Effects of Sodium-glucose Cotransporter 2 Inhibitor Monotherapy on Weight Changes in Patients With Type 2 Diabetes Mellitus: a Bayesian Network Meta-analysis

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ABSTRACT

Purpose: The aim of this study was to systematically evaluate the effect of sodium-glucose cotransporter 2 (SGLT2) inhibitor monotherapy on the weight of patients with type 2 diabetes mellitus (T2DM) and to compare different SGLT2 inhibitors with other oral glucose-lowering medications.

Methods: PubMed, EMBASE, Cochrane Library, and the ClinicalTrials.gov Web site were searched for relevant randomized controlled trials. Patients with T2DM in the included studies were administered SGLT2 inhibitor monotherapy for at least 12 weeks. The primary outcome was the change in weight from baseline; the secondary outcome was the proportion of patients achieving a weight reduction ≥5%. A pairwise meta-analysis using the DerSimonian-Laird random effects model and a network meta-analysis with Bayesian Markov chain Monte Carlo random effects models were performed.

Findings: : A total of 29 randomized controlled trials (11,999 patients) with a low risk of bias were identified. The results showed that the mean weight loss ranged from −2.26 kg (95% credible interval [CrI], −2.71 to −1.76) with canagliflozin 300 mg to −0.79 kg (95% CrI, −1.54 to −0.05) with ipragliflozin 25 mg compared with metformin. Compared with linagliptin and sitagliptin, the mean weight loss ranged from −3.17 kg (95% CrI, −3.67 to −2.57) with canagliflozin 300 mg to −0.93 kg (95% CrI, −1.92 to 0.05) with ipragliflozin 25 mg. Canagliflozin 300 mg reduced weight to a greater extent than the other SGLT2 inhibitors, with a probability of 99.44%. SGLT2 inhibitors also improved the proportions of patients achieving ≥5% weight loss. The effect of SGLT2 inhibitors on weight reduction was associated with dosage.

Implications: Available evidence from randomized controlled trials suggests that SGLT2 inhibitor monotherapy exerts more beneficial effects on weight reduction than both metformin and dipeptidyl peptidase 4 inhibitors. The weight reduction effect of 300 mg canagliflozin is greater than that of most other SGLT2 inhibitors. More types of SGLT2 inhibitors in a head-to-head trial, as well as a comparison between SGLT2 inhibitors and glucagon-like peptide 1 receptor agonists, will be involved in our further research. International Prospective Register of Systematic Reviews: CRD42018089761. (*Clin Ther*. 2019;41:322−334)

Keywords: network meta-analysis, SGLT2 inhibitors, type 2 diabetes, weight.

INTRODUCTION

Diabetes mellitus is one of the most common and costly metabolic disorders, and it results from defects in insulin secretion and/or insulin action. Approximately

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422 million people worldwide are currently estimated to have diabetes; moreover, 1 in 3 adults aged >18 years is overweight and 1 in 10 is obese.[1,2] It is estimated that 693 million people aged 18−99 years and 629 million people aged 20−79 years will have diabetes by 2045.[3] As reported, diabetes has become the seventh leading cause of death, causing 1.60 million deaths in 2016, compared with 0.94 million deaths in 2000.[4] The major driving factors of the global diabetes epidemic are overweight and obesity.[5] As the rates of overweight and obesity rise, the overall prevalence of this disorder may continue to increase.[6] In addition, the economic costs of diabetes would also be increased. According to data from the American Diabetes Association, the total costs of diagnosed diabetes rose to $327 billion in 2017 from $245 billion in 2012.[7] Clearly, diabetes mellitus has become one of the most significant health burdens in the world and stands to affect society more heavily over time.

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and insulin deficiency and accounts for >90% of diabetes cases. In addition, the majority of patients with T2DM are overweight or obese.[8] Compared with people with normal weight, overweight or obese people have a greater risk of T2DM and are also associated with a greater risk of cardiovascular disease (CVD) and higher all-cause mortality.[9,10] As previously reported, weight loss can increase glycemic control, improve CVD risk factors, prevent or delay the progression of chronic kidney disease, and decrease the use of medications related to diabetes, hypertension, and lipid lowering.[11−13] In particular, weight loss has been shown to delay the progression from prediabetes to T2DM and improve glycemic control, with severe calorie restriction even reversing the progression of T2DM in established T2DM.[14,15] Therefore, in addition to its effects on glycemic control, weight reduction has become one of the key therapeutic goals in both the prevention and management of T2DM, and it should be encouraged in patients with T2DM.

The currently available glucose-lowering medications for T2DM include sulfonylureas, thiazolidinedione, metformin, α-glucosidase inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors. Certain agents used for the treatment of diabetes directly contribute to weight loss through their pharmacologic action.[13] For example, metformin was shown to induce modest weight losses of 0.6−3.5 kg due to its effects on the central nervous system and reduced appetite and food intake.[16,17] GLP-1 receptor agonists are associated with an average weight loss of 2−3 kg in long-term studies by inhibiting gastric emptying, appetite, and food intake.[17,18] However, GLP-1 receptor agonists lead to varied weight loss among agents.[19]

Another novel class of oral glucose-lowering drugs is the SGLT2 inhibitors, which target the kidneys to reduce blood glucose levels by increasing urinary glucose excretion. Because the pharmacology of SGLT2 inhibitors is independent of insulin, these drugs increase urinary glucose excretion by reducing renal glucose reabsorption and lowering the plasma glucose level in patients with T2DM who have a low risk of hypoglycemia.[20,21] In addition, pancreatic β-cell function or the degree of insulin resistance cannot be affected by the mechanisms of action of these drugs, and they also lead to weight loss, reduced blood pressure, and an improved lipid profile.[22] SGLT2 inhibitors therefore have the potential to be used widely in the treatment of T2DM.

Some studies have shown that SGLT2 inhibitors exert positive effects on glycemic control and blood pressure, slowing the progression of kidney disease and reducing cardiovascular events in patients with T2DM.[23,24] Although studies have also assessed the effects of SGLT2 inhibitors on weight, most of these have included patients continuing their previous treatments or combining SGLT2 inhibitors with other oral glucose-lowering drugs; alternatively, studies have compared only SGLT2 inhibitors versus placebo. For example, one study included trials that investigated the effect of SGLT2 inhibitors combined with metformin; however, metformin may affect weight in patients with T2DM.[25] Thus, the results of the study on weight do not allow us to determine whether the observed effects were caused by the SGLT2 inhibitors or another oral glucose-lowering drug used as a background treatment. Also, as previously mentioned, both metformin and GLP-1 receptor agonists lead to weight loss, whereas the effect among different GLP-1 receptor agonists varies. Therefore, what are the effects of various SGLT2 inhibitors on weight? What are the differences compared with other oral antidiabetic agents such as

metformin? Accordingly, the objective of the present study was to systematically evaluate the effect of SGLT2 inhibitor monotherapy on the weight of patients with T2DM who cannot achieve standard glycemic targets. We compared different SGLT2 inhibitors versus other oral glucose-lowering drugs by using a Bayesian network meta-analysis.

MATERIALS AND METHODS

Search Strategy

PubMed, EMBASE, and the Cochrane Library were searched for relevant studies from their dates of inception through January 2018. We also searched the ClinicalTrials.gov Web site. The following relevant terms were used: "sodium-glucose cotransporter 2 inhibitors," "SGLT-2 inhibitors," "SGLT2 inhibitors," "dapagliflozin," "empagliflozin," "canagliflozin," "ipragliflozin," "ertugliflozin," "luseogliflozin," "tofogliflozin," "remogliflozin," "sotagliflozin," and "sergliflozin." The references cited in the included articles were studied to identify additional studies.

Inclusion and Exclusion Criteria

Articles were included if they met the following conditions: (1) they described randomized controlled trials (RCTs); (2) they investigated the effects of SGLT2 inhibitor treatments in patients with T2DM aged >18 years; (3) the treatment group was administered SGLT2 inhibitor monotherapy with no background drug therapy during the study, and the control group received placebo or other oral glucose-lowering medications or received different dosages of SGLT2 inhibitor; (4) the study length was longer than 12 weeks; and (5) the primary outcome was change in weight from baseline, with studies ideally reporting the proportion of patients achieving ≥5% weight reduction.

Studies were excluded for any of the following reasons: (1) if they involved patients with type 1 diabetes mellitus; (2) the study length was shorter than 12 weeks; (3) the study did not report weight; or (4) they were published as conference abstracts, books, letters, or comments.

Study Selection, Data Extraction, and Quality Assessment

Two investigators independently performed the assessments and screenings according to the title and abstract of the initial study selected. The investigators then assessed the studies based on a review of the full-text articles. If an agreement could not be reached or there were any uncertainties, a third reviewer discussed the study with the original investigators until a final decision was reached. Two reviewers extracted the relevant information using a previously prepared table and discussed and assessed the quality of the included studies based on the Cochrane risk of bias.[26]

Data Synthesis and Analysis

A traditional pairwise meta-analysis was performed with Stata version 14.0 (StataCorp, College Station, Texas) using a DerSimonian-Laird random effects model.[27] The weight mean difference (WMD) between trial arms was calculated as the effect size for continuous outcomes, and the odds ratios (ORs) were calculated for dichotomous outcomes, both with 95% CIs. The I^2 statistic was calculated as a measure of the statistical heterogeneity among studies. If I^2 values were >50%, it would indicate significant statistical heterogeneity; otherwise, it indicates no significant statistical heterogeneity.

For indirect and mixed comparisons, we performed a network meta-analysis within a Bayesian framework using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) software with the gemtc package[28,29]; further analyses were conducted with Stata version 14.0. The pooled estimates were obtained by using the Markov chains Monte Carlo method. Four Markov chains were run simultaneously with different arbitrarily chosen initial values. Each chain used 50,000 iterations with a burn-in of 20,000. The results of the network meta-analysis were summarized with effect sizes (WMD or ORs) and their credible intervals (CrIs). A loop-specific approach was used to evaluate the presence of local inconsistency in the network meta-analysis models, and inconsistency was defined as disagreement between direct and indirect evidence with a 95% CI excluding 0.[30] The ranking probabilities for all the treatments were estimated. The treatment hierarchy was summarized and reported as surface under the cumulative ranking curve (SUCRA) probabilities and mean ranks.[31] A high SUCRA probability and a low mean rank indicate a highly effective intervention in terms of weight.

To determine whether the results were affected by study characteristics, a subgroup network meta-analysis was performed for weight changes from baseline according to the following variables: sex ratio, age group, treatment duration, diabetes duration, baseline BMI, baseline glycosylated hemoglobin level, and baseline weight. To detect the presence of any dominant publication bias, we also plotted a comparison-adjusted funnel plot for the network meta-analysis.[31]

This network meta-analysis was registered at the International Prospective Register of Systematic Reviews (CRD42018089761).

RESULTS

Search Results and Study Characteristics

Overall, the search identified 3723 citations, and 1287 duplicates were removed. After screening the titles and abstracts, we excluded 2436 articles, and the full text of a total of 115 potentially eligible articles was retrieved (Fig. 1). Twenty-nine RCTs (11,999 patients) published between 2009 and 2018 were included in the analysis, and the study period ranged from 12 to 76 weeks. In addition, 7 SGLT2 inhibitors (canagliflozin [n = 5],[32–36] dapagliflozin [n = 7],[37–43] empagliflozin [n = 7],[44–50] ertugliflozin [n = 2],[51,52] ipragliflozin [n = 3],[53–55] luseogliflozin [n = 3],[56–58] and tofogliflozin [n = 2][59,60]) were included. One article reported 2 trials,[40] and another article reported 3 trials with different study arms.[38] As a result, a total of 32 trials were included in the network analysis. Most studies were multicenter studies and covered different geographical regions worldwide. Other detailed characteristics of the included studies are shown in Supplemental Table I (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) .

Most of the included studies were of high quality and had a low risk of bias. All the studies were double-blinded. In addition, 89.66% of the studies adequately described the randomization procedure, whereas only 44.83% of the studies reported details of the method of concealed allocation. All the studies had low risks of performance and detection biases.

