Efficacy of canagliflozin combined with antidiabetic drugs in treating type 2 diabetes mellitus: Meta-analysis of randomized control trials

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Keywords
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ABSTRACT
Aims/Introduction: Canagliflozin has been proposed as an effective treatment for type 2 diabetes. This meta-analysis of randomized control trials aimed to evaluate the effect of canagliflozin combined with other hypoglycemic drugs.

Materials and Methods: We searched Medline, Embase, Cochrane Library, Google Scholar and ClinicalTrials.gov for randomized control trials comparing canagliflozin combined with conventional antidiabetic drugs vs placebo. Our main end-points were glycemic control and change in weight. We assessed pooled data by use of a random-effects model.

Result: Of 161 identified studies, six were eligible and were included in our analysis (n = 4670 participants). Compared with the placebo, mean changes in glycosylated hemoglobin were -0.60% (95% confidence interval -0.67 to -0.54%; I² = 0%) for canagliflozin 100 mg, and -0.76% (95% confidence interval -0.84 to -0.68%; I² = 20%) for canagliflozin 300 mg with bodyweight loss.

Conclusion: Canagliflozin as an add-on drug to other antidiabetic drugs effectively lowers blood glucose without significant weight gain.

INTRODUCTION
Type 2 diabetes mellitus is a chronic metabolic disorder seriously influencing the health, quality of life and life expectancy of patients, as well as placing a burden on the healthcare system. Insulin resistance and β-cell dysfunction are the two critically important factors in the pathogenesis of the hyperglycemia of type 2 diabetes1. The effect of existing hypoglycemic drugs is insulin-dependent, either by enhancing insulin secretion or by improving insulin sensitivity. As the function of pancreatic islet β-cell declines in the progression of type 2 diabetes, the efficacy of conventional insulin-dependent antidiabetic drugs tends to be subdued2.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antihyperglycemic drugs with an insulin-independent action on reducing glucose renal reabsorption and increasing urinary glucose excretion3,4. In the statement published by the American Diabetes Association and the European Association for the Study of Diabetes, SGLT2 inhibitor is recommended at any stage of type 2 diabetes, even after insulin secretion has waned significantly5. Canagliflozin is one of the first members of this class that have received approval to treat type 2 diabetes in Europe and the USA. Promising results have been shown in individual clinical studies in controlling glycemia, causing weight loss, reducing systolic and diastolic blood pressure, and cardiovascular risk6. That might have a beneficial impact on disease progression.

A previous meta-analysis reviewed the efficacy and safety of canagliflozin in patients7 with type 2 diabetes7, which was not registered before carried out. Meanwhile, the meta-analysis7 used the 300-mg canagliflozin data only. We therefore carried out a meta-analysis to evaluate the synergistic effect of canagliflozin 100-mg dose and 300-mg dose vs a placebo in...
combination with other antidiabetic medications in adult patients with type 2 diabetes on the key outcomes of glycemic control and weight regulation.

MATERIALS AND METHODS
Data sources and search strategy
The present systemic review and meta-analysis is in accordance with the recommendation set forth in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

The search of relevant studies included MEDLINE (via PubMed), EMBASE (via OVID), Cochrane Library, Google Scholar and ClinicalTrials.gov from inception to January 2015. We used the following combined text and MeSH terms: ‘canagliflozin’ and ‘diabetes’, and applied no language restrictions. All potentially eligible studies for review were considered, and results of trials were retrieved. In addition, a manual search of journals was carried out to track relevant randomized controlled trials (RCTs) that were not indexed by normal keywords.

161 records founded
Abstracts and titles reviewed \( n = 72 \)
Duplicates 68
Not RCT \( n = 13 \)
Duration < 12 weeks \( n = 1 \)
23 RCTs met inclusion criteria
Monotherapy \( n = 13 \)
No placebo \( n = 3 \)
CANA twice daily \( n = 1 \)

