the diversity of participants, we performed the sensitivity analysis by omitting each study sequentially. When removing the trial of

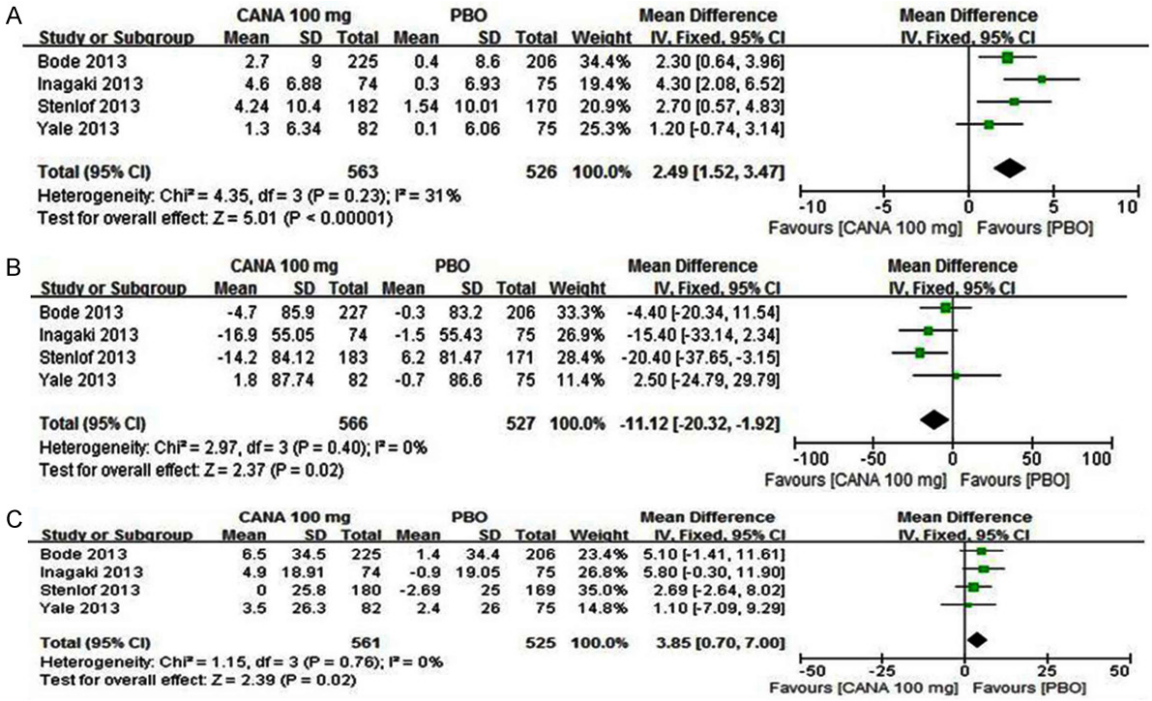

Figure 6. Forest plots of Lipid profile. A: HDL-C. B: Triglycerides. C: LDL-C.

Inagaki 2013 [45], which included Japanese patients only, the heterogeneity decreased in meta-analysis, but the conclusions for all outcomes were unchanged. Similarly, when excluded the trial by Yale et al. [49], which carried out among participants with stage 3 chronic kidney diseases, the results remained unchanged, and this confirmed the stability of the overall values.

Discussion

Main findings and interpretations

In this systematic review and meta-analysis, we analyzed evidence from 7 RCTs compared canagliflozin with placebo or other antidiabetic therapies for patients with T2DM. A total of 4,606 participants were included in these trials. Our results shows that there were more subjects in canagliflozin groups achieving HbA1c < 7.0% than in placebo groups. The reduction in HbA1c was accompanied by a significant decrease in body weight, which is consistent among included studies. No significant difference was found between canagliflozin and glimepride groups. In addition, apart from the predominant adverse genitourinary tract infections effects, canagliflozin was well tolerated, with similar incidence of overall adverse events compared with other groups. In some studies, it is suggested that the combination of canagliflozin and sulfonylurea provides protective effects against side effects. Increased incidence of genitaltract infections was probably due to glucosuria associated with the use of canagliflozin. For other endpoints, there was a trend to increase HDL-C as well as LDL-C, and decrease triglycerides in canagliflozin groups. However, this is inconsistent between studies. Finally, both systolic and diastolic blood pressures were modestly reduced in canagliflozin groups compared with placebo or glimepride groups.

Study strengths and limitations

Our study has some important strength. Because individual studies have insufficient statistical power, our systematic review of 7 RCTs involving 4,606 participants increased the power to detect a potential association and provided more reliable estimates. All the original studies used a randomized controlled trial design, which greatly reduced the likelihood of recall- and selection biases. Moreover, trials included were mainly of moderate to low risk. In

addition, the associations remained unchanged in the sensitivity analysis.