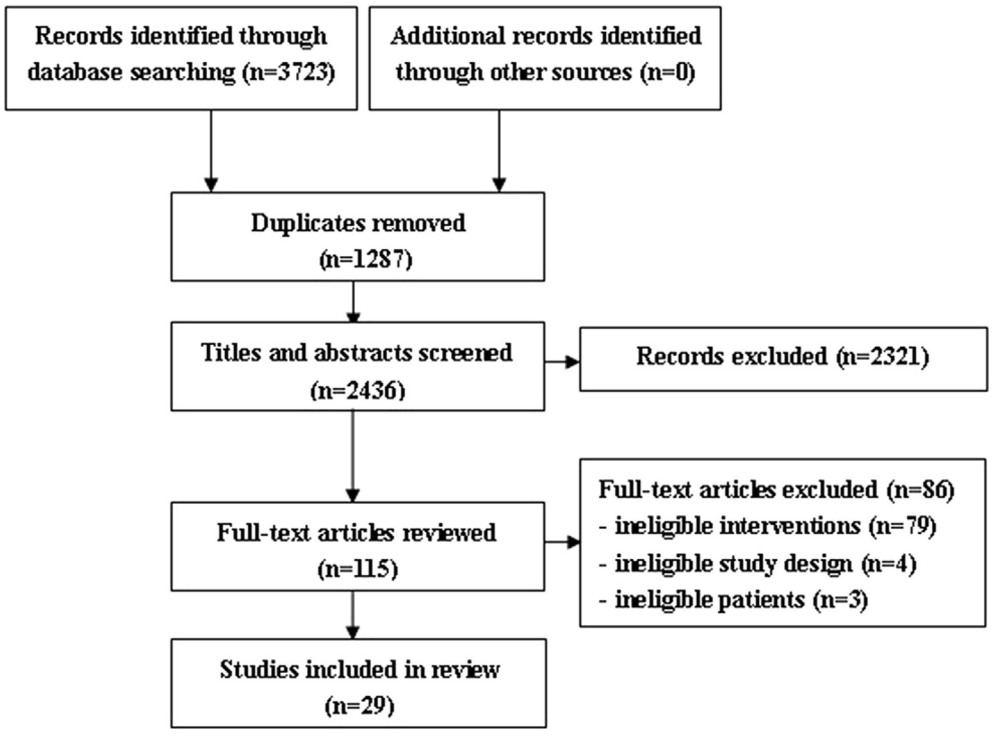

Fig. 1. Flow diagram of the study selection process.

The details of the risk of bias are shown in Supplemental Figures 1 and 2 (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) .

Evidence Network

The following 17 treatments were included: canagliflozin (100 mg and 300 mg), dapagliflozin (5 mg and 10 mg), empagliflozin (10 mg and 25 mg), ertugliflozin (5 mg and 15 mg), ipragliflozin (25 mg and 50 mg), luseogliflozin (2.5 mg and 5 mg), tofogliflozin (20 mg), placebo, metformin, sitagliptin 100 mg, and linagliptin 5 mg. Networks of evidence based on the effects of routine clinical dosages on weight change from baseline are shown in Fig. 2, and the percentages of patients achieving ≥5% weight loss are graphically displayed in Fig. 3.

Direct Pairwise Meta-analysis and Network Meta-analysis of SGLT2 Inhibitors on Weight Changes From Baseline

We analyzed only certain dosages of each drug based on the approved or routine clinical dosages, and 17 treatments in total were included.[61–67] The results are shown in Table I. In the direct comparisons, the largest weight reduction was observed in the assessment of the canagliflozin group (300 mg) versus the placebo group (WMD, −2.73 kg; 95% CI, −3.19 to 2.28). Compared with the metformin group, the canagliflozin 300-mg group was also associated with a significant reduction (WMD, −1.80 kg; 95% CI, −2.63 to −0.97). The results of the network meta-analysis indicated that treatment with all SGLT2 inhibitors and metformin, except for linagliptin 5 mg (WMD, −0.37 kg; 95% CrI, −1.07 to 0.34), had a significant reduction effect on weight compared with placebo. Among the SGLT2 inhibitors, the mean weight loss ranged from −2.78 kg (95% CrI, −3.09 to −2.57) with canagliflozin 300 mg to −1.30 kg (95% CrI, −1.99 to −0.63) with ipragliflozin 25 mg after placebo correction. Compared with metformin, all SGLT2 inhibitors were associated with a significant reduction in weight, ranging from −2.26 kg (95% CrI, −2.71 to −1.76) with canagliflozin 300 mg to −0.79 kg

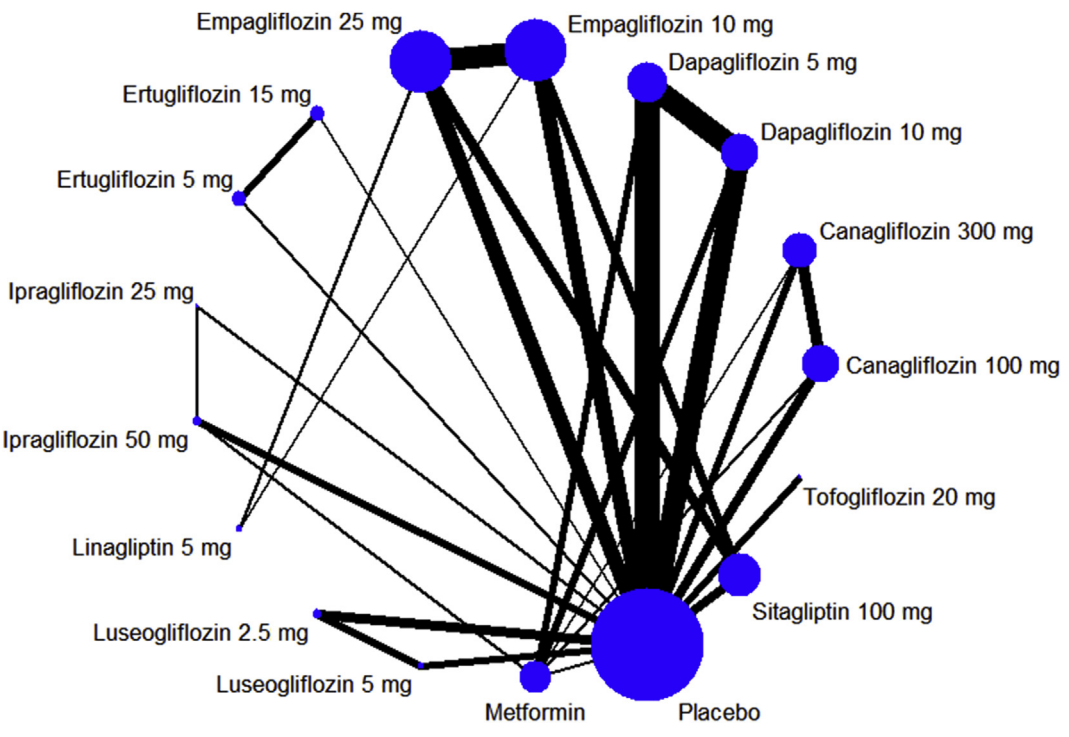

Fig. 2. Network evidence structure of eligible comparisons regarding weight changes from baseline.

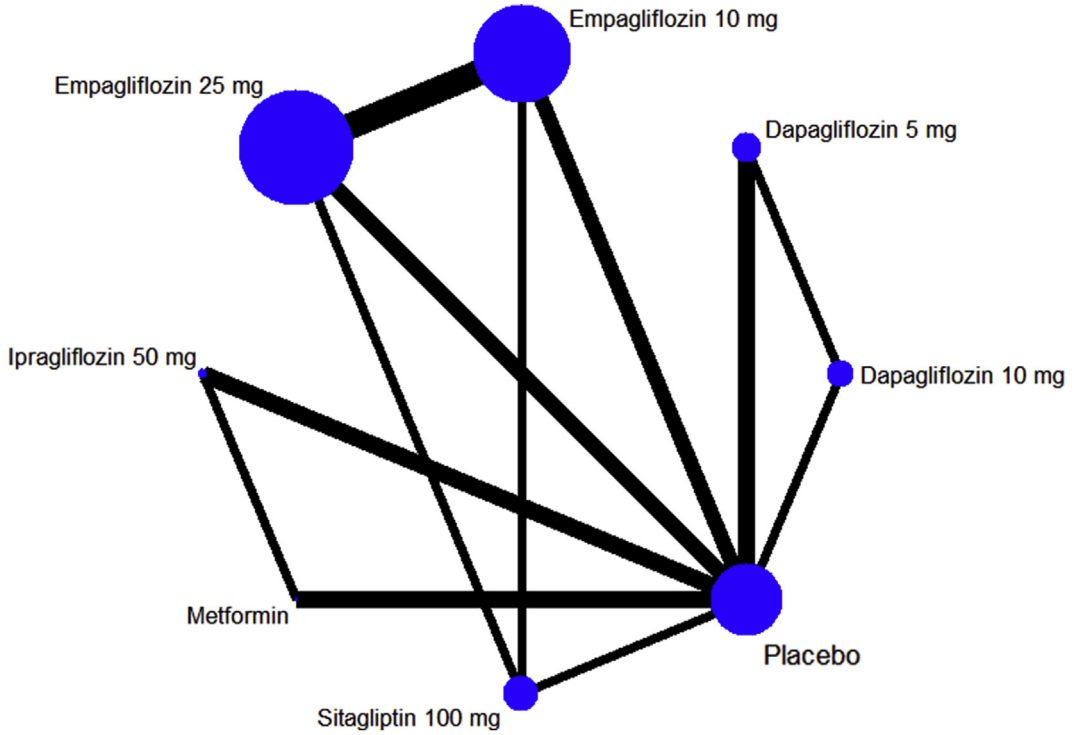

Fig. 3. Network evidence structure of eligible comparisons regarding the proportions of patients achieving ≥5% weight loss.

(95% CrI, −1.54 to −0.05) with ipragliflozin 25 mg. In addition, compared with the effects of the DPP-4 inhibitors, similar effects on weight reduction were obtained with all SGLT2 inhibitors, except for ipragliflozin 25 mg (WDM, −0.93 kg; 95% CrI, −1.92 to 0.05) compared with linagliptin 5 mg. It is noteworthy that no significant differences were detected between any pairs of SGLT2 inhibitors, with the exception of the comparisons with canagliflozin 300 mg.

We also studied the effect of several potential baseline characteristics, such as sex ratio and treatment duration, in subgroup analyses. Most SGLT2 inhibitors had a significant reduction in weight regardless of baseline characteristics compared with placebo. When the sex ratio (male to female ratio) was <1, there were no significant differences in weight loss between dapagliflozin 5 mg (WDM, −2.22 kg; 95% CrI, −5.32 to 0.95) and dapagliflozin 10 mg (WDM, −2.22 kg; 95% CrI, −5.32 to 0.95) and placebo; when diabetes duration was <5 years (WDM, −1.33 kg; 95% CrI, −2.67 to 0.05) and baseline weight was >75 kg (WDM, −1.22 kg; 95% CrI, −2.47 to 0.11), there were no significant differences in weight loss between ipragliflozin 50 mg and placebo; however, there were significant differences between the drugs and placebo before subgroup analysis. The detailed results of the subgroup analysis are shown in Supplemental Table II (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) .

Direct Pairwise Meta-analysis and Network Meta-analysis of SGLT2 Inhibitors for the Proportions of Patients Achieving ≥5% Weight Reduction

The results of direct comparisons and network meta-analysis are shown in Supplemental Table III (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) . Only 8 treatments were included in the analysis. Direct pairwise meta-analysis

indicated that dapagliflozin and empagliflozin increased the proportions of patients achieving ≥5% weight loss compared with placebo, except for the ipragliflozin 50-mg group (OR, 2.33; 95% CI, 0.96 to 5.63). The results of the network analysis also showed an improvement in the proportions of patients achieving ≥5% weight loss, compared with placebo, in the dapagliflozin 5-mg (OR, 5.70; 95% CrI, 2.28 to 15.11) and dapagliflozin 10-mg (OR, 8.57; 95% CrI, 2.71 to 27.44) groups and the empagliflozin 10-mg (OR, 7.70; 95% CrI, 3.28 to 21.34) and empagliflozin 25-mg (OR, 10.20; 95% CrI, 4.59 to 28.93) groups. Compared with sitagliptin 100 mg, only the empagliflozin 10-mg group (OR, 4.68; 95% CrI, 1.75 to 13.48) and the empagliflozin 25-mg group (OR, 6.21; 95% CrI, 2.33 to 17.74) showed a great increase in the proportions of patients achieving ≥5% weight loss. Compared with metformin, no group reported a statistically significant difference.

