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# Comparative efficacy of once-weekly semaglutide versus SGLT-2 inhibitors in patients inadequately controlled with one to two oral antidiabetic drugs: a systematic literature review and network meta-analysis

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## ABSTRACT

**Objective** To determine the comparative efficacy of once-weekly semaglutide relative to sodium-glucose cotransporter 2 inhibitors (SGLT-2is) licensed in Europe and North America among patients with type 2 diabetes (T2D) inadequately controlled with 1–2 oral antidiabetics (OADs), using a network meta-analysis (NMA). Design systematic review and network meta-analysis. Data Sources EMBASE, MEDLINE and CENTRAL were searched from January 1994 to August 2017.

**Methods** Randomised controlled trials with ≥20 weeks of treatment evaluating once-weekly semaglutide or SGLT-2is. Primary outcomes included change from baseline in: HbA1c, weight, systolic blood pressure, postprandial blood glucose and fasting plasma glucose. Fixed-effect and random-effect Bayesian NMA were used to indirectly compare treatment effects at 26 (±4) weeks. Metaregression and sensitivity analyses were conducted. Model selection was performed using the deviance information criterion and consistency was assessed by comparing indirect (edge-splitting) to direct evidence.

**Results** Forty-eight publications representing 21 trials were included. The mean differences (MD) in change from baseline in HbA1c of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from −0.56% for canagliflozin 300 mg (95% credible interval (CrI): −0.76 to −0.33%), to −0.95% for dapagliflozin 5 mg (95% CrI: −1.20 to −0.69%). The MD in change from baseline in weight of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from −1.35 kg for canagliflozin 300 mg to −2.48 kg for dapagliflozin 5 mg, while change from baseline in fasting plasma glucose ranged from −0.41 mmol/L for canagliflozin 300 mg to −1.37 mmol/L for dapagliflozin 5 mg. Once-weekly semaglutide was not statistically differentiable than all SGLT-2is in reducing systolic blood pressure. NMA was not feasible for postprandial blood glucose and safety outcomes.

**Conclusion** Once-weekly semaglutide demonstrated statistically significant and clinically meaningful reductions in HbA1c and body weight in T2D patients inadequately

### Strengths and limitations of this study

► Use of highly sensitive searches in the peer-reviewed literature supplemented with hand searches of leading diabetes research conferences.
► High quality of study data from the involvement of two independent researchers for study selection and data extraction.
► Robust analytical results from a variety of sensitivity analyses conducted.
► Limited patient and study characteristics from conference proceedings leading to difficulties in determining population heterogeneity.
► Lack of direct comparisons from the shortage of reported comparisons in available literature.

controlled with 1–2 OADs compared to all SGLT-2is licensed in Europe and North America.

## INTRODUCTION

Type 2 diabetes (T2D) is a chronic condition characterised by a reduction in both insulin production and pancreatic beta-cell function, as well as by increased insulin resistance.[1] In 2017, it was estimated that 425 million adults were living with diabetes, with approximately 90% of cases being T2D.[2] Over the past decades, the prevalence of diabetes has been steadily rising. In 2017, there were up to 4 million deaths directly caused by, or related to, diabetes.[2] Effective treatments to help improve glycaemic control are essential to curbing the high morbidity and mortality of this global diabetes epidemic.

According to the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and National

Institute for Clinical Excellence (NICE) UK guidance on T2D, metformin, an oral antidiabetic drug (OAD), should be considered as first-line treatment.[3–5] The first stage of intensification following treatment failure consists of either adding another antidiabetic agent, such as dipeptidyl peptodase-4 inhibitor, pioglitazone or sulfonylurea, to metformin.[6] Following failure of these treatments, a triple therapy is considered. Some guidelines, such as ADA,[7] include glucagon-like peptide-1 (GLP-1) receptor agonist and insulin-based therapies as considerations for both dual and triple therapy, while others, such as NICE,[6] include them only as considerations for triple therapy.

Once-weekly semaglutide belongs to the GLP-1 receptor agonist drug class. It has shown promising results in the Semaglutide Unabated Sustainability in Treatment of T2D (SUSTAIN) programme, a series of global phase III randomised controlled trials (RCTs) of once-weekly semaglutide encompassing more than 8000 people with T2D. Sodium-glucose cotransporter 2 inhibitors (SGLT-2is) are another class of antidiabetics that have been approved by regulatory agencies within the past decade. Evidence has shown that these are potential options for a variety of treatment-experienced T2D populations.

At present, there is no direct evidence comparing the efficacy of once-weekly semaglutide relative to SGLT-2is. Despite the lack of head-to-head evidence, network meta-analyses (NMA) can be used to make indirect comparisons and to simultaneously review the therapeutic landscape.[8–11] These methods use the evidence base of RCTs comparing the interventions to each other and select common comparators, as identified through systematic literature reviews (SLRs).

