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SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis

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ABSTRACT

Objective: Because of the lack of head-to-head trials, the aim was to indirectly compare sodium glucose transporter-2 (SGLT-2) inhibitors in the treatment of type 2 diabetes.

Design: Systematic review and network meta-analysis.

Data sources: MEDLINE and EMBASE were searched from January 2005 to January 2015.

Eligibility criteria: Randomised controlled trials assessing the efficacy of SGLT-2 inhibitors in patients with type 2 diabetes inadequately controlled with diet and exercise alone or metformin monotherapy. Minimum duration 24 weeks. Indirect comparison was undertaken using Bayesian methods.

Results: In monotherapy, a greater proportion of patients achieved a glycated haemoglobin (HbA1c) level of <7% on canagliflozin 300 mg than on canagliflozin 100 mg (risk ratio (RR) 0.72%, 95% credible intervals (CrI) 0.59% to 0.87%) and dapagliflozin 10 mg (RR 0.63, 95% CrI 0.48 to 0.85) but there were no significant differences compared with either dose of empagliflozin. In monotherapy, canagliflozin 300 mg reduced HbA1c more than other SGLT-2 inhibitors (mean difference ranged from 0.20% to 0.64%). There were no significant differences in weight reduction. All the flozins reduced systolic blood pressure (SBP) more than placebo, ranging from a reduction of 6 mm Hg with canagliflozin 300–2.6 mm Hg with empagliflozin 10 mg. In dual therapy with metformin, all flozins were more effective than placebo for achieving HbA1c <7%, and reducing HbA1c, weight and SBP. The proportions achieving HbA1c level of <7% were mostly similar. Canagliflozin 300 mg reduced HbA1c more than the other drugs but this just reached statistical significance only against canagliflozin 100 mg (MD 0.15, CrI 0.04 to 0.26).

Conclusions: There were few differences among the SGLT-2 inhibitors, but in monotherapy, the glucose-lowering effect of canagliflozin 300 mg is slightly greater than most other SGLT-2 inhibitors.

Strengths and limitations of this study

- In the absence of head-to-head comparisons of different sodium glucose transporter-2 inhibitors, a Bayesian network meta-analysis was used to compare the efficacy of the drugs.
- Studies were identified by a systematic search, and data abstraction and quality assessment of the studies were done independently by two authors.
- The study also includes the newer drugs in this class namely luseogliflozin, ipragliflozin and tofogliflozin.
- Safety data were not compared. The trials were for a maximum of 26 weeks duration.

INTRODUCTION

The newest class of drugs for type 2 diabetes are the sodium glucose co-transporter 2 receptor (SGLT-2) inhibitors. These reduce the reabsorption of renal-filtered glucose back into the bloodstream, thereby leading to loss of glucose in the urine. In the UK, the first three drugs in this class to reach the market, dapagliflozin, canagliflozin and empagliflozin, have been approved by the National Institute for Health and Care Excellence (NICE).[1–3]

In addition to the SGLT-2 transport system in the kidney, there is also a related transport system in the gut, SGLT-1. Most SGLT-2 inhibitors have no significant effect of SGLT-1, but one of the class, canagliflozin, does affect SGLT-1, and it has been suggested by Polidori *et al*[4] that canagliflozin may reduce blood glucose by a dual action in both gut and kidney. However, that suggestion followed a very short-term study of canagliflozin in healthy individuals, and the gut effect was seen only with higher doses (>200 mg).

A second study by Polidori and colleagues from Janssen Research and Development looked at the SGLT-1 effect in people with type 2 diabetes[5] and found that canagliflozin 300 mg, but not 150 mg, reduced postprandial plasma glucose, by about 0.5 mmol/L (from graph) for about 2 h after

administration, since it depends on an intestinal drug action not a systemic one. Would a change of that magnitude be enough to make a clinically meaningful difference in glycated haemoglobin (HbA1c), experienced once a day?

If the SGLT-1 effect is clinically significant in people with type 2 diabetes, then one might expect canagliflozin 300 mg to be more potent in reducing HbA1c levels than other SGLT-2 inhibitors without the SGLT-1 effect. The usual starting dose of canagliflozin is 100 mg once daily.

In the absence of head-to-head trials, the relative potencies can only be assessed by an indirect comparison by a network meta-analysis (NMA). We have therefore carried out two NMAs, one of five drugs in monotherapy and the other of four drugs in dual therapy with metformin. The aim was to determine whether the glucose-lowering effect of canagliflozin would be greater than that of other flozins without the SGLT-1 effect. Secondary aims were to compare effects on weight loss and blood pressure, and on proportions achieving HbA1c targets.

METHODS

Information sources and search strategy

A systematic search was undertaken to identify all the relevant studies. The searches were carried out in MEDLINE, MEDLINE In-process and EMBASE from January 2005 to September 2014 using search strategies given in online supplementary appendix S1. The search strategy was modified for other databases. The searches were updated in January 2015 and no new studies were found to be relevant. The reference lists of all the included studies were also checked for possible inclusions.

Study selection

Abstracts retrieved by the searches were screened for inclusion or exclusion. The studies were included if they met the following criteria: randomised controlled trial (RCT) assessing the efficacy of any SGLT-2 inhibitors in monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise, and in dual therapy in patients with inadequate control on metformin monotherapy. We compared the efficacies of only licensed doses, and in the data extraction tables, details of arms with other doses are omitted. Minimum duration was 24 weeks. The included studies should have reported either proportion of patients achieving an HbA1c target of <7.0% or mean change in HbA1c from baseline to 24 weeks. We also sought changes in body weight and systolic blood pressure (SBP) from baseline to 24 weeks.

Risk of bias assessment

The quality of studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias.[6] The items assessed were (1) sequence generation, (2) allocation concealment, (3) blinding of outcome assessor, (4) incomplete outcome data and (5) selective outcome reporting. They were graded as unclear, high or low risk of bias.

Study selection and data abstraction

The studies were screened for inclusion and exclusion by one author and checked by a second. Any disagreements were resolved through discussion. There was no need for a third reviewer to resolve any disagreements regarding inclusion or exclusion. Data extraction forms were completed by one author and checked by a second author. Similarly, quality assessment was done by one author and checked by a second.

Summary measures

The proportion of patients achieving an HbA1c level target of <7.0% at 24 weeks was summarised as risk ratio (RR). The treatment effects of continuous outcomes, that is, mean change in HbA1c, body weight or SBP from baseline to 24 weeks were summarised as weighted mean difference.

Data synthesis and model implementation

The treatment effects were assessed using a Bayesian approach to provide probability distributions for treatment effect parameters, with 95% credible intervals (CrIs) instead of 95% CI.

A Bayesian NMA method was used to analyse all the data, preserving randomised treatment effects within trials and accounting for correlation between comparisons with three arms. The freely available software, WinBUGS V.1.4.3, was used. The statistical heterogeneity in treatment effect estimates was estimated using between-study variance (ie, square root of the SD of underlying effects across trials) with 95% CrI.[7] Since our NMA included different trials comparing different SGLT-2 inhibitors, the distribution of treatment effect modifiers cannot only vary across trials for a particular comparison (as with standard pairwise meta-analysis, causing heterogeneity), but also between comparisons (causing inconsistency). If there is an imbalance in the distribution of treatment effect modifiers between different types of direct comparisons, the related indirect comparisons will be biased.[8] To estimate inconsistency in the networks of evidence, we calculated the difference between indirect and direct estimates whenever indirect estimates could be constructed with a single common comparator.[9] Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CrI excluding 0 for MD and 1 for RR.[10] The model convergence was assessed using trace plots and the Brooks-Gelman-Rubin statistic. The analysis was undertaken using two Markov chains, which was ran simultaneously. The model was found to be converging adequately after 20 000 samples for both chains. We ran the model further using 70 000 samples and the results

presented in the paper are based on these samples as we discarded the first 20 000 samples. The probability of a treatment being the most effective (first best), the second best, and so on was also calculated. The results have been presented graphically with median ranks.

Both fixed-effect and random-effect models were used. The Bayesian Deviation Information Criterion (DIC) was used to compare the two models to see which was appropriate to compare treatment effects. The DIC measures the fit of the model while penalising it for the number of effective parameters. The model with the lowest DIC value was considered as the most appropriate NMA model. Based on DIC values obtained from the two models and also because of small number of studies available for the NMA, a fixed-effect model was chosen. Owing to small number of studies, it would have been difficult to estimate between-studies variance if a random-effect model was implemented.

We excluded the Bolinder 2012 trial[11] of dapagliflozin because it recruited patients with very good baseline HbA1c (mean 7.2%) who would have less to gain. The primary outcome of the study was body composition and HbA1c was an exploratory variable. The low baseline HbA1c meant that the reduction in HbA1c was much smaller that in other trials, creating heterogeneity. However details are reported in tables and the Bolinder study was included in a sensitivity analysis.

The Henry 2012 trial[12] was unusual in that patients on no drug therapy were randomised straight to dual therapy with dapagliflozin and metformin (vs placebo and metformin) without trying monotherapy first. It is also included in a sensitivity analysis.

We also used the ipragliflozin trial by Kashiwagi *et al*[24] only in sensitivity analysis because it had unusual features—an adjusted difference in HbA1c of 1.3%, which was made up of a reduction of 0.87% on ipragliflozin and a rise of 0.38% on placebo, despite weight loss on placebo. More of the placebo group (52%) had by chance had prior treatment with other glucose-lowering drugs than in the ipragliflozin arm (35%, p=0.045). No patients in the placebo group achieved HbA1c <7.0%, so in order to run the model we used 0.5% as achieving that.

We used a software called DigitizeIt to calculate SD from a published figure for an outcome mean change in HbA1c for a study[13] assessing efficacy of canagliflozin in patients inadequately controlled with diet and exercise.

