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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.

INTRODUCTION

The newest class of drugs for type 2 diabetes are the sodium glucose co-transporter 2 (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 SGLT2 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 al4 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 diabetes5 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. 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 V1.4.3, 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. 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. 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. Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CrI excluding 0 for MD and 1 for RR. 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 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 than 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 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 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 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

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**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 trials12–24 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 trials11 12 14 15 17 18 of dapagliozin, three trials13 19 22 of canagliozin, two trials of empagliozin16 20 one each of luseogliflozin,21 ipragliozin24 and tofogliflozin.23

Eight trials13 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 studies11 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 studies15 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, seven15 17 18 20–23 monotherapy and five12 14 16 19 24 dual therapy studies provided adequate information on efficacy of SGLT-2 inhibitors. For mean change in SBP, five monotherapy studies13 15 20 22 23 and three dual therapy studies16 19 24 reported sufficient data. Stenlof et al.13 did not report weight SDs for the two doses of canagliozin, so this study could not be included. The weight data for canagliozin 100 mg come from Inagaki 2014 where the 100 and 200 mg doses of canagliozin 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 dapagliozin 10 mg, tofogliflozin 10 and 40 mg because of wide CIs (figure 8).

Using canagliozin 300 mg as the baseline, patients on canagliozin 100 mg (RR=0.72, 95% CrI 0.59 to 0.87) and dapagliozin 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 canagliozin 300 mg (figure 5). The proportions of patients achieving HbA1c <7% were similar among empagliozin 10 mg, canagliozin 100 mg and dapagliozin 10 mg.

Canagliozin 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: canagliozin 100 mg MD from canagliozin 300 mg=0.20 (95% CrI 0.05 to 0.36); empagliozin 25 mg (MD 0.37, 95% CrI 0.16 to 0.58); tofoglizin relative to placebo, SGLT-2 inhibitors reduced SBP compared with placebo, CR 0.19 to 0.74); tofoglizin 10 mg (MD 0.46, 95% CrI 0.19 to 0.73); empagliozin 10 mg (0.49, 95% CrI 0.29 to 0.69); and dapagliozin 10 mg (MD=0.64, 95% CrI 0.45 to 0.83; figure 6).

Canagliozin 100 mg led to greater weight reduction than the other flozins; this reaching statistical significance was compared with empagliozin 25 mg (MD 0.85, 95% CrI 0.37 to 1.33); empagliozin 10 mg (MD 1.07, 95% CrI 0.59 to 1.56); tofoglizin 10 mg (MD 1.13, 95% CrI 0.45 to 1.80); luseogliflozin 2.5 mg (MD=0.47, 95% CrI 0.19 to 0.74); tofoglizin 10 mg (MD 0.46, 95% CrI 0.19 to 0.73); empagliozin 10 mg (0.49, 95% CrI 0.29 to 0.69); and dapagliozin 10 mg (MD=0.64, 95% CrI 0.45 to 0.83; figure 7).

SBP was reduced by all the flozins relative to placebo, with reductions ranging from 6.1 mm Hg for canagliozin 300 mg to 2.6 mm Hg for empagliozin 10 mg, though (figure 8) in some cases CIs were wide and the reductions were not statistically significant. Among the flozins, only empagliozin 10 mg gave a difference that was statistically significant against canagliozin (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 al24 (ipragliozin), Henry et al12 (dapagliozin) and Bolinder et al11 (dapagliozin). 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 al11 study was included in the sensitivity analysis of mean change in HbA1c and weight. Kashiwagi et al24 was also included for sensitivity analysis of mean change in SBP.
Table 1 Baseline characteristics of all included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants and baseline data</th>
<th>Intervention/outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dapagliflozin</strong></td>
<td></td>
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<tr>
<td>Bailey et al^1^</td>
<td>N: 534</td>
<td>Interventions</td>
</tr>
<tr>
<td>Setting: multicentre (n=80)</td>
<td>Patient's with type 2 diabetes inadequately controlled with metformin (≥1500 mg/day)</td>
<td>Comparator</td>
</tr>
<tr>
<td>Design: four-arm, double-blind, placebo-controlled RCT, dual therapy. Only 10 mg arm included in NMA</td>
<td>Age (years): dapagliflozin 52.7, SD 9.9; placebo+metformin 53.7, SD 10.3</td>
<td>Placebo+metformin</td>
</tr>
<tr>
<td>Follow-up: 24 weeks; 102 weeks</td>
<td>Hba1c (%): dapagliflozin 7.92, SD 0.82; placebo+metformin 8.11, SD 0.96</td>
<td>Outcomes</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m^2): dapagliflozin 31.2, SD 5.1; placebo+metformin 31.8, SD 5.3</td>
<td>Primary outcomes: change in HbA1c from baseline to 24 weeks</td>
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<tr>
<td></td>
<td></td>
<td>Other outcomes</td>
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<tr>
<td></td>
<td></td>
<td>change in FPG, change in total body weight, the proportion of patients achieving a HbA1c &lt;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</td>
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</table>