We sought to conduct an SLR and NMA to determine the efficacy of once-weekly semaglutide relative to SGLT-2is licensed in both Europe and North America among patients (aged ≥18 years) with T2D with inadequate glycaemic control using 1–2 OADs. A separate study has evaluated the comparative efficacy and safety of once-weekly semaglutide and SGLT-2i in T2D patients inadequately controlled with metformin.[12]

## METHODS
### Systematic literature review
An SLR to identify pertinent RCTs was performed by searching MEDLINE, EMBASE and CENTRAL through Ovid from January 1994 to 5 April 2016, with updates on 3 October 2016 and 16 August 2017. Manual searches of the proceedings from four conferences published 2013–2017 were also performed: International Society for Pharmacoeconomics and Outcomes Research, International Diabetes Federation, EASD and ADA scientific sessions. The search strategy used in this study was designed for a larger SLR with highly sensitive search algorithms that ran concurrently and allowed for most currently used diabetes pharmacotherapies and for a more diverse population. The search strategies were shared with the

sister study, but study selection and subsequent steps were separate.[12]

All steps of the SLR, including study selection, were conducted in dual and independently. Discrepancies were resolved through consensus and a third reviewer was used as needed. Study eligibility criteria were defined a priori according to the population, interventions, comparisons, outcomes and study design (PICOS) to ensure that potentially relevant studies were selected in a systematic manner with a minimal risk of introducing bias in accordance with guidance published by the Centre for Reviews and Dissemination, and the Cochrane Handbook for Systematic Reviews.[13 14] Studies published in English meeting the following criteria were included; (1) adults aged 18 years or older with T2D inadequately controlled with 1–2 prior OADs; (2) 1.0 or 0.5 mg doses of once-weekly semaglutide, or any approved doses of SGLT-2is that are licensed in Europe and North America; (3) reported one or more efficacy outcome(s); change from baseline $Hb_{A1c}$, weight, body mass index (BMI), and systolic blood pressure (SBP), postprandial blood glucose (PPG), fasting plasma glucose (FPG), proportion of patients achieving <7% or ≤6.5% $Hb_{A1c}$, proportion of patients achieving ≥5 or 10% wt loss, safety outcomes and triple composite outcome (based on reaching <7.0% $HbA_{1c}$, having no hypoglycaemic events and no weight gain) and (4) RCT studies with treatment duration of as low as 20 weeks, including cross-over trials with a minimum 20-week assessment of efficacy outcomes at cross-over, because this was viewed as the amount of time for an antidiabetic to have its full effect on HbA1c, the primary outcome to most clinical studies of interest.[15] In addition, only phase III trials were included in order to align the results with the SUSTAIN clinical trial study design. See online supplementary appendix for the full PICOS statement.

Data were extracted in duplicate using a standardised tool from the final list of eligible studies. Change from baseline data was extracted for continuous outcomes. In cases where change from baseline was not available, appropriate information to calculate change from baseline was extracted (see online supplementary appendix). Proportion of patients in each treatment arm with the event data was extracted for dichotomous outcomes. In addition, information on study design characteristics, inclusion/exclusion criteria, patient characteristics, interventions, definition and results for the outcomes of interest and other contextual factors was extracted.

The quality of individual trials was assessed across six conceptual domains using the Cochrane Risk of Bias Assessment[14]; selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. Each domain was scored as low, unclear or high risk of bias, with disagreements again resolved by consensus discussions with a third reviewer.

### Analysis methods
In order to gauge the suitability of conducting an NMA, a feasibility assessment was conducted to assess:

(1) whether the RCT evidence for the interventions of interest formed a connected evidence network for each outcome of interest and time point; (2) the homogeneity of outcomes reported and data time points and (3) the distribution of study characteristics, subject characteristics and disease definitions that may impact treatment effects across direct comparisons of the evidence network for outcomes and time points of interest.[10 16]

Based on the findings of the feasibility assessment, the results of the RCTs that formed a complete evidence network, and were deemed comparable, were synthesised by means of NMA to determine the relative treatment efficacy of once-weekly semaglutide, canagliflozin, dapagliflozin and empagliflozin at 26-week time points (±4 weeks), across the outcomes of interest.