We calculated the inconsistency between direct and indirect comparisons for the outcomes; the results are shown in Supplemental Figures 3 and 4 (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) . All loops were consistent, as their 95% CIs included 0 according to the forest plots. Therefore, the results of our network meta-analysis are relatively reliable. In addition, the comparison-adjusted funnel plots for the 2 outcomes are shown in Supplemental Figures 5 and 6 (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) . It was suggested that the publication bias in the results of these 2 outcomes was low.

Ranking of the Effects of Different Dosages of SGLT2 Inhibitors on Weight

We performed another network meta-analysis that included all SGLT2 inhibitors at different dosages, and this analysis included 36 treatments in total. The ranking probability and the mean SUCRA values obtained for the 17 routine clinical dosages are shown in Table II, and the results of the 36 treatments are shown in Supplemental Table IV (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) . Regardless of the inclusion of 17 or 36 treatments, canagliflozin 300 mg consistently resulted in the greatest reduction in weight, with probabilities of 99.44% (rank 1) and 98.66% (rank 1). The relationship between SUCRA probability and dosages was tested based on the network meta-analysis of 36 treatments, and the results showed that the effect on weight changes from baseline was associated with the dosage of all SGLT2 inhibitors. The trend of the graphs for dosage and SUCRA probability obtained for the 7 SGLT2 inhibitors are shown in Supplemental Figure 7 (given in the online version at doi: 10.1016/j.clinthera.2019.01.001 . The ranking probability and the mean SUCRA values obtained for the 15 treatments on the proportions of patients achieving at least 5% weight loss are shown in Supplemental Table IV (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) . Metformin, sitagliptin, and placebo were not as effective as SGLT2 inhibitors, such as dapagliflozin, with lower SUCRA probabilities of 22.07% (rank 13), 16.21% (rank 14), and 3.71% (rank 15), respectively.

DISCUSSION

SGLT2 inhibitors show good performance in improving glycemic control, exerting cardiovascular benefits, and reducing blood pressure, although they increase the risks of genital infection and fractures.[68,69] Our network meta-analysis found that, compared with placebo, metformin, and DPP-4 inhibitors, 7 types of SGLT2 inhibitors can reduce weight in patients with inadequately controlled T2DM. Due to a lack of head-to-head trials among SGLT2 inhibitors, the main strength of the present study is that it provides a comprehensive evaluation of 7 SGLT2 inhibitors on weight reduction from baseline and the proportions of patients achieving ≥5% weight loss compared with placebo, metformin, and DDP-4 inhibitors through a network meta-analysis; moreover, it is suggested that canagliflozin 300 mg exhibited the greatest reduction on weight. It is particularly noteworthy that the effect of the 7 SGLT2 inhibitors on weight reduction from baseline was associated with dosage.

To the best of our knowledge, previous reviews assessed the effects of only a few SGLT2 inhibitors, and no studies assessed the effect on the proportions of patients achieving ≥5% weight loss, which is also an important outcome related to weight.[23–25] Furthermore, the relationship between the effect on weight changes and dosage was seldom assessed according to a network meta-analysis. It is worth mentioning that our study found that the weight

Table I. Weight mean difference with 95% credible intervals of the network meta-analysis for weight changes from baseline. Results of direct comparisons are listed in the upper triangle; the estimation is located at the intersection of the row-defining treatment and the column-defining treatment. Results of network meta-analysis are listed in the lower triangle; the estimation is located at the intersection of the column-defining treatment and the row-defining treatment. Significant results are given in bold. Can100 = canagliflozin 100 mg; Can300 = canagliflozin 300 mg; Dap5 = dapagliflozin 5 mg; Dap10 = dapagliflozin 10 mg; Emp10 = empagliflozin 10 mg; Emp25 = empagliflozin 25 mg; Ert5 = ertugliflozin 5 mg; Ert15 = ertugliflozin 15 mg; Ipr25 = ipragliflozin 25 mg; Ipr50 = ipragliflozin 50 mg; Lin5 = linagliptin 5 mg; Lus2.5 = luseogliflozin 2.5 mg; Lus5 = luseogliflozin 5 mg; Met = metformin; NA = not available; Sit100 = sitagliptin 100 mg; Tof20 = tofogliflozin 20 mg.

Can100	0.89 (0.76, 1.03)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	−0.9 (−1.73, −0.07)	−2.03 (−2.12, −1.93)	NA	NA
0.84 (0.50, 1.17)	Can300	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**−1.8 (−2.63, −0.97)**	**−2.73 (−3.19, −2.28)**	NA	NA
−0.42 (−0.82, 0.05)	**−1.26 (−1.69, −0.73)**	Dap10	−0.14 (−0.42, 0.13)	NA	NA	NA	NA	NA	NA	NA	NA	NA	**−1.18 (−1.83, −0.54)**	**−1.39 (−1.78,−0.10)**	NA	NA
−0.40 (−0.82, 0.07)	**−1.24 (−1.68, −0.72)**	0.02 (−0.34, 0.39)	Dap5	NA	NA	NA	NA	NA	NA	NA	NA	NA	**−0.87 (−1.30, −0.44)**	**−1.33 (−1.70,−0.98)**	NA	NA
−0.19 (−0.63, 0.27)	**−1.03 (−1.50, −0.52)**	0.23 (−0.26, 0.68)	0.21 (−0.29, 0.68)	Emp10	0.17 (−0.07,0.42)	NA	NA	NA	NA	**−1.5 (−2.07, −0.93)**	NA	NA	NA	**−1.66 (−1.97,−1.36)**	**−2.00 (−2.76,−1.25)**	NA
−0.11 (−0.55, 0.35)	**−0.95 (−1.41, −0.43)**	0.32 (−0.17, 0.76)	0.29 (−0.20, 0.77)	0.08 (−0.23, 0.40)	Emp25	NA	NA	NA	NA	**−1.3 (−1.87, −0.73)**	NA	NA	NA	**−1.76 (−2.26,−1.26)**	**−2.21 (−3.01,−1.40)**	NA
0.14 (−0.55, 0.89)	−0.69 (−1.42, 0.09)	0.56 (−0.16, 1.29)	0.54 (−0.19, 1.31)	0.33 (−0.39, 1.09)	0.25 (−0.48, 1.01)	Ert15	−0.29 (−0.79, 0.21)	NA	NA	NA	NA	NA	NA	**−2.12 (−2.61,−1.63)**	NA	NA
−0.13 (−0.89, 0.66)	**−0.97 (−1.75, −0.15)**	0.29 (−0.52, 1.06)	0.26 (−0.54, 1.06)	0.06 (−0.75, 0.86)	−0.01 (−0.83, 0.78)	−0.28 (−0.88, 0.32)	Ert5	NA	NA	NA	NA	NA	NA	**−1.72 (−2.35,−1.10)**	NA	NA
−0.63 (−1.36, 0.15)	**−1.47 (−2.21, −0.67)**	−0.21 (−0.97, 0.52)	−0.24 (−0.99, 0.52)	−0.44 (−1.17, 0.33)	−0.53 (−1.28, 0.25)	−0.78 (−1.73, 0.20)	−0.51 (−1.48, 0.53)	Ipr25	0.12 (−0.38,0.62)	NA	NA	NA	NA	**−1.3 (−1.81,−0.79)**	NA	NA
−0.54 (−1.17, 0.18)	**−1.38 (−2.04, −0.62)**	−0.11 (−0.80, 0.55)	−0.14 (−0.82, 0.55)	−0.35 (−1.00, 0.38)	−0.43 (−1.10, 0.30)	−0.67 (−1.58, 0.22)	−0.40 (−1.33, 0.57)	0.10 (−0.57, 0.76)	Ipr50	NA	NA	NA	−0.78 (−1.87, 0.31)	**−1.37 (−1.77,−0.97)**	NA	NA
−1.56 (−2.31, −0.78)	**−2.39 (−3.16, −1.59)**	**−1.13 (−1.94, −0.37)**	**−1.16 (−1.96, −0.37)**	**−1.37 (−2.03, −0.71)**	**−1.45 (−2.10, −0.80)**	**−1.70 (−2.68, −0.75)**	**−1.43 (−2.42, −0.41)**	−0.93 (−1.92, 0.05)	**−1.03 (−2.01, −0.09)**	Lin5	NA	NA	NA	NA	NA	NA
−0.31 (−0.78, 0.22)	**−1.14 (−1.64, −0.57)**	0.12 (−0.42, 0.61)	0.09 (−0.44, 0.62)	−0.12 (−0.64, 0.42)	−0.20 (−0.71, 0.34)	−0.44 (−1.25, 0.30)	−0.17 (−0.99, 0.67)	0.33 (−0.49, 1.10)	0.24 (−0.53, 0.93)	**1.25 (0.43, 2.06)**	Lus2.5	0.36 (−0.22, 0.93)	NA	−0.27 (−2.76, 2.22)	NA	NA
0.01 (−0.51, 0.59)	**−0.83 (−1.37, −0.20)**	0.43 (−0.14, 0.98)	0.41 (−0.17, 1.00)	0.20 (−0.36, 0.78)	0.12 (−0.44, 0.72)	−0.13 (−0.95, 0.68)	0.13 (−0.70, 1.03)	0.65 (−0.20, 1.46)	0.55 (−0.24, 1.30)	**1.57 (0.71, 2.42)**	0.32 (−0.15, 0.79)	Lus5	NA	**−1.91 (−2.30,−1.53)**	NA	NA
−1.42 (−1.84, −0.96)	**−2.26 (−2.71, −1.76)**	**−1.00 (−1.38, −0.65)**	**−1.02 (−1.44, −0.62)**	**−1.23 (−1.70, −0.73)**	**−1.32 (−1.80, −0.81)**	**−1.56 (−2.32, −0.82)**	**−1.29 (−2.09, −0.46)**	**−0.79 (−1.54, −0.05)**	**−0.89 (−1.54, −0.25)**	0.13 (−0.65, 0.95)	**−1.12 (−1.66, −0.58)**	**−1.43 (−2.02, −0.85)**	Met	**−0.43 (−0.63, −0.23)**	NA	NA
−1.94 (−2.21, −1.59)	**−2.78 (−3.09, −2.37)**	**−1.51 (−1.84, −1.20)**	**−1.53 (−1.89, −1.19)**	**−1.74 (−2.07, −1.39)**	**−1.82 (−2.15, −1.47)**	**−2.07 (−2.74, −1.42)**	**−1.80 (−2.54, −1.06)**	**−1.30 (−1.99, −0.63)**	**−1.39 (−2.03, −0.81)**	−0.37 (−1.07, 0.34)	**−1.63 (−2.03, −1.23)**	**−1.94 (−2.41, −1.48)**	**−0.51 (−0.87, −0.15)**	Placebo	−0.13 (−0.85, 0.59)	**2.15 (1.48, 2.83)**
−2.33 (−2.81, −1.77)	**−3.17 (−3.67, −2.57)**	**−1.91 (−2.42, −1.39)**	**−1.93 (−2.46, −1.37)**	**−2.14 (−2.55, −1.69)**	**−2.22 (−2.64, −1.78)**	**−2.47 (−3.23, −1.68)**	**−2.20 (−3.03, −1.35)**	**−1.69 (−2.48, −0.90)**	**−1.79 (−2.54, −1.05)**	−0.77 (−1.51, 0.00)	**−2.02 (−2.59, −1.43)**	**−2.34 (−2.95, −1.69)**	**−0.90 (−1.44, −0.35)**	−0.39 (−0.80, 0.03)	Sit100	NA
0.21 (−0.39, 0.89)	−0.63 (−1.24, 0.09)	0.64 (−0.01, 1.28)	0.61 (−0.04, 1.29)	0.40 (−0.24, 1.09)	0.32 (−0.31, 1.00)	0.07 (−0.79, 0.96)	0.34 (−0.55, 1.30)	0.85 (−0.05, 1.74)	0.76 (−0.10, 1.56)	**1.77 (0.87, 2.69)**	0.53 (−0.16, 1.21)	0.20 (−0.51, 0.94)	**1.63 (0.97, 2.33)**	**2.14 (1.59, 2.72)**	**2.54 (1.83, 3.23)**	Tof20

reduction effects of 7 SGLT2 inhibitors were associated with dosage. A previous study reported that the glucose-lowering effect of 300 mg of canagliflozin was greater than that of dapagliflozin and empagliflozin.[24] Our findings revealed few differences among the other SGLT2 inhibitors, and the effect of canagliflozin 300 mg was not only greater than those of dapagliflozin and empagliflozin but also greater than those of the other types of SGLT2 inhibitors, metformin, and the DPP-4 inhibitors. However, it should be noted that the results obtained in our study showed that only linagliptin 5 mg and sitagliptin 100 mg did not result in a significant weight reduction compared with placebo.