RESULTS

Study selection and characteristics

A total of 535 abstracts were retrieved from the searches (figure 1). After removing 73 duplicate articles, there were 462 articles left for title and abstract screening. A

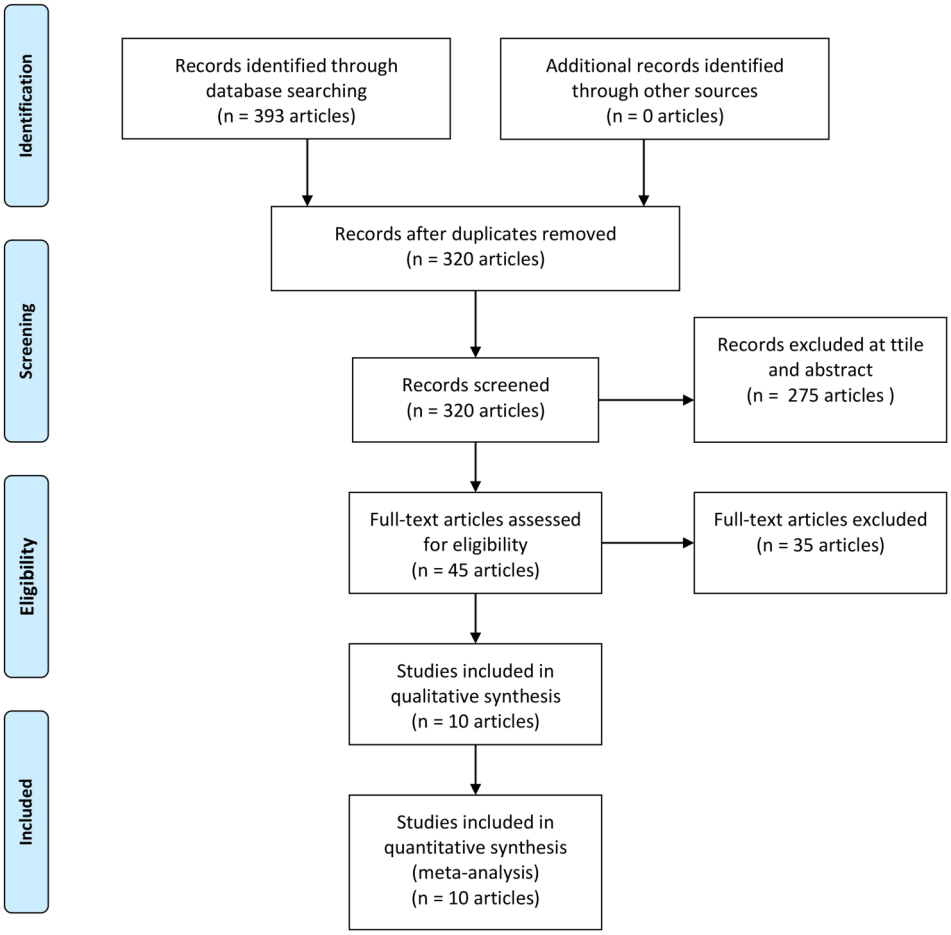


Figure 1 Study selection flow diagram.

total of 417 articles were excluded on the basis of title and abstracts. Forty-five articles were included for full-text screening. Thirteen trials[12–24] met all the inclusion criteria and were included for the analysis. Table 1 gives characteristics of all the included studies. We have summarised baseline characteristics and results obtained in trials in tables 2 and 3. We included six trials[11 12 14 15 17 18] of dapagliflozin, three trials[13 19 22] of canagliflozin, two trials of empagliflozin[16 20] one each of luseogliflozin,[21] ipragliflozin[24] and tofogliflozin.[23]

Eight trials[13 15 17 18 20–23] compared the efficacy of SGLT-2 inhibitors in monotherapy with placebo in patients inadequately controlled with diet and exercise. Six studies[11 12 14 16 19 24] compared flozins with placebo in dual therapy in patients failing to achieve glycaemic control on metformin alone.

Not all studies reported all the outcomes. Data on mean change in HbA1c were reported by all studies. Six monotherapy studies[13 15 17 18 20 22] reported the proportion achieving HbA1c of <7.0% as did five dual therapy studies.[12 14 16 19 24] For mean change in weight, seven[15 17 18 20–23] monotherapy and five[12 14 16 19 24] dual therapy studies provided adequate information on efficacy of SGLT-2 inhibitors. For mean change in SBP, five monotherapy studies[13 15 20 22 23] and three dual therapy studies[16 19 24] reported sufficient data. Stenlof *et al*[13] did not report weight SDs for the two doses of canagliflozin, so this study could not be included. The weight data for canagliflozin 100 mg come from Inagaki 2014 where the 100 and 200 mg doses of canagliflozin were used. We excluded the 200 mg dose since this is not a standard dose.

The networks comparing different SGLT-2 inhibitors for proportion of patients achieving HbA1c level of <7% in monotherapy and dual therapy are shown in figures 2 and 3.

As aforementioned, for other outcomes, some SGLT-2 inhibitors could not be included in the analysis due to inadequate information.

Risk of bias of included trials

Most of the included studies were high in quality, with low risk of bias. There were some studies where risk of bias could not be judged due to inadequate information. In this case, the risk of bias item was judged as unclear. Details of risk of bias are shown in figure 4. All the studies were funded by pharmaceutical companies.

Monotherapy

All SGLT-2 inhibitors were all significantly more effective than placebo for increasing proportion of patients achieving HbA1c <7% (figure 5), reducing the mean change in HbA1c (%) from baseline (figure 6), and reducing mean weight from baseline (figure 7). All SGLT-2 inhibitors reduced SBP compared with placebo, but this failed to reach statistical significance for dapagliflozin 10 mg, tofogliflozin 10 and 40 mg because of wide CIs (figure 8).

Using canagliflozin 300 mg as the baseline, patients on canagliflozin 100 mg (RR=0.72, 95% CrI 0.59 to 0.87) and dapagliflozin 10 mg (RR=0.63, 95% CrI 0.48 to 0.85) were 28% and 37% less likely to have achieved HbA1c <7% compared with those on canagliflozin 300 mg (figure 5). The proportions of patients achieving HbA1c <7% were similar among empagliflozin 10 mg, canagliflozin 100 mg and dapagliflozin 10 mg.

Canagliflozin 300 mg gave the largest reduction in HbA1c (−1.23%) compared with placebo. Compared with the other flozins, some differences appeared not only statistically significant but also clinically meaningful: canagliflozin 100 mg MD from canagliflozin 300 mg=0.20 (95% CrI 0.05 to 0.36); empagliflozin 25 mg (MD 0.37, 95% CrI 0.16 to 0.58); tofogliflozin 40 mg (MD 0.39, 95% CrI 0.12 to 0.66); luseogliflozin 2.5 mg (MD=0.47, 95% CrI 0.19 to 0.74); tofogliflozin 10 mg (MD 0.46, 95% CrI 0.19 to 0.73); empagliflozin 10 mg (0.49, 95% CrI 0.29 to 0.69); and dapagliflozin 10 mg (MD=0.64, 95% CrI 0.45 to 0.83; figure 6).

Canagliflozin 100 mg led to greater weight reduction than the other flozins; this reaching statistical significance was compared with empagliflozin 25 mg (MD 0.85, 95% CrI 0.37 to 1.33); empagliflozin 10 mg (MD 1.07, 95% CrI 0.59 to 1.56); tofogliflozin 10 mg (MD 1.13, 95% CrI 0.45 to 1.80); luseogliflozin 2.5 mg (MD 1.20, 95% CrI 0.63 to 1.77); and dapagliflozin 10 mg (MD 1.37, 95% CrI 0.92 to 1.83; figure 7).

SBP was reduced by all the flozins relative to placebo, with reductions ranging from 6.1 mm Hg for canagliflozin 300 mg to 2.6 mm Hg for empagliflozin 10 mg, though (figure 8) in some cases CIs were wide and the reductions were not statistically significant. Among the flozins, only empagliflozin 10 mg gave a difference that was statistically significant against canagliflozin (figure 8; 300 mg: MD 3.55, 95% CrI 0.60 to 6.44; 100 mg: MD 2.56, 95% CrI 0.30 to 4.75).

For some comparisons, between-study variance was small suggesting no heterogeneity; however, the CrIs were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for all outcomes.

Dual therapy

For dual therapy, we undertook sensitivity analyses by including Kashiwagi *et al*[24] (ipragliflozin), Henry *et al*[12] (dapagliflozin) and Bolinder *et al*[11] (dapagliflozin). Data for all the outcomes were not available from these studies. Therefore, a sensitivity analysis including the first two studies was undertaken for the proportions of patients achieving HbA1c level of <7%, mean change in HbA1c and mean change in weight. Bolinder *et al*[11] study was included in the sensitivity analysis of mean change in HbA1c and weight. Kashiwagi *et al*[24] was also included for sensitivity analysis of mean change in SBP.

Table 1 Baseline characteristics of all included studies

Study	Participants and baseline data	Intervention/outcomes
Dapagliflozin		
Bailey et al[14]	*N*: 534	Interventions
Setting: multicentre (n=80)	*Participants*: patients with type 2 diabetes inadequately controlled with metformin (≥1500 mg/day)	10 mg dapa once daily+metformin
Design: four-arm, double-blind, placebo-controlled RCT, dual therapy. Only 10 mg arm included in NMA	*Age (years)*: dapa 10 mg+metformin 52.7, SD 9.9; placebo+metformin 53.7, SD 10.3	Comparator
Follow-up: 24 weeks; 102 weeks	*HbA1c (%)*: dapa 10 mg+metformin 7.92, SD 0.82; placebo+metformin 8.11, SD 0.96	Placebo+metformin
	BMI (kg/m^2): dapa 10 mg+metformin 31.2, SD 5.1; placebo+metformin 31.8, SD 5.3	Outcomes
		Primary outcomes: change in HbA1c from baseline to 24 weeks
		Other outcomes: change in FPG, change in total body weight, the proportion of patients achieving an HbA1c <7% at 24 weeks, change in HbA1c percentage at week 24 for patients with a baseline HbA1c of 9% or more and percentage change from baseline in bodyweight, and decreases in bodyweight of 5% or more
Bolinder et al[11]	*N:* 180	Intervention
Setting: multicentre (n=40) in Bulgaria, Czech Republic, Hungary, Poland and Sweden	*Participants*: patients with type 2 diabetes inadequately controlled with metformin (≥1500 mg/day)	10 mg dapa once daily (n=89)+metformin
Design: two-arm, double-blind, placebo-controlled RCT in dual therapy	*Age (years)*: dapa 10 mg+metformin 60.6, SD 8.2; placebo+metformin 60.8, SD 6.9	Comparator
Duration: 24 weeks	*HbA1c (%)*: dapa 10 mg+metformin 7.19, SD 0.44; placebo+metformin 7.16, SD 0.53. Note the very low baseline level	Placebo (n=91)+metformin
	BMI (kg/m^2): dapa 10 mg+metformin 32.1, SD 3.9; placebo+metformin 31.7, SD 3.9	Outcomes
		Primary outcome: change from baseline at week 24 in total body weight
		Other outcomes: change from baseline at week 24 in waist circumference, total FM as measured by DEXA; proportion of patients achieving a body weight reduction of at least 5% at week 24
Ferrannini et al[15]	*N*: 274	Intervention
Setting: multicentre (n=85) in the USA, Canada, Mexico and Russia	*Participants*: patients with type 2 diabetes mellitus inadequately controlled with diet and exercise, naïve to treatment	10 mg dapa (n=70)
Design: double-blind, parallel-group, placebo-controlled, phase 3 RCT in monotherapy	*Age (years)*: dapa 10 mg 50.6, SD 9.97; placebo 52.7, SD 10.3	Comparator
Duration: 24 weeks	*HbA1c (%)*: dapa 10 mg 8.01, SD 0.96; placebo 7.84, SD 0.87	Placebo (n=75)
	BMI (kg/m^2): dapa 10 mg+metformin 33.6, SD 5.4; placebo+metformin 32.3, SD 5.5	Outcomes
		Primary outcome: change from baseline in HbA1c at week 24
		Other outcomes: change from baseline at week 24 in FPG and body weight
Henry et al[12]	*N*: 638	Intervention
—Two studies (focusing on study 2)	*Participants*: patients with type 2 diabetes inadequately controlled with diet and exercise, naïve to treatment	10 mg dapa+metformin XR (n=211)
Setting: multicentre (n=131)—hospitals and clinics in North America, Latin America, Europe and Asia	*Age (years)*: dapa 10 mg+metformin 51.5, SD 10.1;	Comparator
		Placebo+metformin XR (n=208)