Analyses were performed within a Bayesian framework, which involves data, a likelihood distribution, a model with parameters and prior distributions. The model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared with an overall reference treatment. Based on these basic parameters, the relative efficacy between each of the competing interventions was obtained. All analyses were conducted using non-informative priors in line with NICE technical support documents (see model code in online supplementary appendix).[8]

Fixed-effect or random-effect models were applied depending on values for the deviance information criterion (DIC). A difference in DIC of about three points was considered meaningful and the model with lowest DIC was selected as best-fit model.[17] Where binary data were analysed, a logit link was used in the standard normal NMA regression setup to obtain ORs and relative risks (RRs) for each comparison in the network. For continuous outcomes, a normal likelihood NMA setup with an identity link function was used to calculate mean difference (MD) as the relative treatment effect.

For the NMA, ranking probabilities were estimated for all treatments of being at each rank for each intervention. A treatment hierarchy was determined using the probability of being the best treatment by using the surface under the cumulative ranking curve (SUCRA; score of 0–1 where 1 is best). To determine whether there were issues of inconsistency, independent means models, to evaluate direct evidence, and edge-splitting, to evaluate indirect evidence, were used to generate two posterior distributions for the mean treatment effect.[18] The difference in posterior means generated by the two sets of evidences was then used as an estimate of inconsistency within the network.

In our feasibility assessment, we found that NMA was not possible for the following outcomes: proportion of patients achieving ≤6.5% HbA1c, proportion of patients achieving ≥5 or 10% wt loss, BMI, PPG (mmol/L), safety outcomes and triple composite outcome. This was either because the network was disconnected between once-weekly semaglutide and SGLT-2is or the data were not available at 26±4 weeks.

In addition to the principal analyses, the following sensitivity analyses were conducted: (i) removal of three trials with more than 40% Asian patients,[19–21] (this is due to Asian ethnicity being a well-recognised effect modifier in diabetic therapeutics due to a greater level of ß-cell dysfunction in East Asians)[22–24]; and (ii) removal of one trial with high cardiovascular risk.[25] In our feasibility assessment, we observed differences between different direct comparisons in the distribution of the following characteristics: sex, disease duration, weight at baseline, $HbA_{1c}$ at baseline, number of OADs failed at baseline. As such, we conducted metaregression analyses using these variables.

### Patient and public involvement

Patients and public were not involved in the development of this study as it made use of publicly available data.

### RESULTS

Figure 1 displays Preferred Reporting Items for Systematic Reviews and Meta-Analysesflow diagram, showing results separately for the original search and the two updates. A total of 38 828 citations were identified from the three searches including 38 814 via MEDLINE, EMBASE and CENTRAL, and 14 records identified through other sources. Studies in T2D patients with inadequate control on 1–2 OADs were then selected from this large evidence base. The most common reasons for study exclusion were study design, followed by an intervention or population outside the PICOS eligibility criteria. This resulted in 48 publications representing 21 trials included in the SLR.

The complete network of evidence is shown in figure 2 and networks by clinical outcome can be found in online supplementary appendix. Studies were similar with respect to trial characteristics (table 1) and baseline patient characteristics (table 2 and table 3). No evidence of inconsistency was observed in any of the outcomes. Tables on model selection and figures comparing the agreement of direct and indirect evidences are shown in the online supplementary appendix.

A majority of the trials were multicentre, phase III, double-blind trials. The only open-label trials were SUSTAIN 3[26] and SUSTAIN 7.[27] Duration of follow-up was reported in all 21 trials, ranging from 24 to 104 weeks; mean age ranged from 53.5 to 61.0 years[25 28]; mean weight at baseline ranged from 76.9 to 96.0 kg[26 29]; mean SBP ranged from 126 to 135 mm Hg[21 30] and mean baseline HbA1c ranged from 7.2% to 9.3%.[31 32] To note, all trials reported results at the 26-week time point, with the exception of SUSTAIN 2,[33] SUSTAIN 3[26] SUSTAIN 4[34] (23-week time point) and SUSTAIN 7 (28-week time point).[27]