Most of the studies included were multi-country studies with a double-blind design and high quality. The patients in our included studies were of different races, such as white, black or African American, and Asian, and came from different geographical regions. For example, one article was based on 105 sites (study 1) and 131 sites (study 2) in North America, Latin America, Europe, and Asia.[40] Therefore, the results of our study are applicable to most patients worldwide. Due to insufficient data, however, we cannot assess the effect on different races. Nonetheless, we performed a subgroup analysis on other characteristics. As shown in Supplemental Table II (given in the online version at doi: 10.1016/j.clinthera.2019.01.001) , most of the effects of the SGLT2 inhibitors were not influenced by baseline characteristics, but we should note that metformin may be different. The dosage of metformin in the included trials ranged from 500 to 2000 mg in 1 day, whereas in our analysis, we did not distinguish between dosages of metformin, which may be one of the factors contributing to the difference. In addition, sex ratios may also influence the effect, but with limited data in our study, we are uncertain about the correlation. It would be meaningful to study the relationship between weight reduction and sex differences.

Compared with different treatment durations, we found that the mean weight change was greater when the treatment lasted >26 weeks. This finding was not surprising because the mean weight loss was correlated with treatment durations, but what would the result be for treatment durations >1 year? In the present study, only 1 trial with the treatment duration of 76 weeks was included, and these limited data only showed that empagliflozin was effective on weight loss when treating patients for >1 year. More trials with longer treatment durations are expected to explore this issue in the future.

As reported, modest weight losses of 5%−10% were associated with significant improvements in CVD risk factors.[12] Only 8 trials reported this outcome; more trials on this outcome are expected in the future.

Currently, the mechanism through which SGLT inhibitors affect weight is a topic of great interest. There are 2 types of SGLTs: SGLT2 and sodium-glucose cotransporter 1 (SGLT1). SGLT1 is primarily involved in the absorption of glucose and galactose in the intestine, and SGLT2 is expressed in the kidney, which accounts for 90% of total renal glucose absorption. They are both associated with diabetes care.[70] SGLT2 inhibitors discussed in the present study are actually selective inhibitors of SGLT2; for example, ipragliflozin shows a high level of selectivity (254-fold vs SGLT1). These selective SGLT2 inhibitors may mainly exert their effects on weight loss via their inhibitory effect on SGLT2. These medications decrease the reabsorption of glucose, leading to an increase in urinary glucose excretion, and increased urinary glucose excretion results in a loss of 200−300 kcal/d, which may contribute to modest weight loss.[69] However, another trial including healthy subjects with obesity investigated the effects of SGLT2 inhibitors on body composition; the study found that although the mean total daily energy loss values obtained with 2 SGLT2 inhibitors and placebo were ~240 kcal/d, 150 kcal/d, and 0.3 kcal/d, respectively, there were no statistically significant differences between the SGLT2 inhibitors and the placebo group with regard to weight or fat loss.[71] In both healthy subjects with obesity and patients with diabetes, weight and body composition are some of the most important outcomes. Regrettably, we did not analyze the effect on body composition because very few studies reported this outcome.

Another interesting issue is the inhibitors of both SGLT1 and SGLT2. Currently, a new dual SGLT1 and SGLT2 inhibitor (sotagliflozin 400 mg/d) has proved to be effective in reducing weight (–2.98 kg) compared with placebo in type 1 diabetes mellitus.[72] Whether this dual SGLT1 and SGLT2 inhibitor would result in greater weight reduction, compared

Table II. Ranking probability of 17 treatments on weight change from baseline.

Drug	Abbreviation	Weight	
		SUCRA	Rank
Canagliflozin 100 mg	Can100	0.7500	4
Canagliflozin 300 mg	Can300	0.9944	1
Dapagliflzin 5 mg	Dap5	0.4562	10
Dapagliflozin 10 mg	Dap10	0.4237	11
Empagliflzin 10 mg	Emp10	0.5925	8
Empagliflozin 25 mg	Emp25	0.6644	6
Ertugliflozin 5 mg	Ert5	0.6325	7
Ertugliflozin 15 mg	Ert15	0.7962	3
Ipragliflozin 25 mg	Ipr25	0.3519	13
Ipragliflozin 50 mg	Ipr50	0.3938	12
Linagliptin 5 mg	Lin5	0.1412	15
Luseogliflozin 2.5 mg	Lus2.5	0.5037	9
Luseogliflozin 5 mg	Lus5	0.7400	5
Metformin	Met	0.1750	14
Placebo	Placebo	0.0700	16
Sitagliptin 100 mg	Sit100	0.0000	17
Tofogliflozin 20 mg	Tof20	0.8356	2

A higher surface under the cumulative ranking curve (SUCRA) and lower rank denote more effective interventions.

with selective SGLT2 inhibitors such as canagliflozin and dapagliflozin, remains unknown.

The present study has some limitations. First, as reported, modest weight losses of 5%−10% were associated with significant improvements in CVD risk factors.[12] However, only a few trials reported this outcome. Also, considering the limited data regarding other outcomes, such as fat mass, visceral fat, and subcutaneous fat, we could not perform further assessments. Second, no trials that directly compared different SGLT2 inhibitors were included in our study, and it was thus impossible to evaluate the outcomes of such direct comparisons. Further research could involve more types of SGLT2 inhibitors in a head-to-head trial. Third, as mentioned in the Introduction, GLP-1 receptor agonists contribute to weight loss through their pharmacologic action. Regrettably, our study did not include trials comparing GLP-1 receptor agonists versus SGLT2 inhibitors. Such a comparison would make for interesting future research.

CONCLUSIONS

Based on limited data, the present study suggests that SGLT2 inhibitors exert beneficial effects on weight changes compared with placebo, metformin, and 2 DPP-4 inhibitors. The observed weight loss was associated with the treatment dosage, and among the different SGLT2 inhibitors, canagliflozin 300 mg might induce the greatest reduction in weight, with a rank probability of 99.44%. Although the effects of the SGLT2 inhibitors were positive in our study, the results might change as new RCTs are included in the future.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Table S1. Characteristics of RCTs of SGLT2 inhibitor treatment in type 2 diabetes patients included in the network meta-analysis.

study	Study duration (week)	Study ID	Treatment group (once daily dosing)	No. of patients	Duration of diabetes (years)	Age (years)	Men (%)	BMI (kg/m2)	Baseline HbA1c (%)	Baseline Weight (kg)
List2009	12	NCT00263276	Dap2.5mg	59	/	55 ± 11	49	32 ± 5	7.6 ± 0.7	90 ± 20
			Dap5mg	58	/	55 ± 12	48	32 ± 5	8.0 ± 0.9	89 ± 17
			Dap10mg	47	/	55 ± 19	53	31 ± 5	8.0 ± 0.8	86 ± 17
			Dap20mg	59	/	55 ± 10	54	31 ± 5	7.7 ± 0.9	88 ± 18
			Dap50mg	56	/	53 ± 10	45	32 ± 4	7.8 ± 1.0	92 ± 19
			Met	56	/	54 ± 9	48	32 ± 5	7.9 ± 0.9	88 ± 20
			Placebo	54	/	53 ± 11	56	32 ± 5	7.6 ± 0.8	89 ± 18
Ferrannini2010	24	NCT00528372	Dap2.5mg(morning)	65	0.50	53.0 ± 11.7	55.4	32.6 ± 5.5	7.92 ± 0.90	90.8 ± 22.8
			Dap5 mg(morning)	64	0.25	52.6 ± 10.9	48.4	31.9 ± 4.8	7.86 ± 0.94	87.6 ± 17.1
			Dap10mg(morning)	70	0.45	50.6 ± 9.97	48.6	33.6 ± 5.4	8.01 ± 0.96	94.2 ± 18.7
			Dap2.5mg (evening)	67	0.20	54.3 ± 11.5	43.3	32.2 ± 5.3	7.99 ± 0.99	88.3 ± 20.5
			Dap5 mg(evening)	68	0.50	54.5 ± 11.0	42.6	32.8 ± 5.3	7.82 ± 0.91	89.2 ± 20.5
			Dap10mg(evening)	76	0.40	50.7 ± 9.7	51.3	33.3 ± 5.6	7.99 ± 1.05	92.1 ± 22.0
			Dap5 mg(morning)	34	0.65	48.3 ± 9.3	70.6	32.6 ± 4.6	10.82 ± 0.93	88.7 ± 19.2
			Dap10mg(morning)	39	1.40	47.9 ± 12.1	59.0	31.1 ± 5.9	10.73 ± 0.85	87.5 ± 22.7
			Placebo	75	0.50	52.7 ± 10.3	41.3	32.3 ± 5.5	7.84 ± 0.87	88.8 ± 19
Bailey2012	24	/	Dap1mg	72	1.6 ± 2.55	53.7 ± 9.04	52.8	32.53 ± 5.68	7.8 ± 0.98	88.2 ± 18.49
			Dap2.5mg	74	1.5 ± 2.19	53.5 ± 10.61	45.9	31.13 ± 5.47	8.1 ± 1.07	84.3 ± 18.18
			Dap5mg	68	1.4 ± 3.24	51.3 ± 11.51	47.1	30.97 ± 5.68	7.9 ± 1.03	85.4 ± 19.43
			Placebo	68	1.1 ± 1.95	53.5 ± 11.08	54.4	32.47 ± 4.91	7.8 ± 1.12	90 ± 17.98
Henry2012	24	NCT00643851	Dap5mg(Study 1)	203	1.6 ± 3.1	52.3 ± 10.2	45.3	/	9.1 ± 1.4	86.20 ± 21.13
		NCT00859898	Met(Study 1)	201	1.6 ± 2.6	51.8 ± 9.8	47.3	/	9.2 ± 1.3	85.75 ± 19.93
			Dap10mg(Study 2)	219	2.1 ± 3.8	51.1 ± 11.5	47.9	/	9.1 ± 1.3	88.53 ± 19.33
			Met(Study 2)	208	1.9 ± 4.0	52.7 ± 10.4	46.6	/	9.1 ± 1.3	87.24 ± 19.42
Ferrannini 2013	12	NCT00789035	Emp5mg	81	/	59	56.8	28.5	7.9 ± 0.8	82.8 ± 50
			Emp10mg	81	/	58	49.4	28.1	8.0 ± 0.8	76.8 ± 50
			Emp25mg	82	/	57	50	28.3	7.8 ± 0.8	81.2 ± 40
			Placebo	82	/	58	54.9	28.8	7.8 ± 0.8	82.2 ± 50
Fonseca2013	12	NCT01071850	Ipr12.5mg	70	4.08 ± 3.24	53.9 ± 9.6	55.7	31.0 ± 5.9	7.95 ± 0.78	86.0 ± 22.3
			Ipr50mg	67	4.61 ± 4.65	52.6 ± 10.7	50.7	32.2 ± 5.9	8.05 ± 0.81	90.7 ± 20.8
			Ipr150mg	68	5.11 ± 6.46	54.2 ± 10.3	42.6	30.9 ± 6.3	7.83 ± 0.65	83.3 ± 21.6
			Ipr300mg	68	4.48 ± 4.91	54.2 ± 10.7	54.4	30.7 ± 5.0	7.90 ± 0.67	86.7 ± 19.6
			Met	69	4.13 ± 4.71	53.1 ± 11.7	58.0	29.8 ± 5.5	8.03 ± 0.90	84.1 ± 21.8
Inagaki2013	12	NCT01022112	Can50mg	82	/	57.4 ± 10.8	61.0	25.11 ± 4.13	8.13 ± 0.78	65.77 ± 13.56
			Can100mg	74	/	57.7 ± 10.5	70.3	25.61 ± 4.64	8.05 ± 0.86	68.61 ± 14.86
			Can200mg	76	/	57.0 ± 10.7	64.5	25.51 ± 4.30	8.11 ± 0.88	68.97 ± 14.50
			Can300mg	75	/	57.1 ± 10.1	73.3	25.89 ± 3.68	8.17 ± 0.81	71.30 ± 12.19
			Placebo	75	/	57.7 ± 11.0	72.0	26.41 ± 4.34	7.99 ± 0.77	72.56 ± 15.36
Kaku2013	12	NCT00972244	Dap1mg	59	4.89 ± 4.37	55.9 ± 9.7	79.7	/	8.10 ± 0.79	68.4 ± 11.04
			Dap2.5mg	56	4.41 ± 3.97	57.7 ± 9.3	69.6	/	7.92 ± 0.74	66.61 ± 14.29
			Dap5mg	58	5.34 ± 4.51	58.0 ± 9.5	81	/	8.05 ± 0.66	68.92 ± 12.43
			Dap10mg	52	4.73 ± 4.73	56.5 ± 11.5	75	/	8.18 ± 0.69	70.35 ± 17.48
			Placebo	54	4.74 ± 3.82	58.4 ± 10.0	79.6	/	8.12 ± 0.71	68.88 ± 14.94
Roden 2013	24	NCT01289990	Emp10mg	224	/	56.2 ± 11.6	63	28.3 ± 5.5	7.87 ± 0.88	78.4 ± 18.7
			Emp25mg	224	/	53.8 ± 11.6	65	28.2 ± 5.5	7.86 ± 0.85	77.8 ± 18.0
			Sitagliptin100mg	223	/	55.1 ± 9.9	63	28.2 ± 5.2	7.85 ± 0.79	79.3 ± 20.4
			Placebo	228	/	54.9 ± 10.9	54	28.7 ± 6.2	7.91 ± 0.78	78.2 ± 19.9
Stenlof2013	26	NCT01081834	Can100mg	195	4.5 ± 4.4	55.1 ± 10.8	41.5	31.3 ± 6.6	8.1 ± 1.0	85.8 ± 21.4
			Can300mg	197	4.3 ± 4.7	55.3 ± 10.2	45.2	31.7 ± 6.0	8.0 ± 1.0	86.9 ± 20.5
			Placebo	192	4.2 ± 4.1	55.7 ± 10.9	45.8	31.8 ± 6.2	8.0 ± 1.0	87.6 ± 19.5
Inagaki2014	24	NCT01413204	Can100mg	90	4.72 ± 4.59	58.4 ± 10.4	65.6	25.59 ± 4.20	7.98 ± 0.73	69.10 ± 14.48
			Can200mg	88	5.88 ± 5.93	57.4 ± 11.1	81.8	25.43 ± 4.18	8.04 ± 0.77	69.88 ± 14.22