Continued

Table 1 Continued

Study	Participants and baseline data	Intervention/outcomes
Design: double-blind, active controlled trials in dual therapy *Duration*: 24 weeks	placebo+metformin 52.7, SD 10.4 *HbA1c (%)*: dapa 10 mg+metformin 9.1, SD 1.3; placebo +metformin 9.1, SD 1.3 *BMI (kg/m^2)*: NR	Outcomes *Primary outcome*: change from baseline in HbA1c at week 24 *Secondary/other* outcomes: change from baseline at week 24 in FPG and body weight
Ji et al[17] *Setting*: multicentre (n=40) in China (n=26), Korea (n=5), Taiwan (n=5) and India (n=4) *Design*: double-blind, placebo-controlled, parallel-group, RCT, monotherapy *Duration*: 24 weeks	*N*: 393 *Participants*: patients with type 2 diabetes naïve to drug treatment (prescription medication for diabetes including Chinese traditional medicines for diabetes, or prescription medication for diabetes for <24 weeks since diagnosis) *Age (years)*: dapa 10 mg 51.2, SD 9.89; placebo 49.9, SD 10.87 *HbA1c (%)*: dapa 10 mg 8.28, SD 0.95; placebo 8.35, SD 0.95 *BMI (kg/m^2)*: dapa 10 mg 25.76, SD 3.43; placebo 25.93, SD 3.64	Intervention 10 mg dapa (n=133) Comparator Placebo (n=132) Outcomes *Primary outcome*: change from baseline in HbA1c at week 24 *Other outcomes*: change from baseline in FPG at week 24; change from baseline in 2 h PPG at week 24; change from baseline in total body weight at week 24; proportion of patients achieving HbA1c levels of <7% at week 24
Kaku et al[23] *2014* *Setting*: multicentre (n=NR) in Japan *Design*: double-blind, parallel-group, placebo-controlled RCT, monotherapy *Duration*: 24 weeks	N: 261 *Participants*: patients with type 2 diabetes naïve to drug treatment Age (years): dapa 10 mg 57.5, SD 9.3; placebo 60.4, SD 9.7 *HbA1c (%)*: dapa 10 mg 7.46, SD 0.61; placebo 7.50, SD 0.63 *BMI (kg/m^2)*: dapa 10 mg 26.6, SD 4.52; placebo 25.22, SD 4.39	Intervention 10 mg dapa (n=1) Comparator Placebo (n=132) Outcomes *Primary outcome*: change from baseline in HbA1c at week 24 *Other outcomes*: change from baseline in FPG and body weight at week 24; change from baseline in total body weight in patients with baseline BMI of≥25 kg/m^2; fasting insulin and C peptide; seated SBP overall and in patients with baseline seated SBP≥130 mmHg; fasting lipids; proportion of patients achieving HbA1c levels of <7% at week 24 in patients with baseline HbA1c ≥7% and proportion of patients discontinuing treatment due to lack of efficacy or rescued for failing to maintain FPG below prespecified rescue criteria after 24 weeks, and safety
Canagliflozin		
Lavalle-Gonzalez et al[19] *Setting*: multicentre (n=169) in 22 countries *Design*: double-blind, placebo-controlled and active-controlled trial, dual therapy *Duration*: 26 weeks	*N*: 1284 *Participants*: patients with type 2 diabetes inadequately controlled with metformin *Age (years)*: cana 100 mg+metformin 55.5, SD 9.4; cana 300 mg+metformin 55.3, SD 9.2; placebo+metformin 55.3, SD 9.8	Intervention 1. Cana 100 mg+metformin (n=368) 2. Cana 300 mg+metformin (n=367) Comparator 1. Placebo+metformin (n=186) Outcomes

Continued

Table 1 Continued

Study	Participants and baseline data	Intervention/outcomes
	HbA1c (%): cana 100 mg+metformin 7.9, SD 0.9; cana 300 mg+metformin 7.9, SD 0.9; placebo+metformin 8.0, SD 0.9 *BMI (kg/m^2)*: cana 100 mg+metformin 32.4, SD 6.4; cana 300 mg+metformin 31.4, SD 6.3; placebo+metformin 31.1, SD 6.1	*Primary outcome*: change in HbA1c from baseline to week 26 *Other outcomes*: proportion of patients achieving an HbA1c level of <7.0%; change in FPG, 2 h PPG and SBP; change in body weight, triglycerides and HDL-C
Stenlof et al[13] *Setting*: multicentre (n=NR) in 17 countries *Design*: double-blind, placebo-controlled, phase 3 RCT, monotherapy *Duration*: 26 weeks	*N*: 584 *Participants*: patients with type 2 diabetes inadequately controlled with diet and exercise and also on antihypoglycaemic agents who underwent washout (8 weeks and diet and exercise period with placebo run-in period) of the agent *Age (years)*: cana 100 mg 55.1, SD 10.8; cana 300 mg 55.3, SD 10.2; placebo 55.7, SD 10.9 *HbA1c (%)*: cana 100 mg 8.1, SD 1.0; cana 300 mg 0, SD 1.0; placebo 8.0, SD 1.0 *BMI (kg/m^2)*: cana 100 mg 31.3, SD 6.6; cana 300 mg 31.7, SD 6.0; placebo 31.8, SD 6.2	Intervention 1. Cana 100 mg (n=195) 2. Cana 300 mg (n=197) Comparator 1. Placebo (n=192) Outcomes *Primary outcome*: change in HbA1c from baseline to week 26 *Other outcomes*: proportion of patients reaching HbA1c <7.0%; changes from baseline at week 26 in FPG and SBP; per cent changes from baseline in body weight, HDL-C and triglycerides
Inagaki et al[22] *Setting*: multicenter (n=31) in Japan *Design*: double-blind placebo-controlled phase 3 parallel group trial *Duration*: 24 weeks	*N*: 272 *Participants*: patients with type 2 diabetes inadequately controlled with diet and exercise *Age (years):* cana 100 mg 58.4, SD 10.4; placebo 58.2, SD 11.0 *HbA1c (%)*: cana 100 mg 7.98, SD 0.73; placebo 8.04, SD 0.70 *BMI (kg/m^2)*: cana 100 mg 25.59, SD 4.20; placebo 25.85, SD 4.39	Intervention 1. 100 mg canagliflozin (n=90) Comparator 1. placebo (n=93) Outcomes *Primary outcome*: change from baseline in HbA1c at week 24 *Other outcomes*: proportion of patients achieving HbA1c target of <7%, change in FPG, PG at 2 h OGTT, per cent change in body weight, change in waist circumference, BP, HOMA, per cent change in lipids and safety
Empa *Haring et al*[16] *Setting*: multicentre (n=148) in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey and the USA) *Design*: double-blind placebo-controlled phase 3	*N*: 637 *Participants*: patients with type 2 diabetes inadequately controlled with diet and exercise and a stable immediate-release metformin regimen *Age (years)*: empa 10 mg+metformin 55.5, SD 9.9; empa 25 mg+metformin 55.6, SD 10.2; placebo+metformin 56, SD 9.7	Intervention 1. 10 mg empa+metformin (n=217) 2. 25 mg empa+metformin (n=213) Comparator 1. Placebo+metformin (n=207) Outcomes

Continued

Table 1 Continued

Study	Participants and baseline data	Intervention/outcomes
RCT, dual therapy *Duration*: 24 weeks	*HbA1c (%)*: empa 10 mg+metformin 7.94, SD 0.79; empa 25 mg+metformin 7.86, SD 0.87; placebo+metformin 7.90, SD 0.88 *BMI (kg/m²)*: empa 10 mg+metformin 29.1, SD 5.5; empa 25 mg+metformin 29.7, SD 5.7; placebo+metformin 28.7, SD 5.2	*Primary outcome*: change from baseline in HbA1c at week 24 *Other outcomes*: change from baseline to week 24 in body weight and MDG; percentage of patients with baseline HbA1c ≥7.0% who had HbA1c level <7% at week 24; change from baseline in FPG, waist circumference, and SBP and DBP at week 24; percentage of patients with >5% reduction in body weight at week 24; use of rescue medication; and safety
Roden et al[20] *Setting*: multicentre (n=124) in 9 countries (Belgium, Canada, China, Germany, India, Japan, Switzerland and USA) *Design*: double-blind parallel-group RCT, monotherapy *Duration*: 24 weeks	*N*: 899 *Participants*: patients with type 2 diabetes with no previous history to treatment (oral or injected hypoglycaemic agents 12 weeks prior to randomisation) *Age (years)*: empa 10 mg 56.2, SD 11.6; empa 25 mg 53.8, SD 11.6; placebo 54.9, SD 10.9 *HbA1c (%)*: empa 10 mg 7.87, SD 0.88; empa 25 mg 7.86, SD 0.85; placebo 7.91, SD 0.87 *BMI (kg/m²)*: empa 10 mg 28.3, SD 5.5; empa 25 mg 28.2, SD 5.5; placebo 28.7, SD 6.2	Intervention 1. 10 mg empa (n=224) 2. 25 mg empa (n=224) Comparator 1. Placebo (n=228) Outcomes *Primary outcome*: change from baseline in HbA1c at week 24 *Other outcomes*: change from baseline in bodyweight at week 24; change from baseline in SPB and DBP at week 24; proportion of patients with baseline HbA1c level of at least 7% achieving HbA1c level lower than 7.0% at week 24; change from baseline in FPG at week 24; proportion of patients with >5% reduction in bodyweight at week 24; change from baseline in waist circumference at week 24; proportion of patients with uncontrolled BP at baseline who controlled their BP at week 24 (SBP <130 mm Hg and DBP <80 mm Hg); and safety
Luseogliflozin		
Seino et al[21] *Setting*: multicentre (n=23) in Japan *Design*: double-blind, placebo-controlled, parallel-group, comparative, RCT, monotherapy *Duration*: 24 weeks	*N*: 158 *Participants*: patients diagnosed with type 2 diabetes on stable diet therapy for ≥6 weeks and not on any antidiabetic drugs *Age (years)*: luseo 2.5 mg 58.9, SD 10.1; placebo 59.6, SD 9.3 *HbA1c (%)*: luseo 2.5 mg 8.14, SD 0.91; placebo 8.17, SD 0.80 *BMI (kg/m²)*: luseo 2.5 mg 25.98, SD 4.88; placebo 25.34, SD 4.19	Intervention 1. 2.5 mg luseo (n=79) Comparator 1. Placebo (n=79) Outcomes *Primary*: change in HbA1c from baseline to end of treatment *Others*: plasma glucose, insulin, glucagon, serum CPR, intact
Ipragliflozin		
Kashiwagi et al[24] *Setting*: multicentre (n=34) in Japan *Design*: double-blind, placebo-controlled RCT with a	*N*: 168 *Participants*: patients with type 2 diabetes of ≥12 weeks of duration, treated with metformin for ≥6 weeks and with	Intervention 1. Ipra 50 mg+metformin (n=112) Comparator