Table 1 | Basic characteristics of included randomized controlled trials

| Year | Interventions | n | Mean age (years) \(^{†}\) | HbA1c (\(\%\)) \(^{\dagger}\) | FPG (mmol/L or mg/dL) \(^{\dagger}\) | BMI \(^{\dagger}\) | Duration of Interventions (weeks) | Mean duration of diabetes (years) |
|------|--------------|---|---------------------------|------------------------|------------------------|------------------------|-------------------------------|----------------------------------|
| 2012 | PBO + MET    | 65 | 53.3 (7.8)                  | 7.75 (0.83)            | 164 (38) \(^{\ddagger}\)      | 30.6 (4.6)             | 12                            | 64 (5.0)                         |
|      | CANA 50 mg   |   | 53.3 (8.5)                  | 8.00 (0.99)            | 170 (45) \(^{\ddagger}\)      | 31.7 (4.6)             |                               | 5.6 (5.0)                         |
|      | CANA 100 mg QD + MET | 64 | 51.7 (8.0)                  | 7.83 (0.96)            | 168 (42) \(^{\ddagger}\)      | 31.7 (5.0)             |                               | 61 (4.7)                          |
|      | CANA 200 mg QD + MET | 65 | 52.9 (6.9)                  | 7.61 (0.80)            | 160 (37) \(^{\ddagger}\)      | 31.4 (5.2)             |                               | 64 (5.7)                          |
|      | CANA 300 mg QD + MET | 64 | 52.3 (6.9)                  | 7.69 (1.02)            | 159 (44) \(^{\ddagger}\)      | 31.6 (4.9)             |                               | 59 (5.2)                          |
|      | CANA 300 mg BID + MET | 64 | 52.2 (7.1)                  | 7.73 (0.89)            | 157 (34) \(^{\ddagger}\)      | 31.8 (5.2)             |                               | 58 (4.6)                          |
|      | SITA 100 mg QD + MET | 65 | 51.7 (8.1)                  | 7.64 (0.95)            | 158 (42) \(^{\ddagger}\)      | 31.6 (5.0)             |                               | 56 (4.7)                          |
| 2013 | PBO + MET    | 183 | 55.3 (9.76)                | 8.0 (0.9)              | 9.1 (2.1)                | 31.1 (6.1)            | 26                            | 68 (5.3)                          |
|      | CANA 100 mg QD + MET | 368 | 55.5 (9.38)                | 7.9 (0.9)              | 9.3 (2.3)                | 32.4 (6.7)            |                               | 67 (5.4)                          |
|      | CANA 300 mg QD + MET | 367 | 55.3 (9.19)                | 7.9 (0.9)              | 9.6 (2.5)                | 31.4 (6.3)            |                               | 7.1 (5.4)                          |
|      | SITA 100 mg QD + MET | 366 | 55.5 (9.55)                | 7.9 (0.9)              | 9.4 (2.3)                | 32.0 (6.1)            |                               | 68 (5.2)                          |
| 2013 | PBO + MET&SU | 156 | 56.8 (8.3)                  | 8.1 (0.9)              | 9.4 (2.2)                | 32.7 (6.8)            | 52                            | 103 (6.7)                         |
|      | CANA 100 mg QD + MET&SU | 157 | 57.4 (10.5)                | 8.1 (0.9)              | 9.6 (2.3)                | 33.3 (6.3)            |                               | 90 (5.7)                          |
|      | CANA 300 mg QD + MET&SU | 156 | 56.1 (8.9)                  | 8.1 (0.9)              | 9.3 (2.1)                | 33.2 (6.3)            |                               | 94 (6.4)                          |
| 2014 | PBO + MET&PIO | 115 | 58.3 (9.6)                  | 8.0 (1.0)              | 9.1 (2.2)                | 32.5 (6.4)            | 26                            | 101 (6.6)                         |
|      | CANA 100 mg QD + MET&PIO | 113 | 56.7 (10.4)                | 8.0 (0.9)              | 9.4 (2.2)                | 32.3 (6.2)            |                               | 105 (6.6)                         |
|      | CANA 300 mg QD + MET&PIO | 114 | 57.0 (10.2)                | 7.9 (0.9)              | 9.1 (2.3)                | 32.8 (7.7)            |                               | 110 (7.6)                         |
| 2014 | PBO + INS/AHA | 690 | 63.0 (38–82)\(^{§}\)      | 8.3 (0.9)              | 9.2 (2.7)                | 33.1 (6.5)            | 52                            | 160 (7.8)                         |
|      | CANA 100 mg QD + INS/AHA | 692 | 62.0 (32–83)\(^{§}\)      | 8.3 (0.9)              | 9.2 (2.7)                | 33.0 (6.5)            |                               | 164 (7.3)                         |
|      | CANA 300 mg QD + INS/AHA | 690 | 63.0 (37–85)\(^{§}\)      | 8.3 (0.9)              | 9.2 (2.8)                | 33.6 (6.2)            |                               | 163 (7.4)                         |
| 2015 | PBO + MET&MET&SU | 226 | 55.8 (9.4)                  | 7.9 (0.9)              | 8.8 (1.8)                | 25.5 (3.6)            | 18                            | 64 (4.6)                          |
|      | CANA 100 mg QD + MET&MET&SU | 223 | 56.5 (8.3)                  | 8.0 (0.9)              | 8.9 (2.0)                | 26.0 (3.4)            |                               | 68 (4.5)                          |
|      | CANA 300 mg QD + MET&MET&SU | 227 | 56.4 (9.2)                  | 8.0 (0.9)              | 8.9 (2.0)                | 26.0 (3.4)            |                               | 69 (4.9)                          |