Potential limitations of this study should be considered. Firstly, diversity in patient population, baseline clinical characteristics and trial design across included studies could be expected to influence the outcomes. Participants included in Inagaki 2013 [45] were Japanese patients only, while eligible subjects in Yale 2013 [49] were all with stage 3 chronic kidney diseases and much older than subjects in other trials (mean age of 68.5 years). The range of mean disease duration in the included trials was quite different, although was similar between groups in each trial. In some studies there were several uncertainties or inequalities regarding previous or concomitant antidiabetic treatment. Secondly, trials included were mainly designed to assess short-term efficacy outcomes. Therefore, no long-term outcomes were assessed, such as cardiovascular outcomes, cancer risk and deaths. Thirdly, most included trials used last observation carried forward (LOCF) method to impute missing data, which may lead to overstated results. Fourthly, a potential publication bias might influence the findings due to our relatively strict inclusion criteria. Fifthly, in the present meta-analysis, renal function changes, other glycemic efficacy data except HbA1c and renal glycosuria data were not provide due to insufficient original data. Finally, the outcomes of trials may be biased by business interests because all the included trials were sponsored by pharmaceutical companies.

Comparison of the present results with existing literature

Findings in this analysis were consistent with those from previous studies. Three related systematic reviews [50-52] assessing SGLT2 inhibitors as a group were identified through a rapid searching in PubMed. 13 placebo-controlled trials were included in the review of Musso and associates [52], but only 2 of which assessed canagliflozin. Berhan and colleagues [50] examined the efficacy and safety of SGLT2 inhibitors and included 3 trials for canagliflozin. Conclusions from the meta-analysis by Clar and associates [51] were based on 8 trials, only 1 of these trials was for canagliflozin. These three meta-analyses [50-52] demonstrated the favorable effects of SGLT2 inhibitors on glycemic control, body weight and blood pressure improvements, which showed no big differences with ours. However, their conclusions were drawn primarily from dapagliflozin.

Possible underline mechanisms

SGLT2 is a low-affinity high-capacity transporter located in the brush-border membrane of the proximal renal tubule, which accounts for approximately 90% of the reabsorption of glucose from tubular fluid. Competitive inhibitors of SGLT2 that are responsible for renal excretion of glucose provide a unique mechanism to potentially lower the elevated blood glucose levels in patients with diabetes. They act independently from insulin secretion, and thereby minimize the risk of hypoglycemia and weight gain. They also have effects on energy control and balance, which is a distinctive advantage comparing with existing oral hypoglycemic agents [5-10]. Although this group of medications is still under investigation, it appears to be safe and generally well-tolerated. The canagliflozin works through induction of urinary glucose excretion, the rate of which is dependent on glomerular filtration rate and plasma glucose concentration [6, 8]. For this reason, it is hypothesized that canagliflozin will be an effective treatment choice at most stages of the diseases, and in combination with other glucose-lowering therapies. However, the effect of canagliflozin in increasing urinary glucose excretion is attenuated in patients with lower evaluated glomerular filtration rate and it improves glycemic control to a lesser extent in patients with moderate renal impairment compared to patients with normal or mildly impaired renal function. The mechanism for the lipid profile changes we found in our study is still not fully known. LDL-C increase is likely related to the metabolic changes associated with urinary glucose excretion and the improvement in HDL-C and triglycerides may be in relation to the improved glycemic control and weight loss associated with canagliflozin [48].

Unanswered questions of study

In addition to the variables we examined, other factors, including assessing the effect of canagliflozin in βCF, cardiovascular outcomes, long-term effects of canagliflozin on diabetic complications, and renal function changes, merit consideration. Few data were available to assess

the effect of canagliflozin in βCF. Inspection of the canagliflozin homeostasis model assessment beta (HOMA-beta) data seems to indicate that canagliflozin compared to placebo results in increased values of βCF measurements, the effect in comparison with sitagliptin does not seem to be clear-cut [45, 46, 48]. For cardiovascular outcomes, only one trial [45] was planned to assess cardiovascular morbidity but no event occurred. The ongoing trial [53] might be favorable for canagliflozin in the treatment of patients with T2DM regarding to cardiovascular risk for major adverse cardiac events. Moreover, some other long-term effects, including cancer risk, need to be studied in the future.

Conclusions

Implications for practice

Canagliflozin improved glycemic control, reduced body weight and blood pressure, and was generally well tolerated in subjects with T2DM.

Implications for research

Long-term data on cardiovascular and safety outcomes are required. High quality RCTs are needed to verify the efficacy and safety of canagliflozin for patients with T2DM.

Disclosure of conflict of interest

None.

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