Continued

Table 1 Continued

Study	Participants and baseline data	Intervention/outcomes
28 weeks open-label extension *Duration*: 24 weeks with a 28 weeks open-label extension	an HbA1c level of 7.4–9.9% and BMI of 20–45 kg/m^2 *Age (years)*: ipra 50 mg 56.2, SD 10.67; placebo 57.7, SD 9.24 *HbA1c (%)*: ipra 50 mg 8.25, SD 0.719; placebo 8.38, SD 0.738 *BMI (kg/m^2)*: ipra 50 mg 25.96, SD 4.410; placebo 25.47, SD 3.092	1. Placebo+metformin (n=56) Outcomes *Primary outcome*: change in HbA1c from baseline to end of treatment *Other outcomes*: body weight, waist circumference, FPG, FSI, plasma leptin, and adiponectin levels, HOMA-R and HOMA-β and safety outcomes
Togoliflozin *Kaku et al*[23] *Setting*: multicentre (n=33) in specialists and non-specialists hospital in Japan *Design*: double-blind, placebo-controlled, parallel-group RCT *Duration*: 24 weeks	*N*: 235 *Participants*: patients with type 2 diabetes naïve to drug therapy but, only treated with diet and exercise for ≥8 weeks before screening, HbA1c level of ≥7.3% to <10.3%, BMI of ≥18.5 to <45 kg/m^2, per cent changes in HbA1c and body weight from the provisional registration visit to the final registration visit of ≤10% and <5%, respectively, controlled BP and those requiring antihypertensives only those who did not require changing of their dosing regimen. Patients using other antidiabetic drugs were eligible if they had stopped their drug ≥8 weeks before the provisional registration. (HbA1c reported in Japan Diabetes Society or JDS units but, converted to NGSP units) *Age (years):* tofo 10 mg 58.6, SD 9.8; tofo 20 mg 56.6, SD 10.2; tofo 40 mg 57.0, SD 9.1; placebo 56.8, SD 9.9 *HbA1c (%)*: tofo 10 mg 8.45, SD 0.75; tofo 20 mg 8.34, SD 0.81; tofo 40 mg 8.37, SD 0.77; placebo 8.41, SD 0.78 *BMI (kg/m^2)*: tofo 10 mg 25.07, SD 3.53; tofo 20 mg 24.99, SD 4.55; tofo 40 mg 25.78, SD 4.10; placebo 26.00, SD 4.11	Intervention 1. Tofo 10 mg (n=59) 2. Tofo 20 mg (n=60) 3. Tofo 40 mg (n=59) Comparator 1. Placebo (n=57) Outcomes *Primary outcome*: change in HbA1c from baseline to end of treatment *Other outcomes*: 24 h FPG, 2 h PPG, fasting and 2 h postprandial insulin, glycoalbumin, body weight, pancreatic β-cell function (HOMA-β), insulin resistance (HOMA-R) and Matsuda index, insulin, serum lipid levels, adiponectin, BP and waist circumference, and safety outcomes

BMI, body mass index; cana, canagliflozin; CPR, C peptide immunoreactivity; dapa, dapagliflozin; DBP, diastolic blood pressure; DEXA, dual-energy X-ray absorptiometry; empa, empagliflozin; FM, fat mass; FPG, fasting plasma glucose; FSI, fasting serum insulin; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-R, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; ipra, ipragliflozin; luseo, luseogliflozin; NMA, network meta-analysis; NR, not reported; OGTT, oral glucose tolerance test; PPG, postprandial glucose; RCT, randomised controlled trial; SBP, systolic blood pressure; tofo, tofogliflozin.

Table 2 Summary table with results (monotherapy)

	Entry criteria HbA1c (%)	HbA1c baseline	Age baseline	BMI baseline	Weight baseline	eGFR baseline	Per cent HbA1c <7% drug	Per cent HbA1c <7% PBO	Weight loss PBO	Weight loss drug	Reduction HA1c PBO	Reduction HbA1c drug	Difference HbA1c
Dapagliflozin													
Ferrannini *et al*[15]	7 to 10	7.84–8.01	50.6–52.7	32.3–33.6	88.8–94.2	NR	51	32	−2.2	−3.2	−0.23	−0.89	−0.66
Ji *et al*[17]	≥7.5 to ≤10.5	8.28–8.35	49.9–51.2	25.76–25.93	70.92–72.18	NR	50	21.3	−0.27	−2.25	−0.29	−1.11	−0.82
Kaku *et al*[23]	≥6.5 to ≤10	7.46–7.50	57.5–60.4	25.22–26.06	65.96–69.7	66.9–67.8	36	19	−0.84	−2.22	−0.06	−0.45	−0.39
Canagliflozin													
Inagaki *et al*[22]	7 to 10	8.04	58.2–58.4	25.59 to 25.85	68.57–69.10	81.4–84.7	31.5	6.6	−0.76	−3.76	+0.29%	−0.74%	−1.03%
Stenlof *et al*[13]	≥7.0 to ≤10.0	8.0–8.1	55.1–55.7	31.3–31.8	85.8–87.6	NR	45, 62	21	NR	NR	0.14	−0.77; −1.03	−0.91; −1.17
Empagliflozin													
Roden *et al*[20]	≥7.0 to ≤10.0	7.86–7.91	53.8–56.2	28.2–28.7	77.8–78.4	86.8–87.7	35, 44	12	−0.33	−2.26; −2.48	0.08	−0.66; −0.78	−0.74; −0.86
Luseogliflozin													
Seino *et al*[21]	≥6.5 to ≤10.5	8.14–8.17	58.9–59.6	25.34–25.98	66.67–70.19	NR	NR	NR	−0.9	−2.7	+0.13	−0.63	−0.76
Tofogliflozin													
Kaku *et al*[23]	≥7.3 to <10.3	8.34–8.45	56.6–58.6	24.99–26	67.26–71.20	83.78–86.78	NR	NR	−0.356	−2.23 −2.851 −2.971	−0.028	−0.767 −1.017 −0.870	−0.769 −0.990 −0.842

HbA1c in per cent; age in years; BMI in kg/m^2; weight in kg; eGFR in mL/min/1.73 m^2.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NR, not reported; PBO, placebo.

Table 3 Summary table with results (dual therapy)

	Entry criteria HbA1c (%)	HbA1c baseline	BMI baseline	Age baseline	Weight baseline	eGFR baseline	Per cent HbA1c <7% PBO	Per cent HbA1c <7% drug	Weight loss PBO	Weight loss drug	Reduction HA1c PBO	Reduction HbA1c drug	Difference HbA1c
Dapagliflozin													
Bailey *et al*[14]	7–10	7.9–8.2	31.5	52.7–53.7	NR	NR	26	41	0.9	2.9	0.3	0.84	0.54
Bolinder *et al*[11]	6.5–8.5	7.2	31.0	60.6–60.8	90.9–92.1	≥30 to ≥90	NR	NR	0.9	3.0	0.1	0.39	0.29
Henry *et al*[12]	7.5–12	9.1	NR	51.0–52.7	87.2–88.4	NR	35	47	1.4	3.3	1.44	1.98	0.54
Canagliflozin													
Lavalle-Gonzalez *et al*[19]	7.0–10.5	7.9	31.8	55.4	87.2	87.7 to 90.2	29	46; 58	1–2	3.3, 3.7	0.17	0.79, 0.94	0.62, 0.77
Empagliflozin													
Haring *et al*[16] 2014	7–10	7.9	29.2	55.7	81.2	89.0	23	38; 39	0.45	2.0. 2.5	0.13	0.70, 0.77	0.57, 0.64
Ipragliflozin													
Kashiwagi *et al*[24]	7.4–9.9	8.25–8.38	25.47–25.96	56.2–57.7	NR	NR	0	21.4	−0.63	−2.33	0.38	−0.87	−1.30

HbA1c in per cent; age in years; BMI in kg/m^2; weight in kg; eGFR in mL/min/1.73 m^2.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NR, not reported; PBO, placebo.

All SGLT-2 inhibitors were significantly more effective than placebo for achieving HbA1c <7% (figure 9), reducing HbA1c (%) from baseline (figure 10), weight loss (figure 11) and reducing SBP (figure 12). The results were slightly different when the trials by Kashiwagi *et al*[24] and Henry *et al*[12] were included, as discussed later.

Empagliflozin 25 and 10 mg, and canagliflozin 300 mg had higher proportions of patients achieving HbA1c <7% than canagliflozin 100 mg and dapagliflozin 10 mg (figure 9).

Canagliflozin 300 mg gave the greatest reduction in HbA1c (0.77%), but the differences were small (vs canagliflozin 100 mg (MD=0.15, 95% CrI 0.04 to 0.26) and dapagliflozin 10 mg (MD=0.23, 95% CrI −0.01 to 0.47); figure 10). There were no statistically significant differences between the two doses of canagliflozin and the two doses of empagliflozin.

In sensitivity analyses compared with placebo (figure 13), ipragliflozin 50 mg showed the greatest reduction in HbA1c (1.25%) followed by canagliflozin 300 mg (0.77%), empagliflozin 25 mg (0.64%), canagliflozin 100 mg (0.62%), empagliflozin 10 mg (0.57%) and dapagliflozin 10 mg (0.54%), but as noted above, we have reservations about the Kashiwagi study.

All the drugs were associated with greater weight loss than placebo, ranging from a reduction of 1.63 kg on empagliflozin 10 mg to 2.5 kg on canagliflozin 300 mg (figure 11). Canagliflozin 300 mg was statistically significantly better in reducing weight than empagliflozin 10 mg (MD 0.88 kg, 95% CrI 0.16 to 1.61) and ipragliflozin 50 mg (0.81 kg, 95% CrI 0.03 to 1.58; figure 14).

For mean change in SBP, inclusion of the Kashiwagi (ipragliflozin) and Henry studies (dapagliflozin) caused contrasting results. By excluding them, all flozins (canagliflozin 300 and 100 mg, empagliflozin 25 and 10 mg) were associated with significant reduction in SBP compared with placebo, but there were no significant differences among them (figure 12). By including the two studies, all flozins including dapagliflozin and ipragliflozin were found to be significantly better than placebo, but less so than without them, and there were differences between them. Dapagliflozin 10 mg was found to be significantly better than all other flozins, and ipragliflozin 50 mg, canagliflozin 300 mg and empagliflozin 25 mg were found to be better than empagliflozin 10 mg (figure 15).

For some comparisons, between-study variance was small suggesting no heterogeneity; however, the CrIs were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for all outcomes.

The effect of including the Bolinder trial was that the mean reduction in HbA1c on dapagliflozin became significantly less than with canagliflozin 300 mg, empagliflozin 25 mg and canagliflozin 100 mg. The findings for weight did not change. However, as noted earlier,

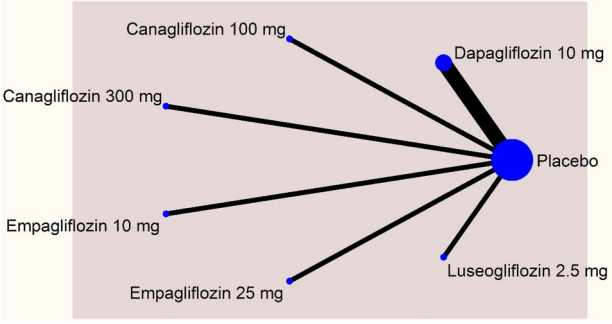


Figure 2 Network plot—monotherapy (mean change in glygated haemoglobin).

patients in the Bolinder trial started at a much lower baseline HbA1c and had a much smaller mean reduction in HbA1c.