(continued on next page)

Table S1. (*Continued*)

study	Study duration (week)	Study ID	Treatment group (once daily dosing)	No. of patients	Duration of diabetes (years)	Age (years)	Men (%)	BMI (kg/m2)	Baseline HbA1c (%)	Baseline Weight (kg)
			Placebo	93	5.63 ± 5.76	58.2 ± 11.0	64.5	25.85 ± 4.39	8.04 ± 0.70	68.57 ± 15.15
Ji2014	24	NCT01095653	Dap5mg	128	1.30 ± 2.0	49.9 ± 10.87	65.9	25.93 ± 3.64	8.35 ± 0.95	72.18 ± 13.23
			Dap10mg	133	1.15 ± 2.3	53.0 ± 11.07	65.6	25.17 ± 3.29	8.14 ± 0.74	68.89 ± 11.43
			Placebo	132	1.67 ± 2.8	51.2 ± 9.89	64.7	25.76 ± 3.43	8.28 ± 0.95	70.92 ± 11.64
Kadowaki 2014	12	NCT01193218	Emp5mg	110	/	57.3 ± 11.2	76.4	26.3 ± 4.2	7.92 ± 0.70	72.3 ± 14.7
			Emp10mg	109	/	57.9 ± 9.4	70.6	25.3 ± 4.4	7.93 ± 0.71	68.1 ± 14.6
			Emp25mg	109	/	57.2 ± 9.7	77.1	25.1 ± 3.8	7.93 ± 0.78	68.3 ± 14.1
			Emp50mg	110	/	56.6 ± 10.3	77.3	25.0 ± 3.6	8.02 ± 0.65	68.2 ± 12.3
			Placebo	109	/	58.7 ± 8.7	73.4	25.6 ± 3.4	7.94 ± 0.74	69.0 ± 12.2
Kaku2014a	24	/	Dap5mg	86	4.59 ± 5.56	58.6 ± 10.4	58.1	24.88 ± 3.91	7.50 ± 0.72	65.81 ± 14.37
			Dap10mg	88	4.93 ± 4.52	57.5 ± 9.3	60.2	26.06 ± 4.52	7.46 ± 0.61	69.70 ± 13.82
			Placebo	87	5.29 ± 6.17	60.4 ± 9.7	59.8	25.22 ± 4.39	7.50 ± 0.63	65.96 ± 12.91
Kaku2014b	24	Japic CTI-101349	Tof10mg	57	6.3 ± 7.1	58.6 ± 9.8	66.7	25.07 ± 3.53	8.45 ± 0.75	67.26 ± 12.67
			Tof20mg	58	6.4 ± 5.1	56.6 ± 10.2	67.2	24.99 ± 4.55	8.34 ± 0.81	68.06 ± 15.82
			Tof40mg	58	6.7 ± 5.5	57.0 ± 9.1	67.2	25.78 ± 4.10	8.37 ± 0.77	68.72 ± 11.91
			Placebo	56	6.0 ± 6.1	56.8 ± 9.9	66.1	26.00 ± 4.11	8.41 ± 0.78	71.20 ± 12.64
Kashiwagi 2014	12	NCT00621868	Ipr12.5mg	73	6.3 ± 5.2	55.3 ± 10.2	58.91	25.6 ± 3.5	8.39 ± 0.90	67.4 ± 12.8
			Ipr25mg	74	6.4 ± 4.9	57.0 ± 10.4	66.21	26.2 ± 4.0	8.32 ± 0.83	69.0 ± 14.5
			Ipr50mg	72	6.6 ± 6.8	55.9 ± 11.4	59.72	25.8 ± 3.5	8.33 ± 0.80	67.8 ± 11.9
			Ipr100mg	72	7.8 ± 7.32	56.0 ± 10.4	68.06	25.9 ± 3.8	8.25 ± 0.76	68.3 ± 12.4
			Placebo	69	6.3 ± 5.5	55.2 ± 9.7	71.01	25.1 ± 3.4	8.36 ± 0.79	66.6 ± 10.6
Seino2014a	24	JapicCTI-111661	Lus2.5mg	79	6.5 ± 5.9	58.9 ± 10.1	75.9	25.98 ± 4.88	8.14 ± 0.91	70.19 ± 13.65
			Placebo	79	6.1 ± 5.4	59.6 ± 9.3	70.9	25.34 ± 4.19	8.17 ± 0.80	66.67 ± 11.23
Seino2014b	12	Japic CTI-101191	Lus1mg	55	4.7 ± 4.1	58.5 ± 9.1	72.7	23.36 ± 3.22	7.95 ± 0.67	66.93 ± 12.76
			Lus2.5mg	56	4.6 ± 4.4	57.4 ± 9.3	67.9	26.43 ± 4.26	7.86 ± 0.69	66.67 ± 11.25
			Lus5mg	54	4.5 ± 4.2	57.3 ± 11.4	75.9	24.79 ± 3.81	8.05 ± 0.75	72.56 ± 13.94
			Lus10mg	58	6.2 ± 5.4	59.6 ± 7.8	63.8	24.51 ± 4	7.77 ± 0.79	60.97 ± 12.74
			Placebo	57	5.1 ± 4.6	57.1 ± 10	71.9	25.15 ± 3.62	7.92 ± 0.84	67.32 ± 13.14
Seino2014c	12	JapicCTI-090908	Lus0.5mg	60	4.90 ± 4.49	55.2 ± 10.1	68.3	25.4 ± 3.54	8.16 ± 0.93	69.7 ± 13.7
			Lus2.5mg	61	6.15 ± 6.50	58.3 ± 9.4	57.4	24.8 ± 3.56	8.07 ± 0.90	65.5 ± 12.2
			Lus5mg	61	5.77 ± 5.55	56.8 ± 9.3	72.1	24.5 ± 3.21	8.16 ± 0.96	66.3 ± 12.4
			Placebo	54	7.30 ± 6.43	57.6 ± 11.0	74.1	25.2 ± 4.26	7.88 ± 0.72	68.3 ± 13.4
Stenlöf 2014	52	NCT01081834	Can100mg	166	4.5 ± 4.4	55.1 ± 10.8	41.5	31.3 ± 6.6	8.0 ± 0.9	85.8 ± 21.4
			Can300mg	166	4.3 ± 4.7	55.3 ± 10.2	45.2	31.7 ± 6.0	7.9 ± 0.9	86.9 ± 20.5
Ikeda 2015	12	NCT00800176	Tof2.5mg	66	4.88 ± 3.92	53.3 ± 10.86	51.5	31.33 ± 4.88	7.99 ± 0.76	85.23 ± 16.47
			Tof5mg	65	5.01 ± 3.60	54.8 ± 10.53	47.7	30.56 ± 5.23	8.01 ± 0.66	82.15 ± 16.35
			Tof10mg	66	5.77 ± 4.38	54.5 ± 10.70	51.5	30.40 ± 4.91	8.00 ± 0.71	83.41 ± 16.56
			Tof20mg	64	5.21 ± 3.93	56.3 ± 0.79	67.2	30.09 ± 4.65	7.92 ± 0.79	84.91 ± 17.31
			Tof40mg	67	6.44 ± 5.81	57.5 ± 9.31	46.3	30.36 ± 4.89	7.92 ± 0.78	81.68 ± 18.69
			Placebo	66	5.98 ± 5.29	53.9 ± 11.12	54.5	30.37 ± 5.47	7.88 ± 0.69	83.73 ± 19.20
Kadowaki2015	52	NCT01193218	Emp10mg	267	/	57.3 ± 9.8	75.7	25.4 ± 4.1	7.94 ± 0.69	69.3 ± 14.5
			Emp25mg	265	/	57.9 ± 10.1	74.0	25.4 ± 3.7	7.93 ± 0.73	68.8 ± 12.7
Kashiwagi2015	16	NCT01057628	Ipr50mg	62	7.53 ± 6.9	60.6 ± 9.4	67.7	25.3 ± 3.1	8.40 ± 0.86	65.5 ± 11.0
			Placebo	67	5.9 ± 5.1	58.3 ± 10.5	71.6	25.6 ± 3.9	8.25 ± 0.68	69.6 ± 12.6
Lewin2015	24	NCT01422876	Emp10mg	132	/	53.9 ± 10.5	48.5	31.5 ± 5.7	8.05 ± 1.03	87.8 ± 24.0
			Emp25mg	133	/	56.0 ± 9.3	57.9	31.2 ± 5.7	7.99 ± 0.97	86.7 ± 19.7
			Linagliptin5mg	133	/	53.8 ± 11.5	56.4	31.9 ± 5.9	8.05 ± 0.89	89.5 ± 20.1
Roden2015	76	NCT01289990 NCT01177813	Emp10mg	224	/	56.2 ± 11.6	63.4	28.3 ± 5.5	7.87 ± 0.88	78.4 ± 18.7
			Emp25mg	224	/	53.8 ± 11.6	64.7	28.2 ± 5.5	7.86 ± 0.85	77.8 ± 18.0
			Sitagliptin100mg	223	/	55.1 ± 9.9	63.2	28.2 ± 5.2	7.85 ± 0.79	79.3 ± 20.4
			Placebo	228	/	54.9 ± 10.9	53.9	28.7 ± 6.2	7.91 ± 0.78	78.2 ± 19.9