\(^{†}\)Measured by mean (standard deviation). \(^{\dagger}\)Measured by mg/dL. \(^{§}\)Measured by mean (range). BID, twice per day; BMI, body mass index; CANA, canagliflozin; FPG, fast plasma glucose; HbA1c, glycosylated haemoglobin; INS, insulin; MET, metformin; PBO, placebo; PIO, pioglitazone; QD, once per day; RCT, randomized controlled trials; SU, sulphonylurea.
Study selection and data extraction
Only randomized clinical trials carried out in adults with type 2 diabetes were included. The treatment intervention included only canagliflozin combined with conventional antidiabetic drugs – canagliflozin monotherapy was excluded. Only studies using a placebo combined with other antidiabetic drugs as the controls were included. In consideration of observing changes in glycosylated hemoglobin (HbA1c) levels, follow-up durations lasted at least 12 weeks. The outcomes assessed were as follows: changes in HbA1c, fasting plasma glucose, and bodyweight between baseline and end of intervention.

Two independent investigators (QM and YS) evaluated the studies according to inclusion and exclusion criteria. Discrepancies were resolved through consensus. The following data from each selected study were extracted: total number of participants, baseline characteristic of participants, trial duration, interventions (doses of canagliflozin and the combined drugs) and efficacy outcomes. Data are presented as mean ± standard deviation, mean and 95% confidence interval (CI), or mean and range, as appropriate.

Quality assessment
Two independent reviewers (DJL and FJ) assessed the risk of bias according to the Cochrane risk of bias tool. The following domains were considered: random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Disagreement was resolved by discussion.

Statistical analysis
The effect of canagliflozin was accessed by three outcomes: glycemic control, as assessed by both HbA1c and FPG, and weight. All the three outcomes were assessed as continuous variables, and reported absolute differences between arithmetic means before and after interventions. We calculated pooled estimates of the mean differences in HbA1c, FPG and weight between intervention groups by using a random-effects model to adequately account for the additional uncertainty associated with interstudy variability in the effect of different combined antidiabetic drugs. Subgroup analysis was carried out according to canagliflozin dose and different indexes in measure. Heterogeneity was assessed with the $I^2$ statistics, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity. We also carried out the sensitivity analyses to test the robustness of our findings. We used Review Manager version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata (version 13.1; Stata Corp, College Station, TX, USA) for all statistical analyses.
RESULTS
Results of search and study characteristics
We identified 161 citations, of which six were included in our analysis (Figure 1). The six trials were all published between 2012 and 2015 (Table 111–16). The trial durations lasted from 12 to 52 weeks. All participants were adult patients with type 2 diabetes. The baseline range of HbA1c was 7.6–8.3%. All studies were compared vs placebo, two trials on a background of

| Study or subgroup | Canagliflozin Mean | Canagliflozin SD | Placebo Mean | Placebo SD | Total Mean | Total SD | Weight Mean Difference | IV, Random, 95% CI |
|-------------------|-------------------|-----------------|--------------|------------|-----------|---------|-----------------------|-------------------|
| 3.1.1 Canagliflozin 100 mg | –0.89 | 0.733 | 0.26 | 0.737 | 114 | 12.5% | –0.63 | [–0.82, –0.44] |
| Forst 2014 | –0.97 | 1.419 | 0.47 | 1.443 | 226 | 6.5% | –0.50 | [–0.76, –0.24] |
| Ji 2015 | –0.79 | 0.841 | 0.17 | 0.807 | 181 | 21.5% | –0.62 | [–0.77, –0.47] |
| Lavalle-Gonzalez 2013 | –0.55 | 0.876 | 0.03 | 0.986 | 639 | 44.5% | –0.58 | [–0.68, –0.48] |
| Neal 2014 | –0.76 | 0.902 | 0.22 | 0.702 | 61 | 5.0% | –0.54 | [–0.84, –0.24] |
| Rosenstock 2012 | –0.74 | 0.984 | 0.01 | 0.931 | 150 | 9.9% | –0.75 | [–0.96, –0.54] |
| Wilding 2013 | 1582 | 1371 | 100.0% | –0.60 | [–0.67, –0.54] |