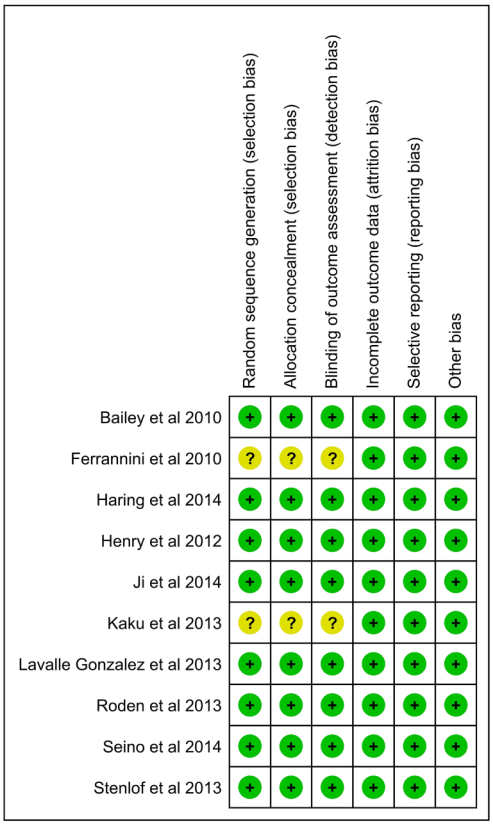
A sensitivity analysis including the Henry and Kashiwagi trials is shown in figure 16. The CIs around ipragliflozin are very wide because no patients in the placebo group achieved HbA1c under 7%.

DISCUSSION

Statement of principal findings

Our NMA showed few differences among the flozins. In monotherapy, canagliflozin 300 mg gave the largest reduction in HbA1c among the SGLT-2 inhibitors in patients with type 2 diabetes with inadequate glycaemic control on diet and exercise alone. However, treatment with canagliflozin would be started with 100 mg and only increased in those with an insufficient response to that dose. Those with a poor response to the 100 mg dose might also have a poor response to 300 mg.

In monotherapy, the reduction in weight was greatest with canagliflozin 100 mg (−3 kg). All the SGLT-2 inhibitors reduced SBP, though wide CIs meant that differences were not always statistically significant. In dual therapy with metformin, canagliflozin 300 mg gave the greatest reductions in HbA1c (0.77%) and weight (−2.5 kg), and these differences were sometimes statistically significant but not clinically so. There were no statistically significant differences among the drugs in reducing SBP.



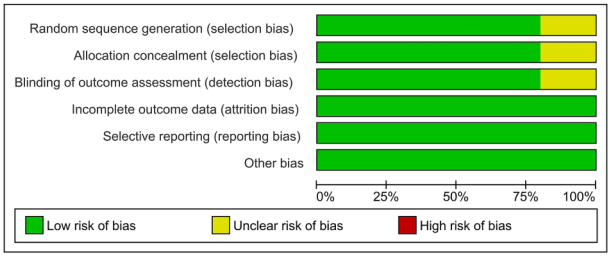
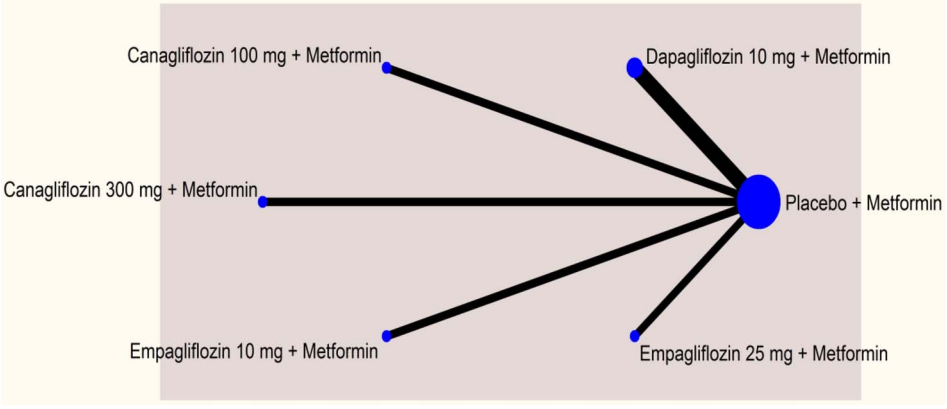


Figure 4 Risk of bias.

Strengths and limitations

We compared the efficacy of SGLT-2 inhibitors in patients with type 2 diabetes inadequately controlled with diet and exercise or metformin monotherapy. The relevant studies were identified systematically. Data extraction and

Figure 3 Network plot—dual therapy (% of patients achieving glycated haemoglobin <7%).



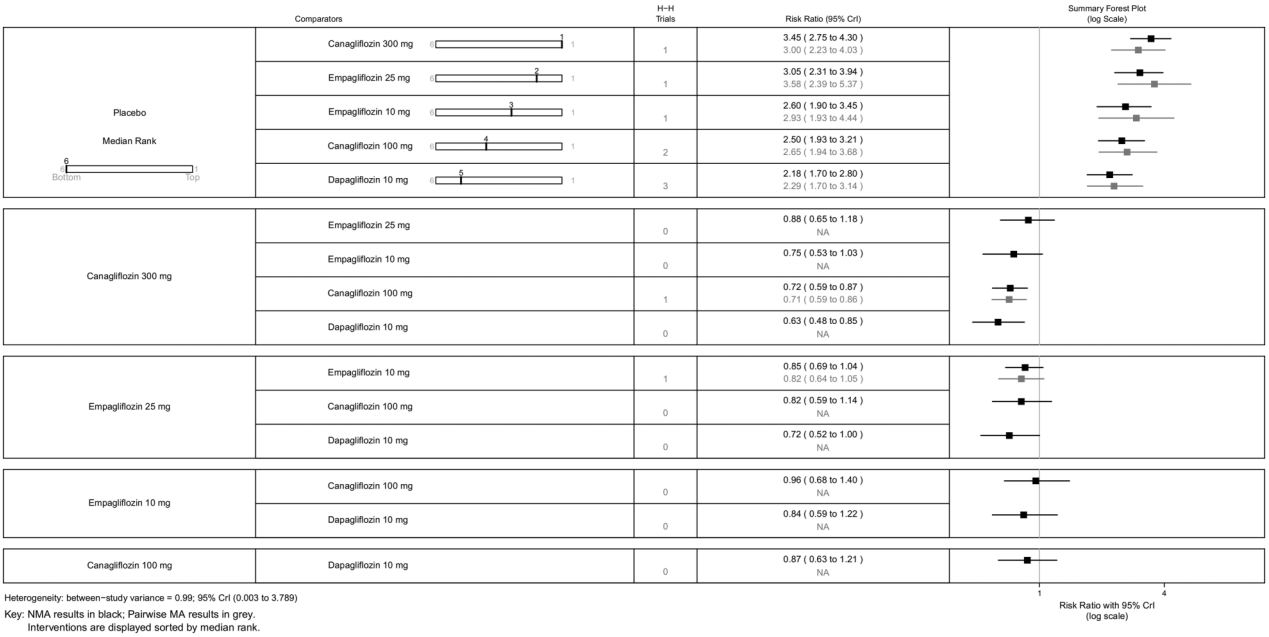


Figure 5 Proportion of patients achieving HbA1c level of <7%—monotherapy. HbA1c, glycated haemoglobin; NA, not available; NMA, network meta-analysis.

quality assessment of the included studies were checked systematically by two authors. Most of the included studies were high in quality but the risk of bias in some studies could not be judged due to lack of information.

Our study has strengths. Unlike conventional pair wise meta-analysis, our NMAs allow for comparisons between SGLT-2 inhibitors that have not been compared head-to-head in RCTs. In addition, combining direct and indirect evidence in NMA offer additional precision by 'borrowing strength' from indirect evidence.[25] Another strength of the NMA is that it treats all comparators as separate treatments while gaining statistical power from including all available data.[26]

The main limitation is the lack of head-to-head trials. The number of trials contributing evidence to several comparisons in the network was small.

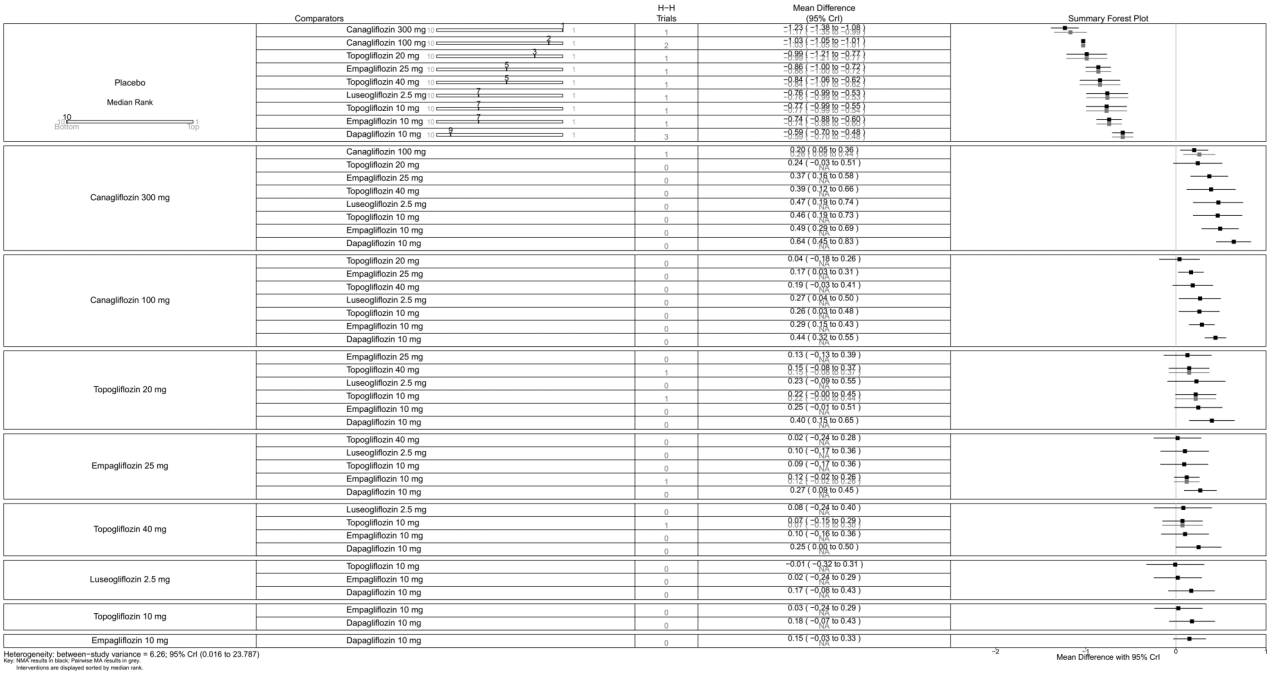


Figure 6 Mean change in HbA1c (%)—monotherapy. HbA1c, glycated haemoglobin; NA, not available; NMA, network meta-analysis.