Table S1. (*Continued*)

study	Study duration (week)	Study ID	Treatment group (once daily dosing)	No. of patients	Duration of diabetes (years)	Age (years)	Men (%)	BMI (kg/m2)	Baseline HbA1c (%)	Baseline Weight (kg)
Rosenstock2016	26	NCT01809327	Can100mg	237	3.5 ± 4.4	54.0 ± 10.7	44.3	32.4 ± 5.4	8.8 ± 1.2	90.2 ± 18.6
			Can300mg	238	3.3 ± 4.4	55.8 ± 9.6	52.5	32.6 ± 5.8	8.8 ± 1.2	93.2 ± 19.9
			Met	237	3.3 ± 4.5	55.2 ± 9.8	48.9	33.0 ± 6.0	8.8 ± 1.2	92.1 ± 20.1
Terra2017	26	NCT01958671	Ert5mg	156	5.11 ± 5.09	56.8 ± 11.4	57.1	33.2 ± 7.4	8.16 ± 0.88	94.0 ± 25.4
			Ert15mg	152	5.22 ± 5.55	56.2 ± 10.8	59.2	32.5 ± 5.7	8.35 ± 1.12	90.6 ± 18.3
			Placebo	153	4.63 ± 4.52	56.1 ± 10.9	53.6	33.3 ± 6.8	8.11 ± 0.92	94.2 ± 25.2
Gupta2017	76	/	Emp10mg	24	/	47.4 ± 8.1	54.2	26.09 ± 3.37	8.35 ± 0.98	68.82 ± 11.81
			Emp25mg	29	/	47.1 ± 8.6	65.5	26.49 ± 4.07	8.09 ± 1.11	68.03 ± 12.46
			Sitagliptin100mg	27	/	49.5 ± 9.4	55.6	26.47 ± 3.61	8.31 ± 0.68	68.48 ± 14.98
			Placebo	28	/	48.7 ± 8.7	42.9	26.85 ± 4.49	7.92 ± 0.70	67.25 ± 12.35
Aronson2018	52	NCT01958671	Ert5mg	156	5.11 ± 5.09	56.8 ± 11.4	57.1	33.2 ± 7.4	8.16 ± 0.88	90.6 ± 18.3
			Ert15mg	152	5.22 ± 5.55	56.2 ± 10.8	59.2	32.5 ± 5.7	8.35 ± 1.12	94.2 ± 25.2

Dap = dapagliflozin; Emp = empagliflozin; Can = canagliflozin; Ipr = ipragliflozin; Ert: = ertugliflozin; Lus = luseogliflozin; Tof = :tofogliflozin; Met = metformin; Linagliptin = Lin; Sitagliptin = Sit.

Table S2. Subgroup network meta-analyses of each treatment for mean weight changes compared with placebo with weight mean difference (95% credible intervals).

Charact-eristics	treatments															
	Can100	Can300	Dap5	Dap10	Emp10	Emp25	Ert5	Ert15	Ipr25	Ipr50	Lin5	Lus2.5	Lus5	Met	Sit100	Tof20
All trials	−1.94 (−2.21, −1.59)	−2.78 (−3.09, −2.37)	−1.53 (−1.89, −1.19)	−1.51 (−1.84, −1.20)	−1.74 (−2.07, −1.39)	−1.82 (−2.15, −1.47)	−1.80 (−2.54, −1.06)	−2.07 (−2.74, −1.42)	−1.30 (−1.99, −0.63)	−1.39 (−2.03, −0.81)	−0.37 (−1.07, 0.34)	−1.63 (−2.03, −1.23)	−1.94 (−2.41, −1.48)	−0.51 (−0.87, −0.15)	0.39 (−0.03, 0.80)	−2.14 (−2.72,-1.59)
Sex Ratio																
Male to female ratio< 1	−1.96 (−3.99, −0.08)	−2.97 (−4.76, −0.97)	−2.22 (−5.32, 0.95)	−2.64 (−5.89, 0.69)										−1.29 (−4.01, 1.72)		
Male to female ratio>1	−1.98 (−2.46, −1.45)	−2.53 (−3.32, −1.76)	−1.52 (−1.98, −1.04)	−1.54 (−1.96, −1.18)	−1.64 (−2.08, −1.16)	−1.78 (−2.18, −1.34)	−1.80 (−2.58, −0.98)	−2.10 (−2.81, −1.32)	−1.27 (−2.01, −0.51)	−1.35 (−1.94, −0.75)	−0.48 (−1.38, 0.45)	−1.64 (−2.08, −1.17)	−1.95 (−2.49, −1.43)	−0.58 (−1.94, 0.73)	0.48 (−0.06, 0.94)	−2.16 (−2.78, −1.52)
Mean Age			−1.43	−1.37	−1.65	−2.02						−1.63	−1.70	−0.28	−0.94	
<55 years			(−2.13, −0.54)	(−2.07, −0.33)	(−2.35, −0.94)	(−2.47, −1.50)						(−2.54, −0.78)	(−2.63, −0.80)	(−0.78, 0.56)	(−1.98, 0.09)	
≥55 years	−2.00 (−2.21, −1.73)	−2.85 (−3.10, −2.53)	−1.70 (−2.12, −1.25)	−1.75 (−2.15, −1.27)	−1.40 (−1.90, −0.96)	−1.46 (−1.93, −0.96)	−1.78 (−2.46, −1.13)	−2.07 (−2.63, −1.50)	−1.25 (−1.82, −0.70)	−1.36 (−1.80, −0.88)		−1.64 (−1.98, −1.30)	−1.95 (−2.43, −1.54)	−1.04 (−1.93, −0.15)	0.97 (0.30, 1.57)	−2.49 (−3.20, −1.74)
Treatment durations	−1.98	−2.53	−1.48	−1.50	−1.68	−1.71			−1.26	−1.33	−0.28	−1.63	−1.95	−0.41	0.74	−2.17
≤24 weeks	(−2.40, −1.50)	(−3.23, −1.80)	(−1.83, −1.15)	(−1.86, −1.12)	(−2.10, −1.21)	(−2.14, −1.25)			(−1.94, −0.56)	(−1.82, −0.80)	(−1.06, 0.49)	(−2.05, −1.20)	(−2.45, −1.45)	(−0.81, 0.03)	(0.12, 1.42)	(−2.74, −1.56)
≥26weeks	−1.98 (−2.92, −0.99)	−2.91 (−3.91, −1.95)			−1.80 (−2.61, −0.90)	−2.01 (−2.78, −1.05)	−1.79 (−2.85, −0.66)	−2.08 (−3.09, −1.02)						−1.09 (−2.50, 0.34)	0.03 (−0.90, 0.80)	
baseline BMI	−2.01	−2.55	−1.31	−1.67	−1.69	−1.83			−1.28	−1.36		−1.64	−1.94		0.41	−2.46
BMI<30	(−2.44, −1.46)	(−3.26, −1.82)	(−1.95, −0.70)	(−2.32, −1.07)	(−2.05, −1.30)	(−2.20, −1.44)			(−1.99, −0.53)	(−1.99, −0.77)		(−2.07, −1.19)	(−2.46, −1.44)		(−0.09, 0.83)	(−3.37, −1.61)
BMI≥30	−1.87 (−2.82, −0.65)	−2.77 (−3.76, −1.55)	−1.20 (−2.15, −0.10)	−1.15 (−1.93, −0.08)			−1.72 (−3.13, −0.33)	−2.15 (−3.53, −0.77)						−0.52 (−1.56, 0.44)		−1.80 (−3.26, −0.36)
baseline HbA1c			−1.49	−1.40	−1.68	−1.84						−1.43			0.67	−1.79
<8%			(−2.27, −0.76)	(−2.25, −0.51)	(−2.15, −1.22)	(−2.22, −1.36)						(−2.32, −0.60)			(0.12, 1.24)	(−2.76, −0.88)
HbA1c ≥ 8%	−1.99 (−2.16, −1.75)	−2.87 (−3.02, −2.52)	−1.82 (−2.25, −1.50)	−1.94 (−2.35, −1.61)	−1.51 (−2.73, −0.24)	−1.82 (−2.85, −0.62)	−1.79 (−2.39, −1.16)	−2.02 (−2.63, −1.54)	−1.28 (−1.79, −0.80)	−1.40 (−1.76, −1.00)		−1.82 (−2.32, −1.19)	−1.89 (−2.61, −1.07)	−0.77 (−1.11, −0.28)	−0.95 (−1.69, 0.32)	−2.60 (−3.14, −1.91)
diabetes duration	−1.91	−2.83	−1.61	−1.68						−1.33		−1.42	−2.10	−0.50		
<5years	(−2.31, −1.21)	(−3.28, −2.14)	(−1.98, −1.15)	(−2.11, −1.22)						(−2.67, 0.05)		(−2.21, −0.66)	(−2.91, −1.29)	(−1.08, 0.13)		
≥5year	−2.08 (−3.15, −0.98)								−1.28 (−2.39, −0.15)	−1.37 (−2.16, −0.51)		−1.71 (−2.57, −0.88)	−1.74 (−2.76, −0.65)			−2.14 (−3.01, −1.33)
baseline weight	−2.02	−2.54	−1.65	−1.65	−1.79	−1.66	−1.90	−1.26	−1.35			−1.64	−1.94		−0.90	−2.51
<75kg	(−2.33, −1.62)	(−3.14, −1.96)	(−2.04, −1.20)	(−2.04, −1.20)	(−2.20, −1.36)	(−2.24, −1.10)	(−2.39, −1.28)	(−1.87, −0.66)	(−1.84, −0.87)			(−1.99, −1.25)	(−2.36, −1.53)		(−1.79, 0.01)	(−3.28, −1.73)
weight≥75kg	−1.90 (−2.31, −1.20)	−2.82 (−3.25, −2.15)	−1.39 (−2.04, −0.81)	−1.26 (−1.77, −0.77)	−1.75 (−2.14, −1.21)	−1.78 (−2.21, −1.23)	−1.71 (−2.63, −0.95)	−1.99 (−2.84, −1.33)		−1.22 (−2.47, 0.11)	−0.39 (−1.11, 0.54)			−0.36 (−0.83, 0.13)	0.65 (0.17, 1.24)	−1.89 (−2.70, −0.96)

We excluded the trials with male-to-female ratio = 1. Can100 = canagliflozin 100mg; Can300 = canagliflozin 300mg; Dap10 = dapagliflozin 10mg; Dap5 = dapagliflozin 5mg; Emp10 = empagliflozin 10mg; Emp25 = empagliflozin 50mg; Ert15 = ertugliflozin 15mg; Ert5 = ertugliflozin 5mg; Ipr25 = ipragliflozin 25mg, Ipr50 = ipragliflozin 50mg, Ert: = ertugliflozin, Lin5 = Linagliptin 5mg; Lus2.5 = luseogliflozin 2.5mg, Lus5 = luseogliflozin 5mg; Met = metformin; Sit 100 = Sitagliptin100mg; Tof20 = :tofogliflozin 20mg, NA = not available.

Table S3. Odds ratio with 95% confidence interval of network meta-analysis for the proportion of patients achieving ≥5% weight loss. Results of direct comparisons are listed in the upper triangle, the estimation is located at the intersection of the row-defining treatment and the column-defining treatment. Results of network meta-analysis are listed in the lower triangle, the estimation is located at the intersection of the column-defining treatment and the row-defining treatment. Significant results are bolded. Dap10=dapagliflozin 10mg; Dap5=dapagliflozin 5mg; Emp10=empagliflozin 10mg; Emp25=empagliflozin 50mg; Ipr50=ipragliflozin 50mg; Met=metformin; Sit100= sitagliptin 100mg; NA= not available.

Dap10	1.39(0.80,2.40)	NA	NA	NA	NA	NA	**5.53(2.39,12.81)**
1.51 (0.52, 4.14)	Dap5	NA	NA	NA	NA	NA	**3.26(1.66,6.41)**
1.13 (0.24, 4.41)	0.76 (0.19, 2.51)	Emp10	0.81(0.61,1.07)	NA	NA	**3.63(1.95,6.74)**	**5.58(3.03,10.29)**
0.85 (0.18, 3.31)	0.56 (0.14, 1.86)	0.75 (0.40, 1.39)	Emp25	NA	NA	**4.62(2.52,8.48)**	**7.55(4.15,13.76)**
3.26 (0.60, 16.15)	2.14 (0.46, 9.50)	2.96 (0.72, 13.89)	3.82 (0.94, 19.10)	Ipr50	1.03(0.25,4.29)	NA	2.33(0.96,5.63)
4.21 (0.54, 33.74)	2.87 (0.43, 20.38)	3.95 (0.71, 29.67)	5.39 (0.91, 38.10)	1.37 (0.30, 6.83)	Met	NA	1.33(0.45,3.94)
5.16 (0.93, 24.22)	3.46 (0.74, 14.86)	**4.68 (1.75, 13.48)**	**6.21 (2.33, 17.74)**	1.66 (0.31, 7.84)	1.16 (0.15, 8.07)	Sit100	1.43(0.62,2.70)
8.57 (2.71, 27.44)	**5.70 (2.28, 15.11)**	**7.70 (3.28, 21.34)**	**10.20 (4.59, 28.93)**	2.60 (0.87, 8.63)	1.95 (0.35, 9.85)	1.65 (0.55, 5.57)	placebo

Results of direct comparisons are listed in the upper triangle, the estimation is located at the intersection of the row-defining treatment and the column-defining treatment. Results of network meta-analysis are listed in the lower triangle, the estimation is located at the intersection of the column-defining treatment and the row-defining treatment. Significant results are bolded. Dap10=dapagliflozin 10mg; Dap5=dapagliflozin 5mg; Emp10=empagliflozin 10mg; Emp25=empagliflozin 50mg; Ipr50=ipragliflozin 50mg; Met=metformin; Sit100= sitagliptin 100mg; NA= not available.