Heterogeneity: Tau2 = 0.00; Chi2 = 2.87, d.f. = 5 (P = 0.72); I2 = 0%
Test for overall effect: Z = 17.51 (P < 0.00001)

Heterogeneity: Tau2 = 0.00; Chi2 = 6.23, d.f. = 5 (P = 0.28); I2 = 20%
Test for overall effect: Z = 18.65 (P < 0.00001)

Figure 3 | Forest plots of overall effect size of glycosylated hemoglobin and subgroup meta-analysis of different dose. CI, confidence interval; d.f., degrees of freedom; SD, standard deviation.

| Study or subgroup | Weighted mean difference (95% CI) | Weighted mean difference (95% CI) |
|-------------------|----------------------------------|----------------------------------|
| CANA 100 mg | Rosenstock, J.et al (2012) | –1.40 [–1.98, –0.92] | 12.29 |
| | Lavalle-Gonzalez, F. J. et al (2013) | –1.65 [–1.99, –1.32] | 18.63 |
| | Wilding, J. P. et al (2013) | –1.60 [–2.10, –1.10] | 13.11 |
| | Forst, T.et al (2014) | –1.63 [–2.05, –1.21] | 15.57 |
| | Neal, B.et al (2014) | –1.10 [–1.40, –0.90] | 21.98 |
| | Ji, L.et al (2015) | –1.03 [–1.38, –0.69] | 18.42 |
| | Subtotal (I-squared = 61.2%, P = 0.025) | –1.37 [–1.62, –1.13] | 100.00 |

| CANA 300 mg | Rosenstock, J.et al (2012) | –1.80 [–2.32, –1.26] | 13.39 |
| | Lavalle-Gonzalez, F. J. et al (2013) | –2.23 [–2.60, –1.90] | 17.90 |
| | Wilding, J. P. et al (2013) | –2.10 [–2.60, –1.60] | 14.08 |
| | Forst, T.et al (2014) | –1.98 [–2.41, –1.56] | 15.93 |
| | Neal, B.et al (2014) | –1.50 [–1.70, –1.20] | 20.52 |
| | Ji, L.et al (2015) | –1.43 [–1.77, –1.09] | 18.17 |
| | Subtotal (I-squared = 71.4%, P = 0.004) | –1.82 [–2.21, –1.53] | 100.00 |

Figure 4 | Forest plots of overall effect size of fasting plasma glucose and subgroup meta-analysis of different dose. CANA, canagliflozin; CI, confidence interval.

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metformin\textsuperscript{11,12}, one study on a background of insulin with or without other antidiabetic drugs\textsuperscript{13}, and three trials on a background of metformin and other antidiabetic drugs (pioglitazone and sulphonylurea)\textsuperscript{14–16}.

**Risk of bias assessment**

The Cochrane Collaboration’s risk of bias tool was used to access risk of bias (Figure 2). Two RCTs had more than one item with unclear risk of bias\textsuperscript{11,12}. All included studies were randomized control trials, and only one study was unclear in random sequence generation\textsuperscript{11}. Allocation concealment was clearly described in three RCTs\textsuperscript{13–15} but was unclear in other three RCTs\textsuperscript{11,12,16}. All trials were double blind and funded by Janssen. The last observations carried out were used to impute the missing data in five RCTs, and incomplete outcome data was unclear in one trial\textsuperscript{15}.

**Glycemic control**

Compared with the placebo, both treatment with canagliflozin 100 mg once daily and 300 mg once daily combined with other antidiabetic drugs improved glycemic control (Figure 3). Supplementation of canagliflozin led to a greater mean reduction in HbA1c levels vs the placebo. In the 100-mg canagliflozin groups, the pooled HbA1c weighted mean difference (WMD) was \(-0.60\%\) (95% CI \(-0.67\% \text{ to } \text{{-0.54}\%}; I^2 = 0\%\)). Results were more significant for the 300-mg dose (WMD \(-0.76\%\); 95% CI \(-0.84 \text{ to } -0.68\%\); $I^2 = 20\%$). All trials showed the decreases in FPG after the add-on of canagliflozin (Figure 4). The overall mean difference between the 100-mg canagliflozin groups and the control groups was \(-1.37 \text{ mmol/L} \) (95% CI \(-1.62 \text{ to } -1.13 \text{ mmol/L}; I^2 = 61.2\%\)), and the 300-mg groups \(-1.82 \text{ mmol/L} \) (95% CI \(-2.11 \text{ to } -1.53 \text{ mmol/L} \)). In our hypothesis, the longer durations of diabetes for the patients who accepted insulin treatment and the differences in FPG baseline of each trial are the sources of observed heterogeneity. To verify the robustness of our findings and explore possible sources of statistical heterogeneity, we also carried out sensitivity analysis. After excluded the incomplete outcome date, the result did not change substantially.