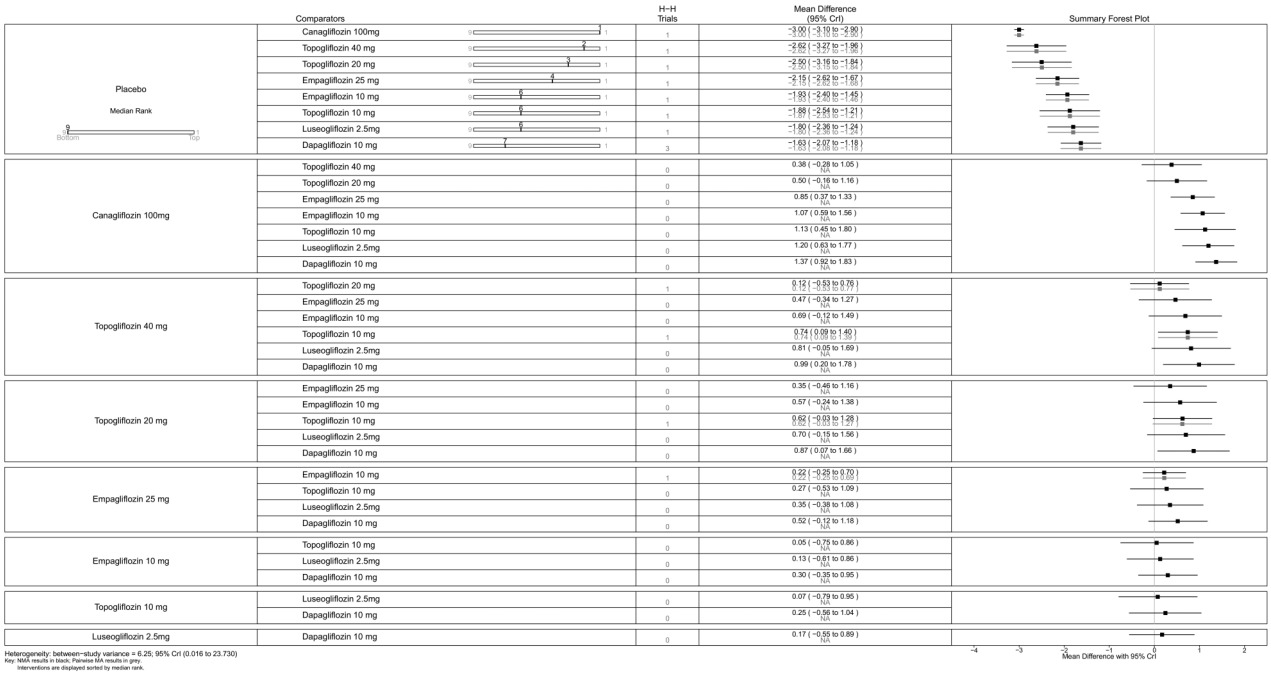


Figure 7 Mean change in weight (kg)—monotherapy. NA, not available; NMA, network meta-analysis.

Another limitation is that in the trials, patients were randomised to canagliflozin 300 mg, whereas in clinical practice, they would be tried on 100 mg daily first.

One of the three dapagliflozin trials, by Kaku *et al*,[18] recruited patients with a baseline HbA1c of only 7.5%, and not surprisingly their reduction in HbA1c was less (0.39%) than in most other trials. Exclusion of this study would raise the mean reduction on dapagliflozin to 0.75% (Astra Zeneca corporate communication, at NICE Appraisal Committee 25 November 2015).

Another factor to be considered is that in the dapagliflozin trials, HbA1c fell in the placebo groups, by 0.29% and 0.23% in the Ji *et al*[17] and Ferrannini *et al*[15] trials. In the Ferrannini trial, weight *fell* significantly by 2.2 kg. In

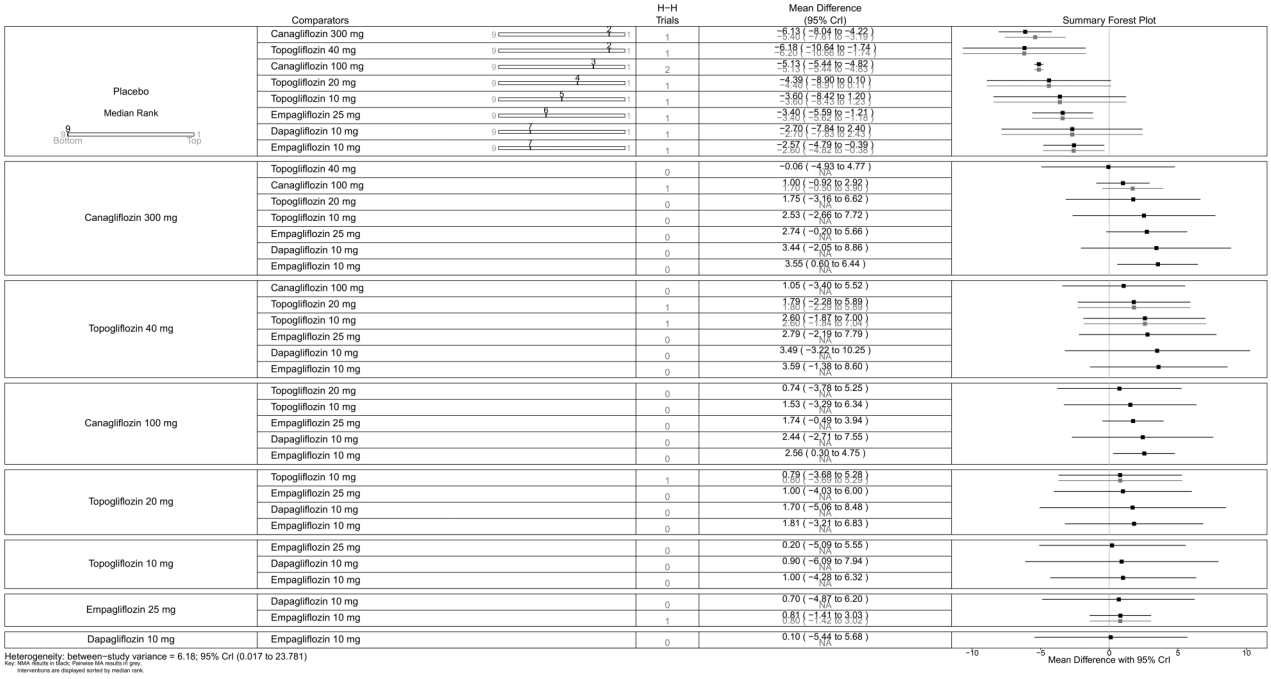


Figure 8 Mean change in SBP (mm Hg)—monotherapy. NA, not available; NMA, network meta-analysis; SBP, systolic blood pressure.

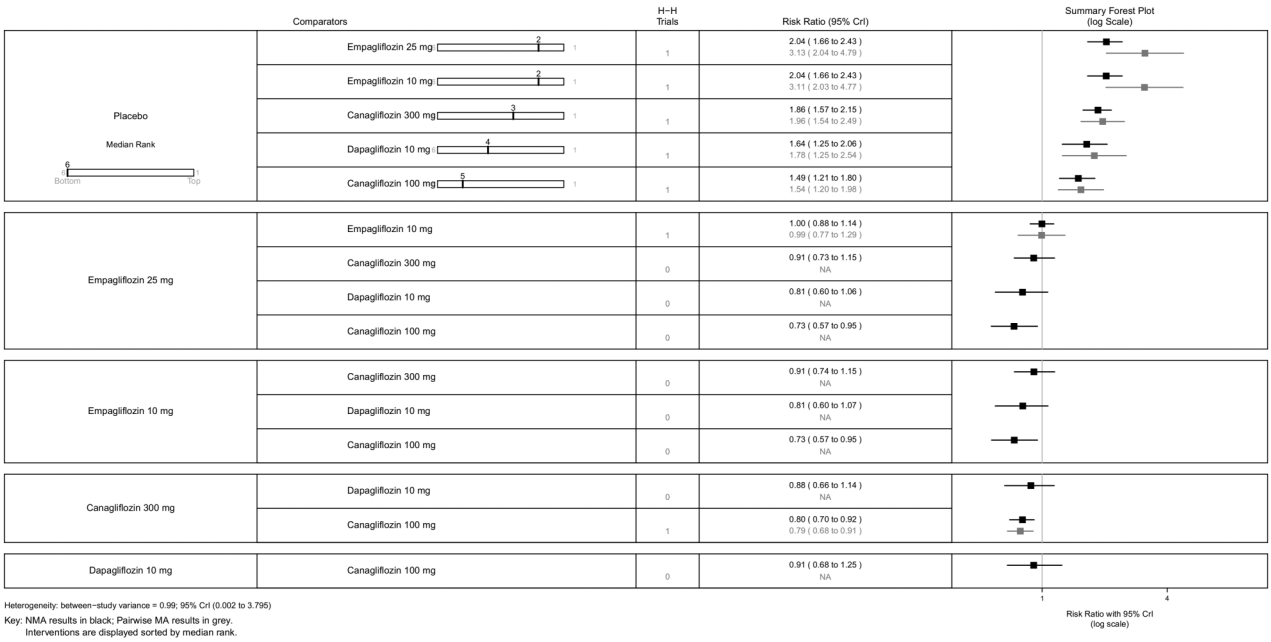


Figure 9 Proportion of patients achieving HbA1c level of <7.0%—dual therapy. HbA1c, glycated haemoglobin; NA, not available; NMA, network meta-analysis.

the placebo groups in the canagliflozin trials, HbA1c *rose* by 0.29%[22] and 0.14% (Stenlof CANTATA-M).[13] Ferranini *et al* suggested that the reduction in HbA1c in the placebo group might have been due to improved adherence to lifestyle advice in that group, but since the placebo tablets matched the dapagliflozin ones, this seems unlikely.

When interpreting weight changes, the baseline body mass indices (BMIs) need to be considered. The trials in China and Japan recruited people with BMIs in the 25–26 range, whereas the European trials had mean BMIs ranging from 28 to almost 34.

Some of the included studies did not report data on all outcomes, and for these, we were not able to

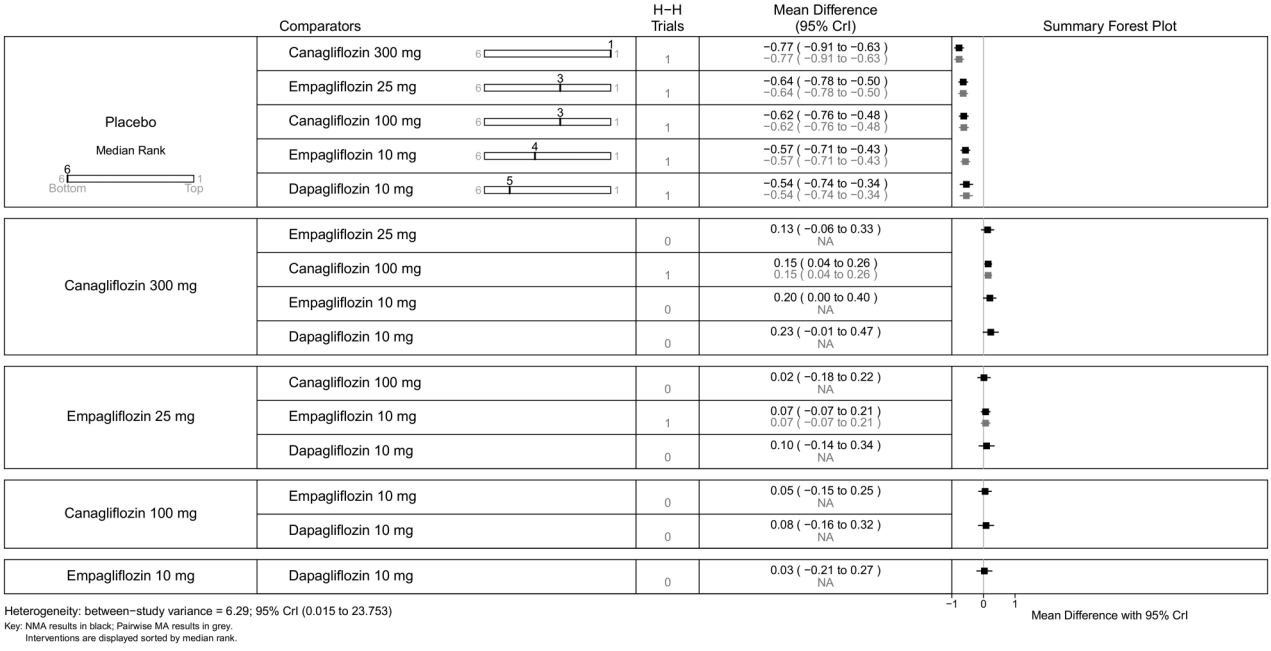


Figure 10 Mean change in HbA1c (%)—dual therapy. HbA1c, glycated haemoglobin; NA, not available; NMA, network meta-analysis.