| **Bolinder et al^1^** | N: 180                        | Intervention         |
| Setting: multicentre (n=40) in Bulgaria, Czech Republic, Hungary, Poland and Sweden | Patient's with type 2 diabetes inadequately controlled with metformin (≥1500 mg/day) | Comparator             |
| Design: two-arm, double-blind, placebo-controlled RCT in dual therapy | Age (years): dapagliflozin 60.6, SD 8.2; placebo+metformin 60.8, SD 6.9 | Placebo+metformin      |
| Duration: 24 weeks | Hba1c (%): dapagliflozin 7.19, SD 0.44; placebo+metformin 7.16, SD 0.53. Note the very low baseline level | Outcomes               |
|                   | BMI (kg/m^2): dapagliflozin 32.1, SD 3.9; placebo+metformin 31.7, SD 3.9 | Primary outcome: change from baseline at week24 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^5^** | N: 274                        | Intervention         |
| Setting: multicentre (n=85) in the USA, Canada, Mexico and Russia | Patients with type 2 diabetes mellitus inadequately controlled with diet and exercise, naïve to treatment | Comparator             |
| Design: double-blind, parallel-group, placebo-controlled, phase 3 RCT in monotherapy | Age (years): dapagliflozin 50.6, SD 9.97; placebo 52.7, SD 10.3 | Placebo+metformin      |
| Duration: 24 weeks | Hba1c (%): dapagliflozin 8.01, SD 0.96; placebo 7.84, SD 0.87 | Outcomes               |
|                   | BMI (kg/m^2): dapagliflozin 33.6, SD 5.4; placebo+metformin 32.3, SD 5.5 | 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         |
| Setting: multicentre (n=131)—hospitals and clinics in North America, Latin America, Europe and Asia | Patients with type 2 diabetes inadequately controlled with diet and exercise, naïve to treatment | Comparator             |
|                   | Age (years): dapagliflozin 51.5, SD 10.1 | Placebo+metformin XR (n=208) |
|                   |                               | Outcomes               |
|                   |                               | Primary outcome: change from baseline to 24 weeks |
|                   |                               | Other outcomes        |
|                   |                               | change in FPG, change in total body weight, the proportion of patients achieving a 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 |