**Bodyweight**

All included trials reported the effect sizes of canagliflozin on bodyweight changes. Three of the studies described the changes by percent changes from the baseline; however, the others by kilogram changes. Subgroup meta-analysis was carried out on different indexes of measure and doses of canagliflozin. The invention of canagliflozin was associated with a significant dose-related reduction in bodyweight that was consistent among both the 100-mg and the 300-mg canagliflozin groups (Figure 5). The significant heterogeneity might be caused by the different combined antidiabetic drugs and the characteristics of body mass index at baseline. The patients with lower body
mass index at baseline\textsuperscript{16} had less weight loss than the others. Both of the two studies on the background of sulphonylurea\textsuperscript{14,16} seemed to have less weight change.

**DISCUSSION**

In a previous systematic review and meta-analysis, canagliflozin was proven to be effective in reducing HbA1c levels and body-weight with a low risk of hypoglycemia in patients with type 2 diabetes\textsuperscript{7}. In agreement with that study, we found that canagliflozin improved glycemic control with a reduction in weight. By contrast, we carried out a Preferred Reporting Items for Systematic Reviews and Meta-Analyses-compliant meta-analysis and also analyzed the effect of canagliflozin 100 mg once daily combined with other antidiabetic treatments, not only the dose of 300 mg.

Findings from our meta-analysis show a beneficial effect of using canagliflozin as an add-on drug to classical hypoglycemic agents. Both doses of 100 and 300 mg once per day canagliflozin are conducive to management of blood glucose and body-weight, which are dose-dependent. The pooled analyses of data from phase 3 studies of canagliflozin showed significant differences in the effects of canagliflozin on HbA1c and bodyweight based on race or ethnicity\textsuperscript{17}.

Weight gain is an undesirable effect in patients with diabetes treated with other drugs (e.g., pioglitazone and insulin), and could lead to insulin resistance increasing. Combination with canagliflozin might offset the negative effects of those antidiabetic drugs on bodyweight. It is thought that weight change with canagliflozin is attributed to the loss of fat mass\textsuperscript{18}. A study in overweight and obese subjects without diabetes showed that the effect of canagliflozin on bodyweight is not only due to urinary caloric loss by increased urinary glucose excretion, but also due to the mild osmotic diuresis\textsuperscript{19}. Canagliflozin is also effective in particular groups. There are dedicated studies of patients with chronic kidney disease showing that canagliflozin at a dose of 100 mg or 300 mg daily provided a meaningful reduction in HbA1c in patients with moderate renal impairment\textsuperscript{20}. It has been proved in numerous trials that SGLT2 inhibitors are effective in glycemic control as monotherapy or in combination with various other glucose-lowering agents\textsuperscript{21}.

The most commonly reported adverse events included genitourinary tract infections, urinary tract infections) and adverse events-related osmotic diuresis, which were transient, mild to moderate in intensity and led to few discontinuations\textsuperscript{7}. In the clinical trials, an increased incidence of bladder and breast cancer was observed with dapagliflozin, which was not seen with canagliflozin\textsuperscript{22}. However, some serious adverse events with chronic SGLT2 inhibitors administration have been of much concern to scholars, these include severe hypoglycemia, acceleration of diabetes-associated sarcopenia and ketosis/ketoacidosis\textsuperscript{23}. Recently, the US Food and Drug Administration has issued a warning that SGLT2 inhibitors for diabetes could result in a serious condition of too much acid in the blood, including canagliflozin, dapagliflozin and empagliflozin. This is a reminder that close observation of patients receiving SGLT2 inhibitor is essential.

A limitation of this meta-analysis is that all the included trials were funded by industry, which carry a high potential risk of bias. Second, most studies used last observation carried forward methods to impute missing data. As discussed elsewhere\textsuperscript{24}, the extent of the impact of using this inappropriate approach on our meta-analysis is unknown. Additionally, the long-term effects of this combined treatment are unknown: the included trials ranged in duration from 12 to 52 weeks. These findings should be confirmed through larger, randomized clinical trials with longer-term follow up.

In conclusion, as an add-on drug to other hypoglycemic drugs, both daily doses of canagliflozin (100 or 300 mg) have beneficial effects on glycemic control and weight regulation in type 2 diabetes.

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**DISCLOSURE**

The authors declare no conflicts of interest.

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