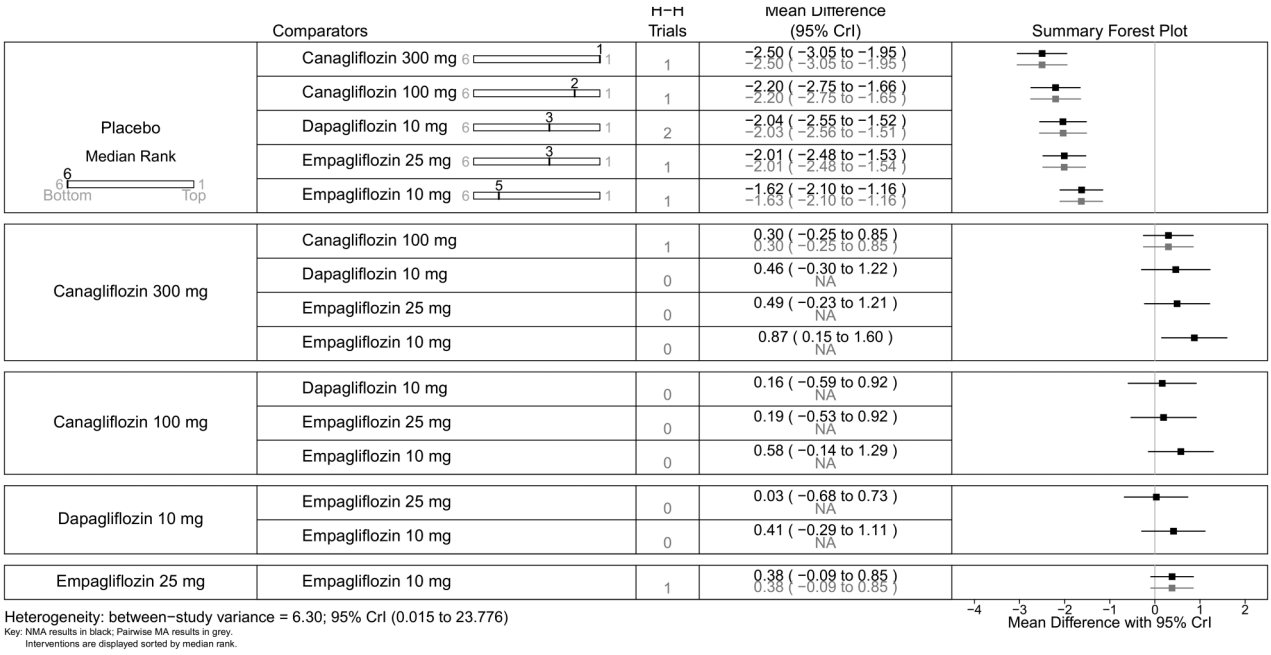


Figure 11 Mean change in weight (kg)—dual therapy. NA, not available; NMA, network meta-analysis.

compare all the SGLT-2 inhibitors against each other. For example, the Seino *et al*[21] trial with the new SGLT-2 inhibitor, luseogliflozin, did not provide data on proportion of patients achieving HbA1c level of <7% and mean change in SBP.

The primary outcomes of both canagliflozin studies were reported at 26 weeks instead of 24 weeks. Therefore, we assumed that the effect of canagliflozin measured at 26 weeks was comparable against other SGLT-2 inhibitors, which reported results at 24 weeks.

The numbers of patients in each centre were often small, such as means of 3.2 patients per centre in the Ferranini trial and 4.5 in the Bolinder one. This must raise questions about how typical the recruits were. We did not compare safety data.

Meaning of the study

In the absence of head-to-head comparison of SGLT-2 inhibitors in patients with type 2 diabetes inadequately controlled with diet and exercise or metformin, this

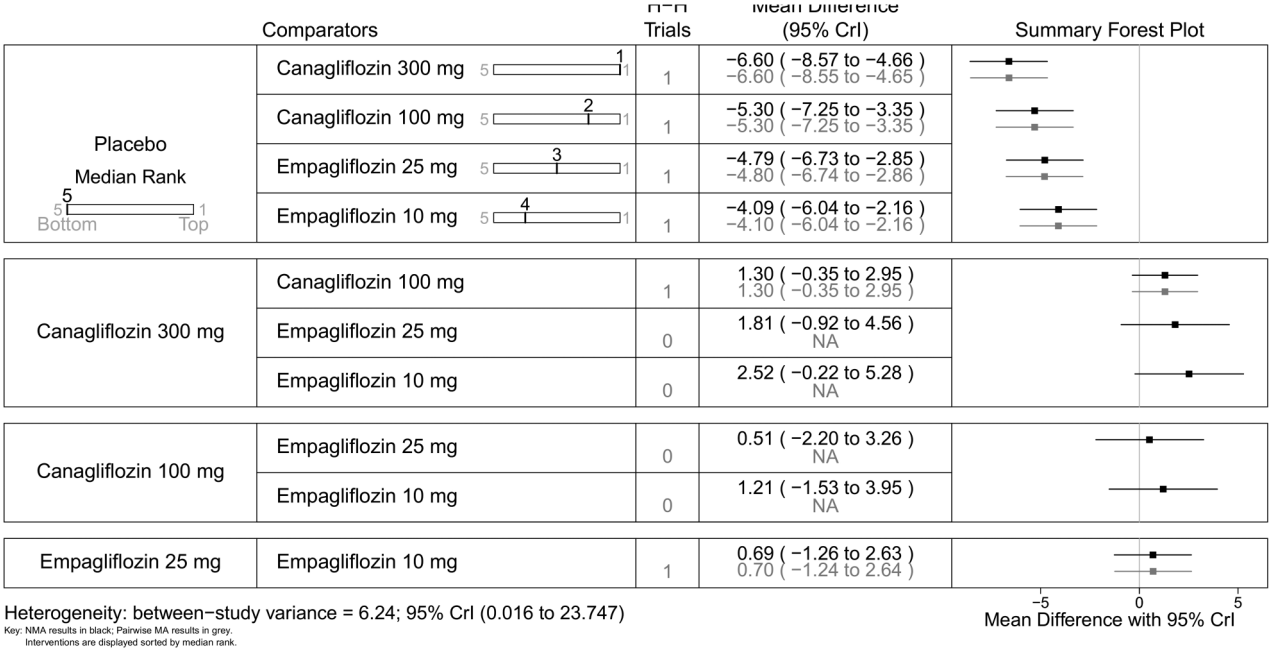


Figure 12 Mean change in SBP (mm Hg)—dual therapy. NA, not available; NMA, network meta-analysis; SBP, systolic blood pressure.

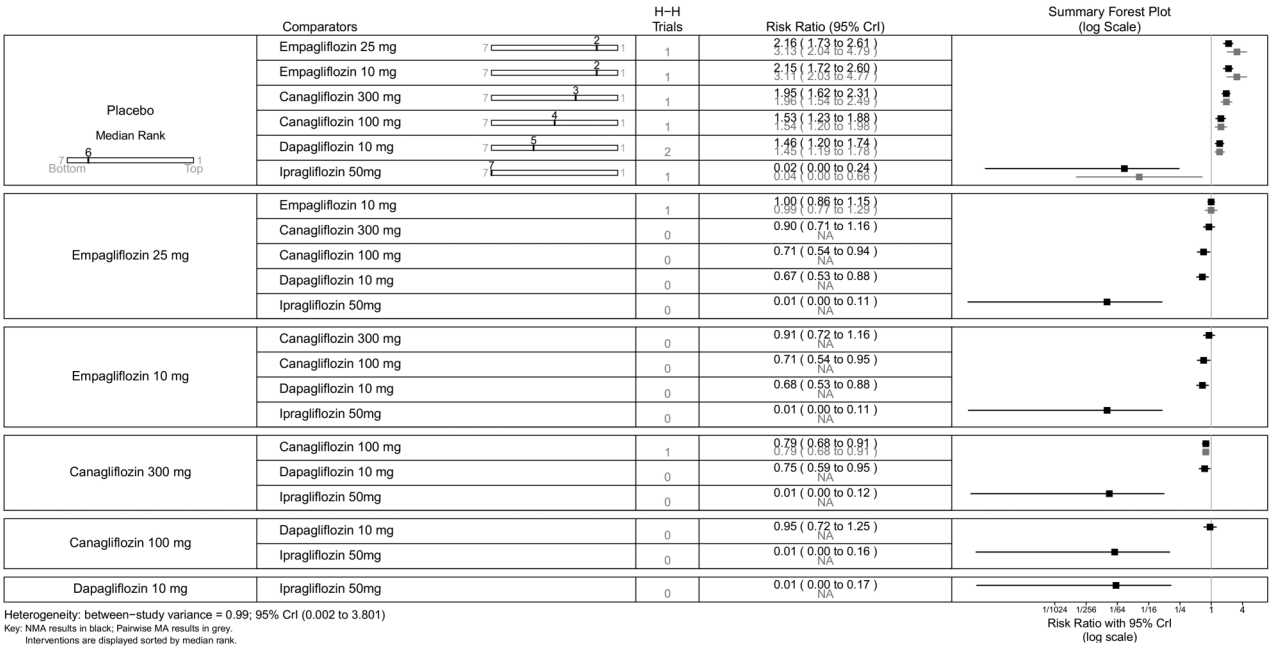


Figure 13 Proportion of patients achieving HbA1c level of <7.0% (dual therapy), sensitivity analysis including Henry *et al*[12] and Kashiwagi *et al*.[24] HbA1c, glycated haemoglobin; NA, not available; NMA, network meta-analysis.

study examines the evidence as to whether any drug is better than others. NICE has approved dapagliflozin 10 mg as an option for the treatment of diabetes in combination with metformin or as an add-on to insulin with or without other glucose-lowering drugs.[1] NICE has approved canagliflozin as dual therapy (in combination with metformin if sulfonylurea is contraindicated) or triple therapy (in combination with metformin plus sulfonylurea or metformin plus thiazolidinediones) or as add on to insulin with or without other antidiabetic drugs.[2] Empagliflozin has also been approved by NICE in combination therapy.[3]

The usual first drug for type 2 diabetes is metformin, with sulfonylurea in those who cannot tolerate