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<tr>
<th>Study</th>
<th>Participants and baseline data</th>
<th>Intervention/outcomes</th>
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| Ji et al, 2017 | Study: multicentre (n=40) in China (n=26), Korea (n=5), Taiwan (n=5) and India (n=4)  
Setting: multicentre (n=NR) in China  
Design: double-blind, active controlled trials in dual therapy  
Duration: 24 weeks  
Intervention: 10 mg dapa (n=133)  
 Comparator: Placebo (n=132)  
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  
Intervention: 10 mg dapa (n=133)  
Comparator: Placebo (n=132)  
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/m²): dapa 10 mg 26.6, SD 4.52; placebo 25.22, SD 4.39 | 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  
Intervention: 10 mg dapa (n=133)  
Comparator: Placebo (n=132)  
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/m²): dapa 10 mg 26.6, SD 4.52; placebo 25.22, SD 4.39 |
| Canagliflozin | Lavalle-Gonzalez et al, 2017 | 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 |  
Intervention  
1. Cana 100 mg+metformin (n=368)  
2. Cana 300 mg+metformin (n=367)  
Comparator  
1. Placebo+metformin (n=186)  
Outcomes  
Continued |
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<tr>
<th>Study</th>
<th>Participants and baseline data</th>
<th>Intervention/outcomes</th>
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</table>
| **Stenlof et al**<sup>13</sup> | Setting: multicentre (n=NR) in 17 countries  
Design: double-blind, placebo-controlled, phase 3 RCT, monotherapy  
Duration: 26 weeks | 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 |
| | 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<sup>2</sup>): 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 |  
N: 584  
Participants: patients with type 2 diabetes inadequately controlled with diet and exercise and also on antihyperglycaemic 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 0.1, SD 0.0; placebo 8.0, SD 1.0  
BMI (kg/m<sup>2</sup>): cana 100 mg 31.3, SD 6.6; cana 300 mg 31.7, SD 6.0; placebo 31.8, SD 6.2 |  
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 achieving HbA1c level of <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**<sup>22</sup> | Setting: multicenter (n=31) in Japan  
Design: double-blind placebo-controlled phase 3 parallel group trial  
Duration: 24 weeks |  
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 |
| | HbA1c (%): cana 100 mg 7.98, SD 0.73; placebo 8.04, SD 0.70  
BMI (kg/m<sup>2</sup>): cana 100 mg 25.59, SD 4.20; placebo 25.85, SD 4.39 |  
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<sup>2</sup>): cana 100 mg 25.59, SD 4.20; placebo 25.85, SD 4.39 |  
1. 100 mg canagliflozin (n=90)  
2. Placebo (n=93)  
Comparator  
1. Placebo (n=93) |  
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**<sup>16</sup> | 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 |  
10 mg empagliflozin+metformin (n=217)  
25 mg empagliflozin+metformin (n=213)  
Comparator  
1. Placebo+metformin (n=207)  
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**<sup>16</sup> |  
Haring et al |  
N: 637  
Participants: patients with type 2 diabetes inadequately controlled with diet and exercise and a stable immediate-release metformin regimen  
Age (years): empagliflozin 10 mg+metformin 55.5, SD 9.9; empagliflozin 25 mg+metformin 55.6, SD 10.2; placebo+metformin 56, SD 9.7 |  
1. 10 mg empagliflozin+metformin (n=217)  
2. 25 mg empagliflozin+metformin (n=213)  
Comparator  
1. Placebo+metformin (n=207) |  
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 |
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<th>Intervention/outcomes</th>
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<tbody>
<tr>
<td>RCT, dual therapy</td>
<td></td>
<td><strong>Primary outcome</strong>: change from baseline in HbA1c at week 24 <strong>Other outcomes</strong>:</td>
</tr>
<tr>
<td><em>Duration</em>: 24 weeks</td>
<td>$HbA1c$ (%): 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 $BMI (kg/m^2)$: 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</td>
<td>change from baseline to week 24 in body weight and MDG; percentage of patients with baseline HbA1c $\geq$7.0% who had HbA1c level $&lt;$7% at week 24; change from baseline in FPG, waist circumference, and SBP and DBP at week 24; percentage of patients with $&gt;$5% reduction in body weight at week 24; use of rescue medication; and safety</td>
</tr>
</tbody>
</table>
| Roden et al<sup>20</sup>   | *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 $BMI (kg/m^2)$: 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 body weight at week 24; change from baseline in SBP 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 body weight 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             |                                | Intervention 1. 2.5 mg luseo (n=79)  Comparator 1. Placebo (n=79)  
*Outcomes*  
**Primary outcome**: change in HbA1c from baseline to end of treatment **Others**: plasma glucose, insulin, glucagon, serum CPR, intact |
| Seino et al<sup>21</sup>   | *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 $\geq$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 $BMI (kg/m^2)$: luseo 2.5 mg 25.98, SD 4.88; placebo 25.34, SD 4.19 | |
| Ipragliflozin              |                                | Intervention 1. Ipra 50 mg+metformin (n=112)  Comparator |
| Kashiwagi et al<sup>24</sup> | *Setting*: multicentre (n=34) in Japan  *Design*: double-blind, placebo-controlled RCT with a duration of ≥12 weeks  N: 168 *Participants*: patients with type 2 diabetes of $\geq$12 weeks duration, treated with metformin for $\geq$6 weeks and with | |