Table S4. Ranking probability of all treatments on weight changes from baseline and the proportion of patients achieving ≥5% weight loss.

Drugs	Abbreviation	Weight change from baseline		proportion of patients achieving >5% weight loss.	
		SUCRA	Rank	SUCRA	Rank
Canagliflozin 50 mg	Can50	0.4306	21	NA	NA
Canagliflozin 100 mg	Can100	0.7023	12	NA	NA
Canagliflozin 200 mg	Can200	0.7926	6	NA	NA
Canagliflozin 300 mg	Can300	0.9866	1	NA	NA
Dapagliflozin 1 mg	Dap1	0.2660	28	0.3950	10
Dapagliflozin 2.5 mg	Dap2.5	0.3480	26	0.2750	12
Dapagliflozin 5 mg	Dap5	0.3860	22	0.5814	6
Dapagliflozin 10 mg	Dap10	0.4766	20	0.7371	4
Dapagliflozin 20 mg	Dap20	0.7711	10	NA	NA
Dapagliflozin 50 mg	Dap50	0.8363	3	NA	NA
Empagliflozin 5 mg	Emp5	0.3689	23	0.5171	7
Empagliflozin 10 mg	Emp10	0.5900	15	0.6944	5
Empagliflozin 25 mg	Emp25	0.6357	13	0.8286	3
Empagliflozin 50mg	Emp50	0.7857	7	0.8721	1
Ertugliflozin 5 mg	Ert 5	0.6183	14	NA	NA
Ertugliflozin15mg	Ert15	0.7834	8	NA	NA
Ipragliflozin 12.5mg	Ipr12.5	0.2437	30	0.4914	9
Ipragliflozin 25 mg	Ipr25	0.3409	27	NA	NA
Ipragliflozin 50 mg	Ipr50	0.3646	24	0.3249	11
Ipragliflozin 100 mg	Ipr100	0.5489	17	NA	NA
Ipragliflozin 150 mg	Ipr150	0.5806	16	0.4950	8
Ipragliflozin 300 mg	Ipr300	0.8254	4	0.8329	2
Linagliptin 5 mg	Lin 5	0.0937	34	NA	NA
luseogliflozin 0.5 mg	Lus0.5	0.1246	32	NA	NA
luseogliflozin 1mg	Lus1	0.2086	31	NA	NA
luseogliflozin 2.5mg	Lus2.5	0.5120	19	NA	NA
luseogliflozin 5 mg	Lus5	0.7169	11	NA	NA
luseogliflozin 10 mg	Lus10	0.7729	9	NA	NA
Metformin	Met	0.0983	33	0.2207	13
Placebo	Placebo	0.0346	35	0.0371	15
Sitagliptin 100mg	Sit100	0.0289	36	0.1621	14
Tofogliflozin 2.5 mg	Tof2.5	0.2571	29	NA	NA
Tofogliflozin 5 mg	Tof5	0.3586	25	NA	NA
Tofogliflozin 10 mg	Tof10	0.5397	18	NA	NA
Tofogliflozin 20 mg	Tof20	0.8091	5	NA	NA
Tofogliflozin 40 mg	Tof40	0.8977	2	NA	NA

NA = not available; Larger SUCRAs and lower rank denote more effective interventions.

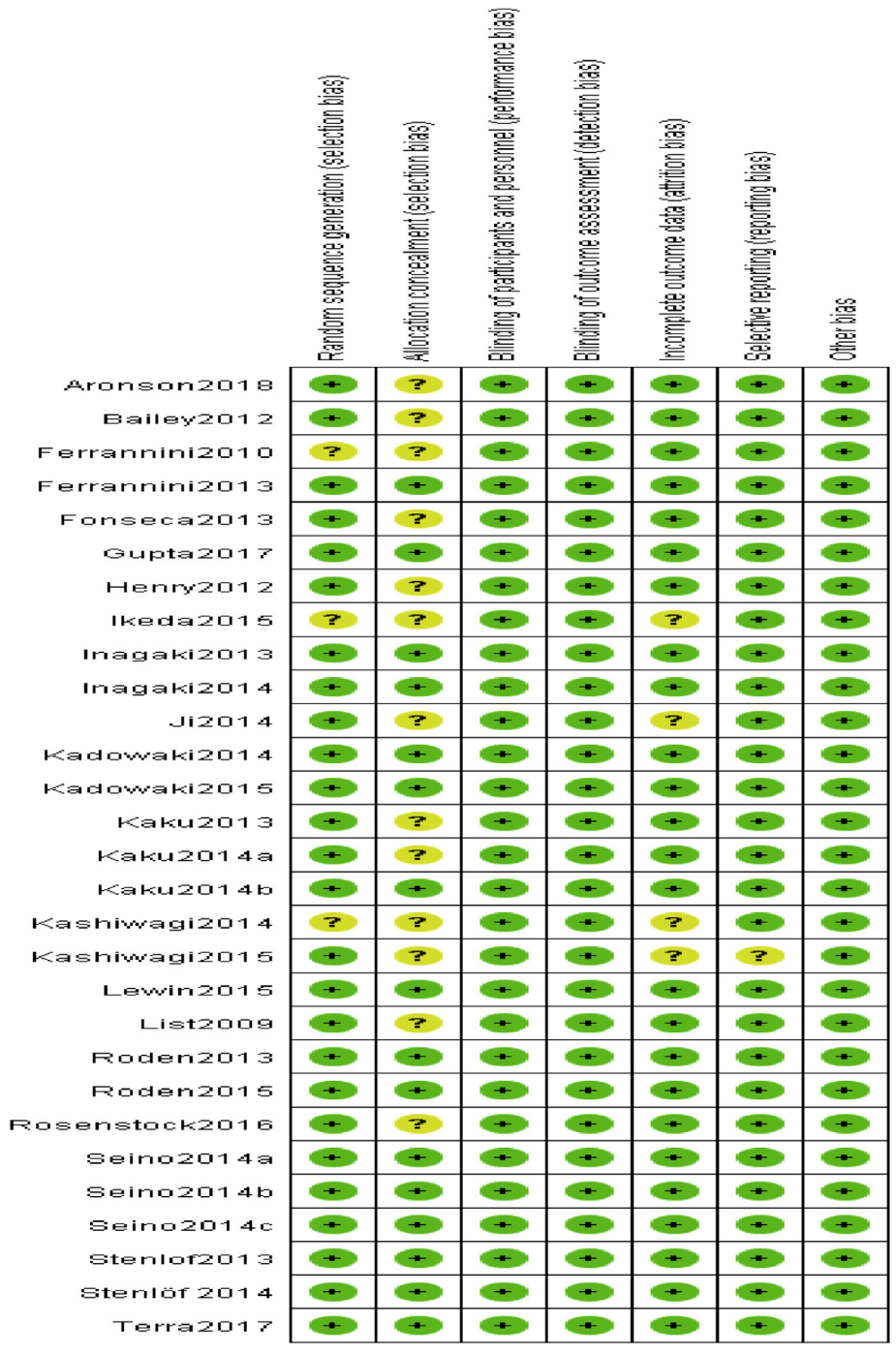

Fig S1. Summary of the risk of bias of included studies regarding SGLT2 inhibitor treatment.

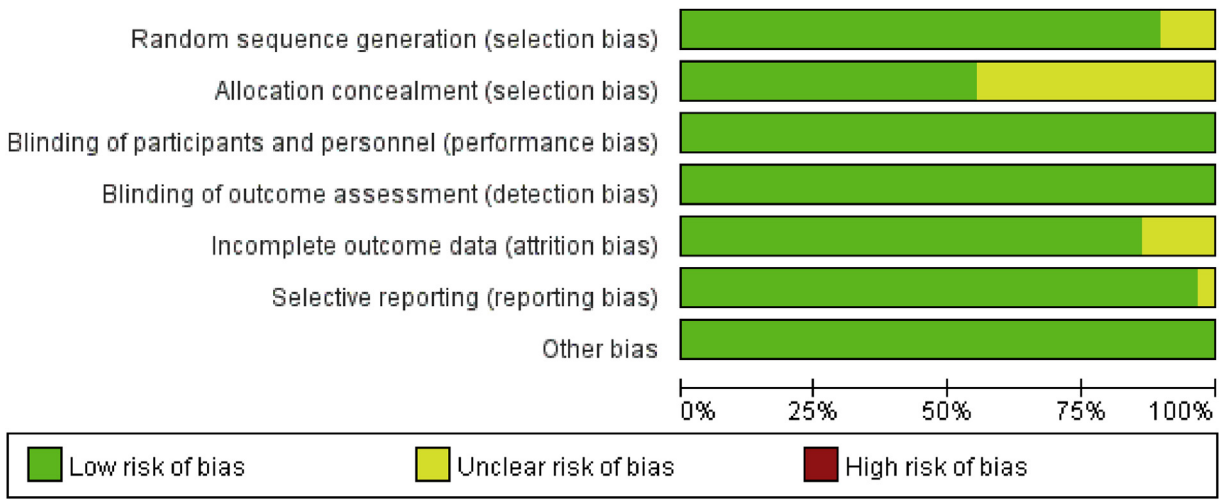

Fig S2. Graph of the risk of bias of included studies regarding SGLT2 inhibitor treatment.

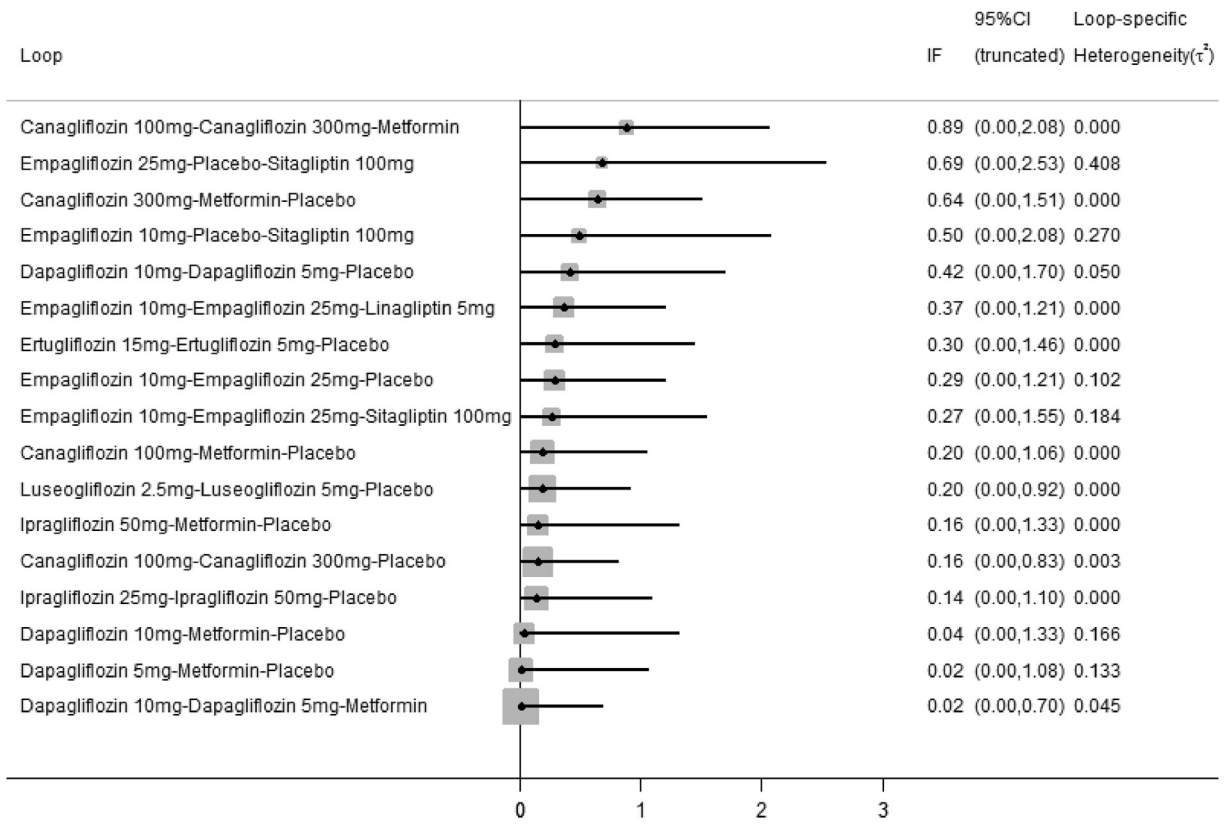

Fig S3. Forest plots of inconsistency check for all closed loops in the network of weight changes from baseline.