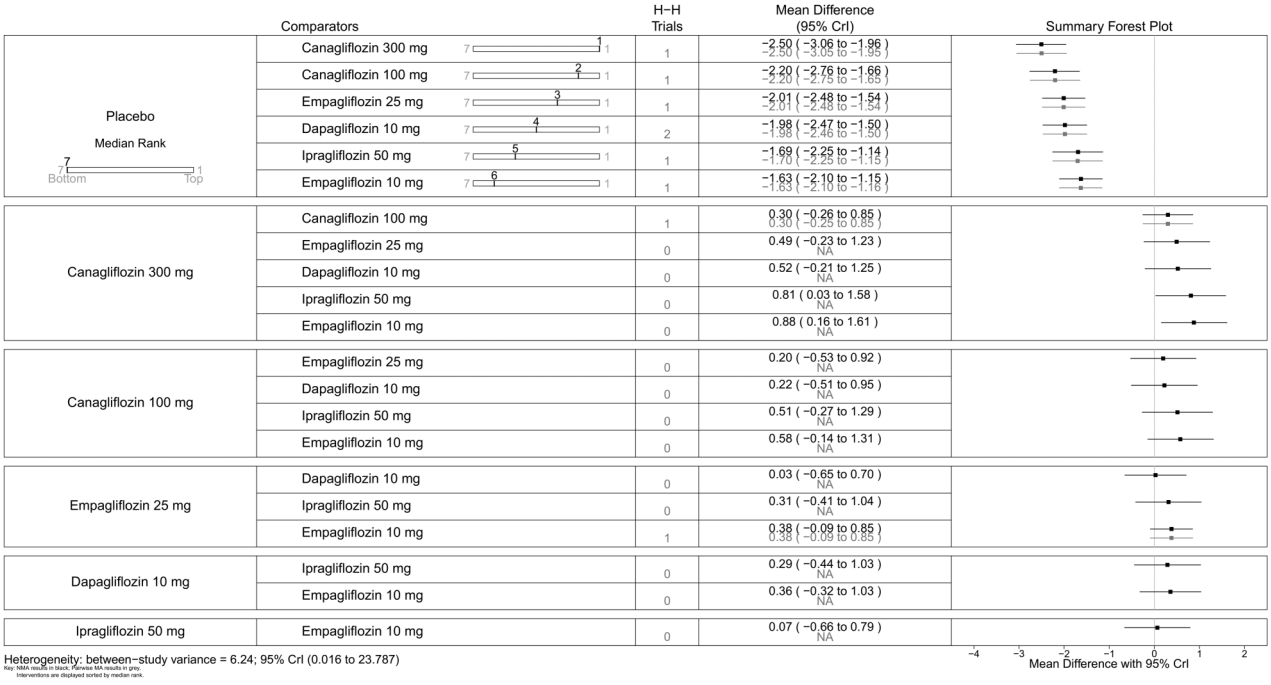


Figure 14 Mean change in weight (kg; dual therapy), sensitivity analysis including Bolinder *et al*,[11] Henry *et al*[12] 2012 and Kashiwagi *et al*.[24] NA, not available; NMA, network meta-analysis.

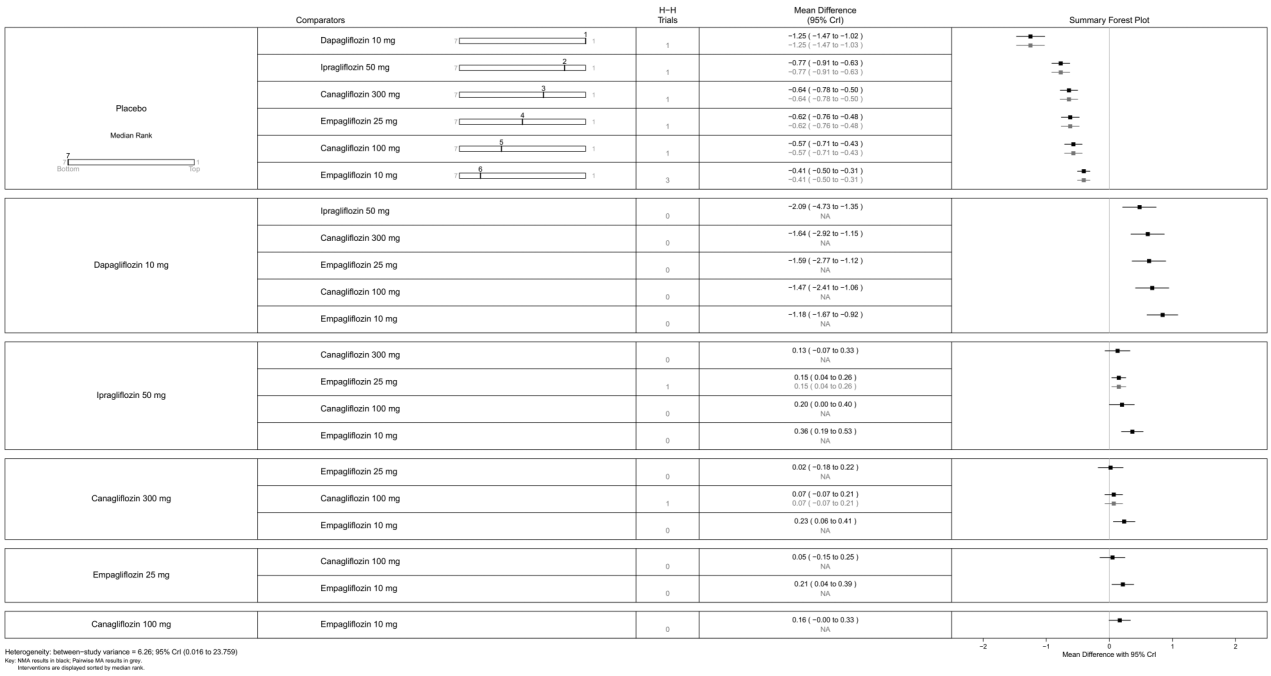


Figure 15 Mean change in SBP (mm Hg; dual therapy), sensitivity analysis including Kashiwagi *et al*.[24] NA, not available; NMA, network meta-analysis; SBP, systolic blood pressure.

metformin. NICE is appraising the use of the flozins in monotherapy in people who cannot take metformin in 2015.[27] It has been pointed out that the flozins are the only oral glucose-lowering drugs that are associated with weight reduction.

A recent mixed treatment comparison, available in abstract only at present,[28] compared the efficacy and safety of canagliflozin in dual therapy (in combination with metformin) using a Bayesian approach against sulfonylureas, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and dapagliflozin. The outcomes compared were HbA1c, weight and hypoglycaemia at 26, 52 and 104 weeks. Pacou *et al* reported that both canagliflozin 100 and 300 mg led to larger reductions in HbA1c level than with DPP-4 inhibitors and dapagliflozin but similar

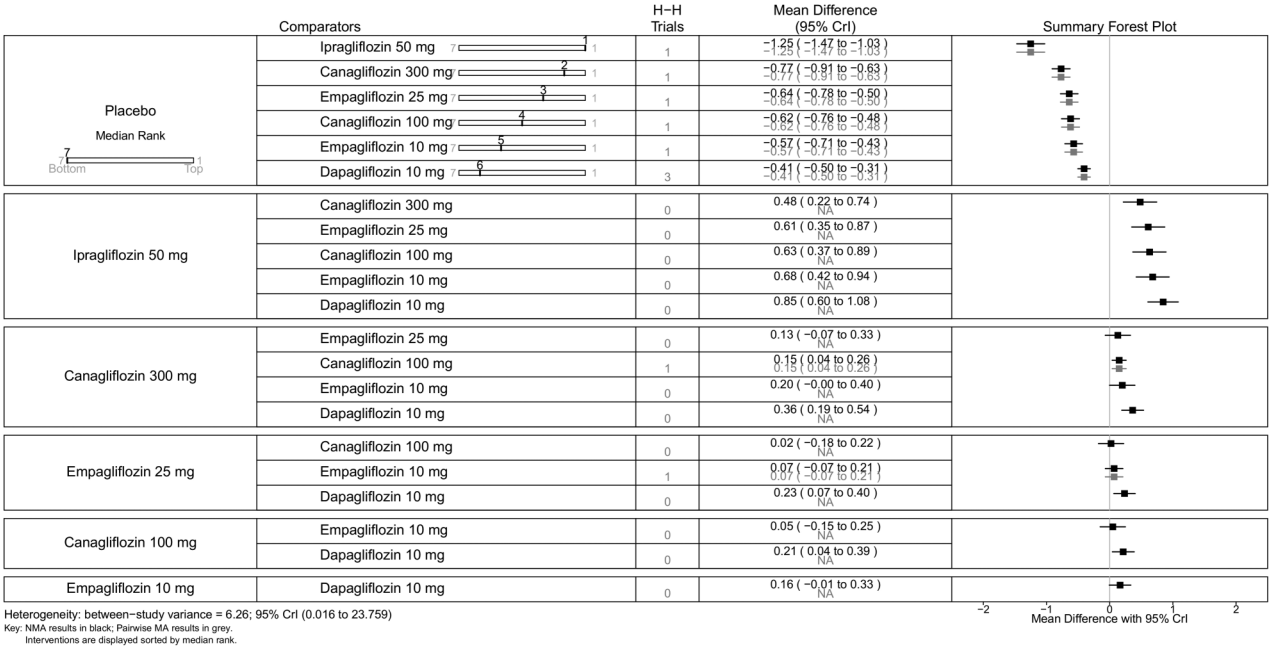


Figure 16 Mean change in HbA1c (%; dual therapy), sensitivity analysis including Bolinder *et al*,[11] Henry *et al*[12] and Kashiwagi *et al*.[24] HbA1c, glycated haemoglobin; NA, not available; NMA, network meta-analysis.

reduction in HbA1c to liraglutide over 104 weeks. The weight reduction was also comparable to GLP-1 analogues. Hypoglycaemia was less frequent with all SGLT-2 inhibitors compared with sulfonylureas. The mixed treatment comparison undertaken by Pacou *et al* (most of whom are associated with Janssen, the manufacturers of canagliflozin) was not available in full, so we were not able to determine which studies were included or to assess the quality of the study.

Our initial question was whether canagliflozin is more potent than other SGLT-2 inhibitors, due to its dual effect on SGLT-2 and SGLT-1 receptors. In monotherapy, both doses of canagliflozin lowered HbA1c slightly more than both doses of empagliflozin, which does not have significant effects on SGLT-1 receptors. These differences were not seen in dual therapy. This suggests that the SGLT-1 effect may not be clinically significant.

There are still unanswered questions. We do not know how long SGLT-2 inhibitors would be effective for, but as the mode of action is independent of insulin release, one might expect them to be effective irrespective of diabetes duration. Women taking these drugs have increases in urinary tract and genital tract infection but these are reported in the trials to be mild in intensity. At present, we do not know if there are long-term adverse effects, either from the class as a whole or from individual drugs. There has been recent concern about diabetic ketoacidosis among people on the SGLT-2 inhibitors.[29 30]

CONCLUSION

There are few clinically significant differences among the drugs. In monotherapy, reductions in HbA1c were largest with canagliflozin and smallest with dapagliflozin. Differences in HbA1c were insignificant in dual therapy.

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