*Continued*
Table 1  Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants and baseline data</th>
<th>Intervention/outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 weeks open-label extension</td>
<td>an HbA1c level of 7.4–9.9% and BMI of 20–45 kg/m²</td>
<td>1. Placebo+metformin (n=56)</td>
</tr>
<tr>
<td><strong>Duration</strong>: 24 weeks with a 28 weeks open-label extension</td>
<td>Age (years): ipra 50 mg 56.2, SD 10.67; placebo 57.7, SD 9.24</td>
<td>Outcomes</td>
</tr>
<tr>
<td></td>
<td>HbA1c (%): ipra 50 mg 8.25, SD 0.719; placebo 8.38, SD 0.738</td>
<td>Primary outcome: change in HbA1c from baseline to end of treatment</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²): ipra 50 mg 25.96, SD 4.410; placebo 25.47, SD 3.092</td>
<td>Other outcomes: body weight, waist circumference, FPG, FSI, plasma leptin, and adiponectin levels, HOMA-R and HOMA-β and safety outcomes</td>
</tr>
</tbody>
</table>

Togoliflozin
Kaku et al

| Setting: multicentre (n=33) in specialists and non-specialists hospital in Japan |
| Design: double-blind, placebo-controlled, parallel-group RCT |
| **Duration**: 24 weeks |

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants and baseline data</th>
<th>Intervention/outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N: 235</td>
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<tr>
<td><strong>Participants</strong>: 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 &lt;10.3%, BMI of ≥18.5 to &lt;45 kg/m², per cent changes in HbA1c and body weight from the provisional registration visit to the final registration visit of ≤10% and &lt;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)</td>
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<tr>
<td>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</td>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>1. Tofo 10 mg (n=59)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²): 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</td>
<td>2. Tofo 20 mg (n=60)</td>
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<td>Comparator</td>
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<td>3. Tofo 40 mg (n=59)</td>
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<td></td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary outcome: change in HbA1c from baseline to end of treatment</td>
<td></td>
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<tr>
<td></td>
<td>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</td>
<td></td>
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</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Entry criteria</th>
<th>HbA1c (%)</th>
<th>HbA1c baseline</th>
<th>Age baseline</th>
<th>BMI baseline</th>
<th>Weight baseline</th>
<th>eGFR baseline</th>
<th>Per cent HbA1c &lt;7%</th>
<th>Per cent HbA1c &lt;7%</th>
<th>Weight loss</th>
<th>Weight loss</th>
<th>Reduction HA1c</th>
<th>Reduction HA1c</th>
<th>Difference HbA1c</th>
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<tr>
<td>Dapagliflozin</td>
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<tr>
<td>Ferrannini et al</td>
<td>7 to 10</td>
<td>7.84–8.01</td>
<td>50.6–52.7</td>
<td>32.3–33.6</td>
<td>88.8–94.2</td>
<td>NR</td>
<td>51</td>
<td>32</td>
<td>−2.2</td>
<td>−3.2</td>
<td>−0.23</td>
<td>−0.89</td>
<td>−0.66</td>
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<tr>
<td>Ji et al</td>
<td>≥7.5 to ≤10.5</td>
<td>8.28–8.35</td>
<td>49.9–51.2</td>
<td>25.76–25.93</td>
<td>70.92–72.18</td>
<td>NR</td>
<td>50</td>
<td>21.3</td>
<td>−0.27</td>
<td>−2.25</td>
<td>−0.29</td>
<td>−1.11</td>
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<tr>
<td>Kaku et al</td>
<td>≥6.5 to 10</td>
<td>7.46–7.50</td>
<td>57.5–60.4</td>
<td>25.22–26.06</td>
<td>65.96–69.7</td>
<td>66.9–67.8</td>
<td>36</td>
<td>19</td>
<td>−0.84</td>
<td>−2.22</td>
<td>−0.06</td>
<td>−0.45</td>
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<tr>
<td>Inagaki et al</td>
<td>7 to 10</td>
<td>8.04</td>
<td>58.2–58.4</td>
<td>25.59 to 25.85</td>
<td>68.57–69.10</td>
<td>81.4–84.7</td>
<td>31.5</td>
<td>6.6</td>
<td>−0.76</td>
<td>−3.76</td>
<td>+0.29%</td>
<td>−0.74%</td>
<td>−1.03%</td>
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<td>Stenlof et al</td>
<td>≥7.0 to ≥10.0</td>
<td>8.0–8.1</td>
<td>55.1–55.7</td>
<td>31.3–31.8</td>
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<tr>
<td>Roden et al</td>
<td>≥7.0 to ≥10.0</td>
<td>7.86–7.91</td>
<td>53.8–56.2</td>
<td>28.2–28.7</td>
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<td>86.8–87.7</td>
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<tr>
<td>Seino et al</td>
<td>≥6.5 to ≤10.5</td>
<td>8.14–8.17</td>
<td>58.9–59.6</td>
<td>25.34–25.98</td>
<td>66.67–70.19</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>−0.9</td>
<td>−2.7</td>
<td>+0.13</td>
<td>−0.63</td>
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<tr>
<td>Kaku et al</td>
<td>≥7.3 to &lt;10.3</td>
<td>8.34–8.45</td>
<td>56.6–58.6</td>
<td>24.99–26</td>
<td>67.26–71.20</td>
<td>83.78–86.78</td>
<td>NR</td>
<td>NR</td>
<td>−0.356</td>
<td>−2.23</td>
<td>−0.028</td>
<td>−0.767</td>
<td>−0.769</td>
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</tbody>
</table>