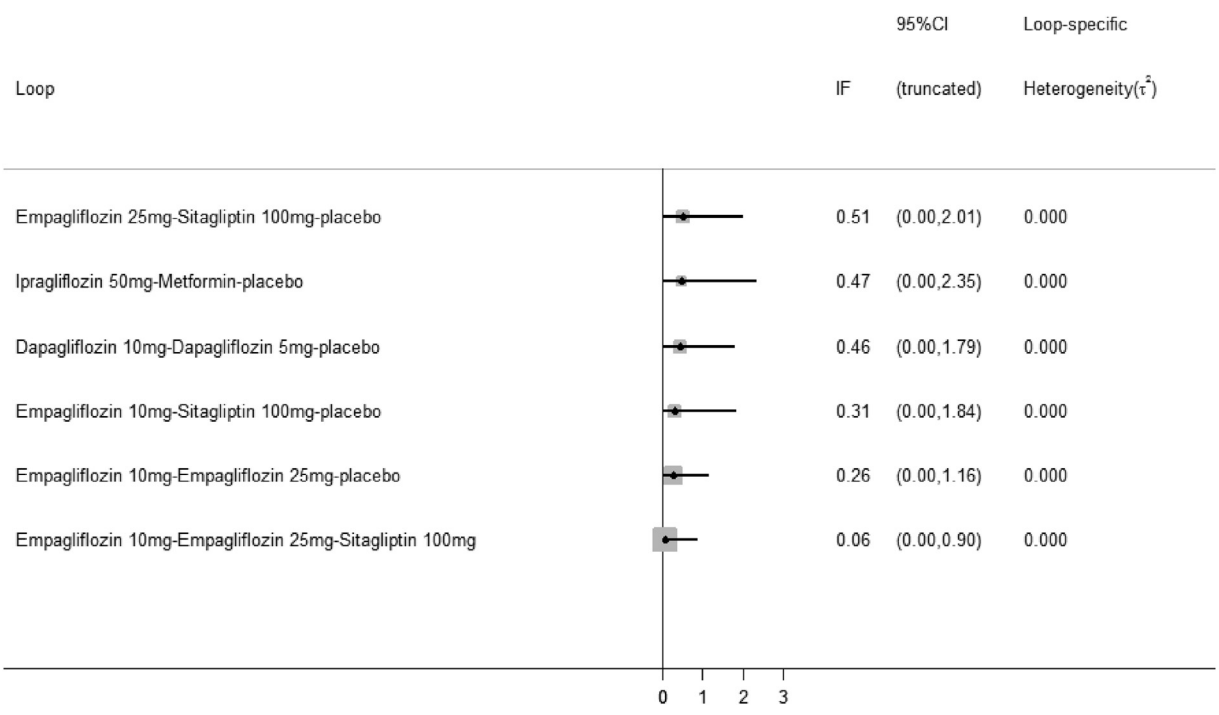

Fig S4. Forest plots of inconsistency check for all closed loops in the network of the proportions of patients achieving $\geq$5% weight loss.

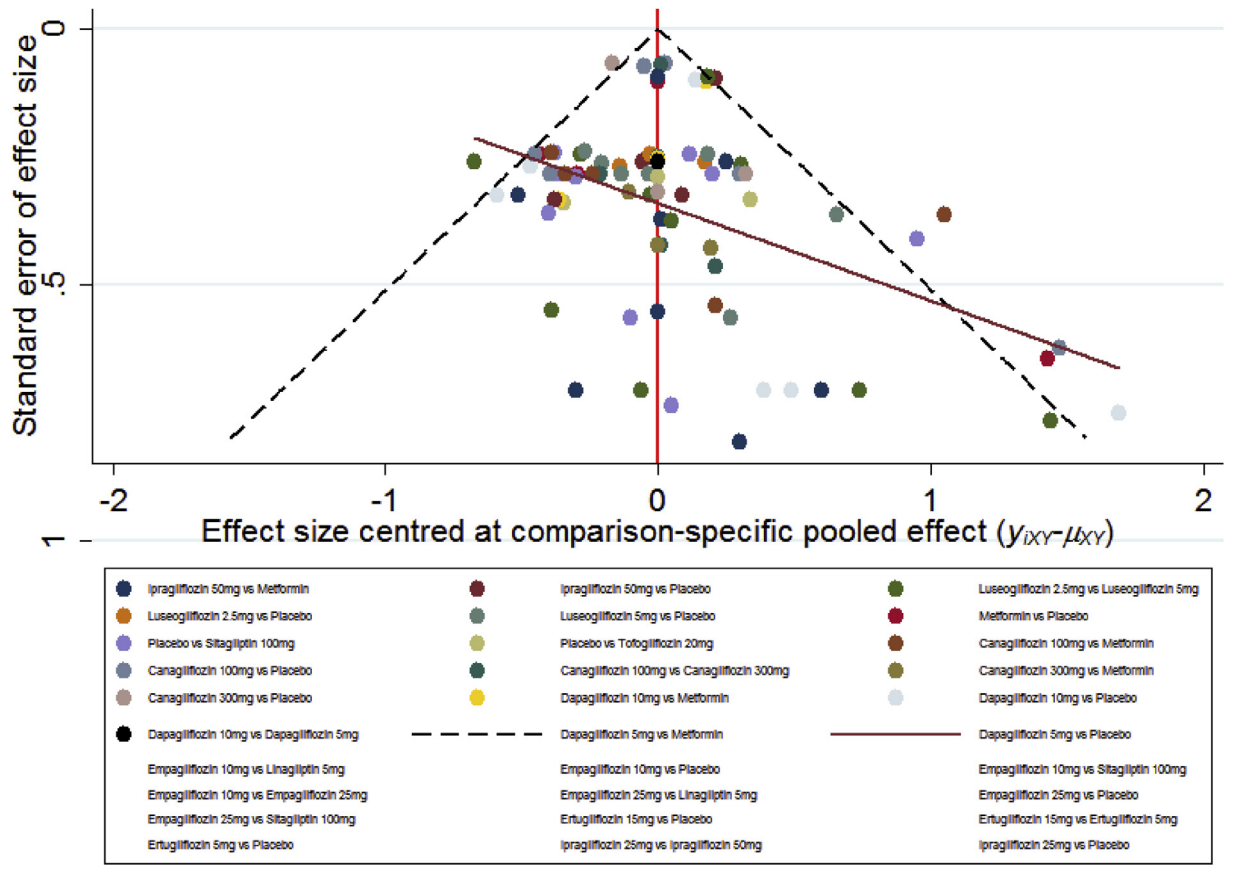

Fig S5. Comparison-adjusted funnel plot for weight changes from baseline.

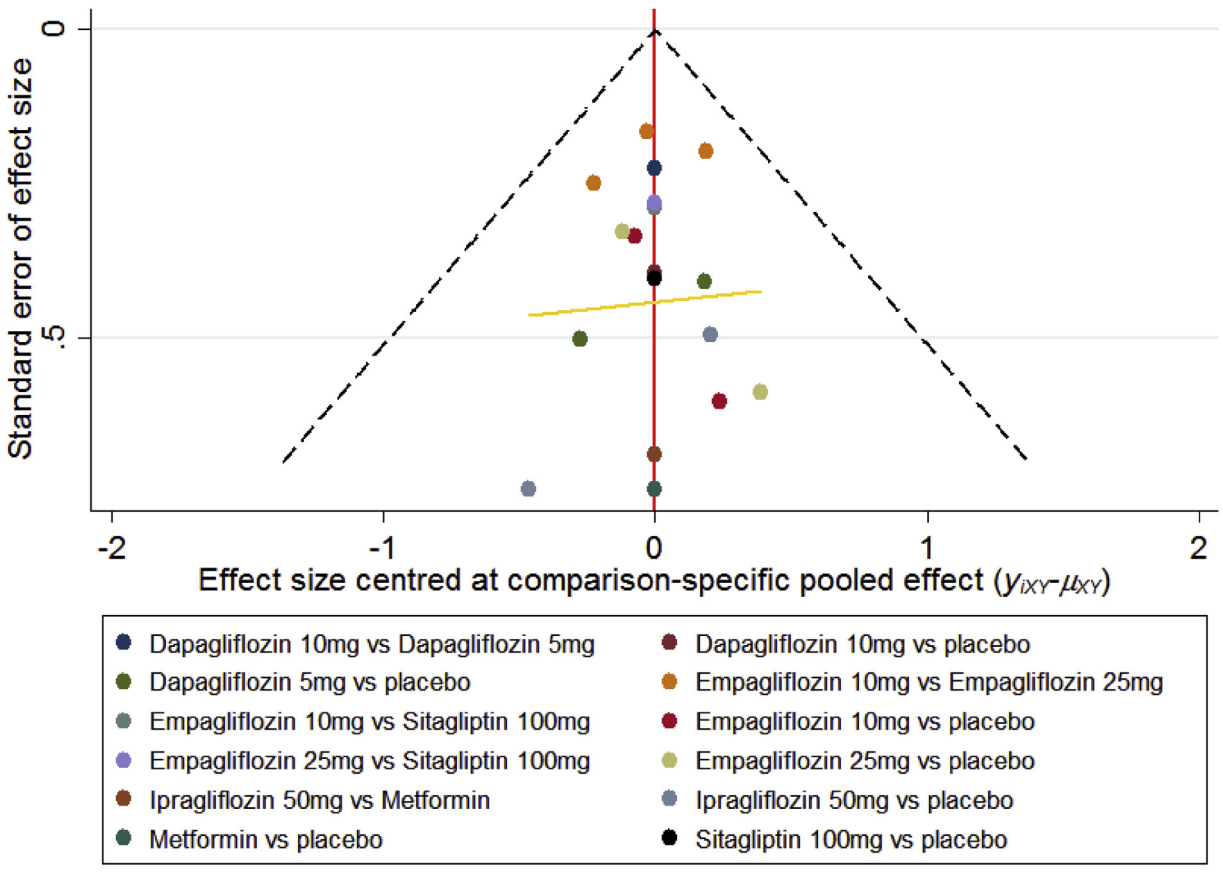

Fig S6. Comparison-adjusted funnel plot for the proportions of patients achieving ≥5% weight loss.

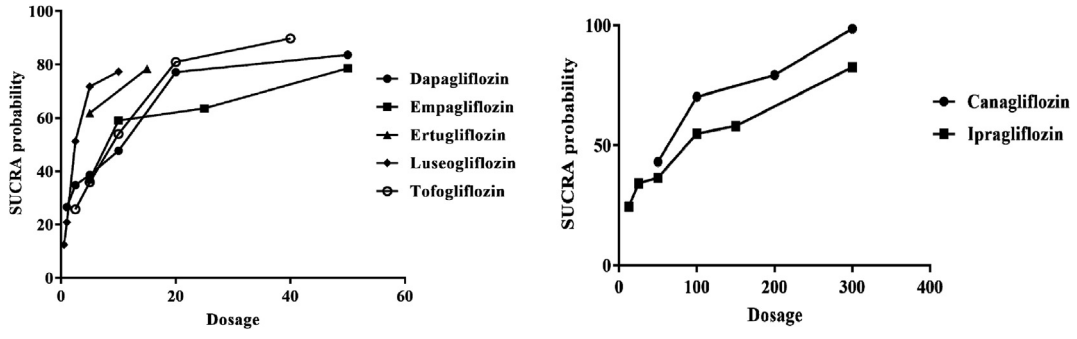

Fig S7. Trend graph between SUCRA probability and dosage.