HbA1c in per cent; age in years; BMI in kg/m²; weight in kg; eGFR in mL/min/1.73 m². 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. and Henry et al. 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 Bolinder trial (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,
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.

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
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.
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

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

**Figure 8** Mean change in SBP (mm Hg)—monotherapy. NA, not available; NMA, network meta-analysis; SBP, systolic blood pressure.
the placebo groups in the canagliflozin trials, HbA1c rose by 0.29% and 0.14% (Stenlof CANTATA-M). 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...

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

**Figure 10**  Mean change in HbA1c (%)—dual therapy. HbA1c, glycated haemoglobin; NA, not available; NMA, network meta-analysis.
compare all the SGLT-2 inhibitors against each other. For example, the Seino \textit{et al.}\textsuperscript{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...
The 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. 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. Empagliflozin has also been approved by NICE in combination therapy.

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

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

**Figure 14** Mean change in weight (kg; dual therapy), sensitivity analysis including Bolinder *et al.*, Henry *et al.* 2012 and Kashiwagi *et al.* NA, not available; NMA, network meta-analysis.
metformin. NICE is appraising the use of the flozins in monotherapy in people who cannot take metformin in 2015.\textsuperscript{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,\textsuperscript{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\textit{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 15 Mean change in SBP (mm Hg; dual therapy), sensitivity analysis including Kashiwagi \textit{et al}.\textsuperscript{24} NA, not available; NMA, network meta-analysis; SBP, systolic blood pressure.

Figure 16 Mean change in HbA1c (%; dual therapy), sensitivity analysis including Bolinder \textit{et al},\textsuperscript{11} Henry \textit{et al}\textsuperscript{12} and Kashiwagi \textit{et al}.\textsuperscript{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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Contributors NW and DSS conceived the study. DSS carried out the systematic review, assisted by NW. OAU carried out the network meta-analysis. All authors were involved in writing the manuscript.

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Competing interests DSS has joined Eli Lilly but was employed by the University of Warwick when this review was undertaken. DSS carried out this work while in Warwick Medical School. DSS and NW were involved in the NICE STA on empagliflozin in combination therapy; NW and DSS were involved in the NICE STA on empagliflozin in combination therapy; and OAU and NW are involved in the NICE appraisal of canagliflozin, dapagliflozin and empagliflozin in monotherapy for type 2 diabetes.

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