The trials were considered to have low-risk of bias based on the assessment using Cochrane Risk of Bias Assessment tool.[14] The only source of high-risk bias came from the lack of blinding and selective reporting in few included trials. Full trial and patient characteristics, and risk of bias
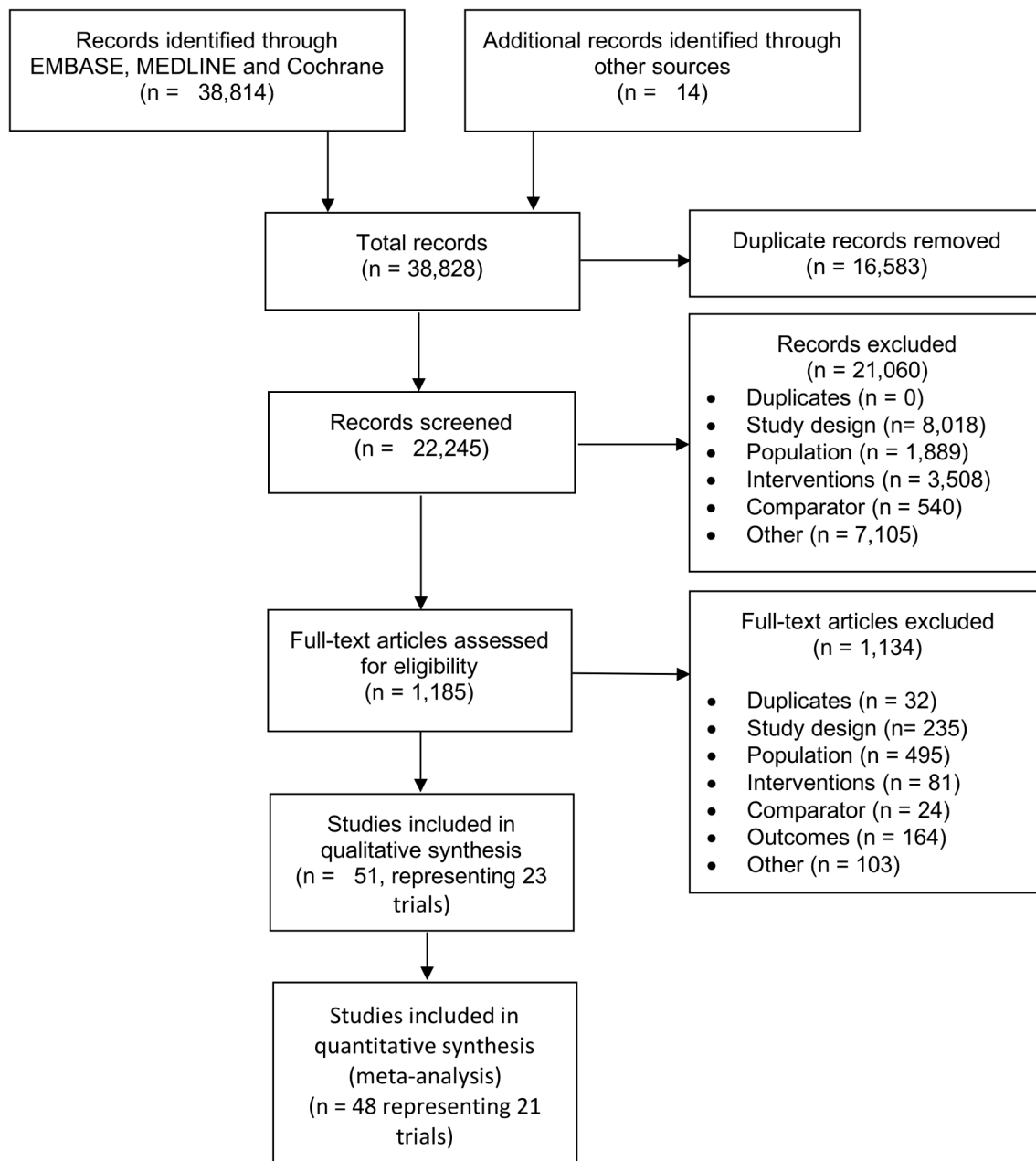
**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram, showing results separately for the original search and the two updates. A total of 38 828 citations were identified from the three searches including 38 814 via MEDLINE, EMBASE and CENTRAL, and 14 records identified through other sources. Studies in T2D patients with inadequate control on 1–2 OADs were then selected from this large evidence base. The most common reasons for study exclusion were study design, followed by an intervention or population outside the PICOS eligibility criteria. This resulted in 48 publications representing 21 trials included in the SLR. OADs, oral antidiabetics; SLRs, systematic literature reviews; T2D, type 2 diabetes

assessments, are provided in the online supplementary appendix.

### Change in HbA$_{1c}$

Change from baseline in HbA$_{1c}$ was the primary outcome for most of the included trials. Twenty-one trials including 53 treatment arms and 11 714 patients reported on 11 treatments.[19–21 25–28 32–45] The random-effect model was chosen as best-fit model because it had the lowest DIC (94.37).

As shown in table 4, there was a strong evidence that once-weekly semaglutide was more efficacious at reducing HbA$_{1c}$ relative to SGLT-2is, at both doses. The MD in change from baseline in HbA$_{1c}$ of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from −0.56% for canagliflozin 300 mg (95% credible interval (CrI): −0.76 to 0.33%) to −0.95% for dapagliflozin 5 mg (95% CrI: −1.20 to −0.69%) indicating that once-weekly semaglutide 1.0 mg was statistically significantly more effective at reducing HbA$_{1c}$. Statistically significant reductions in
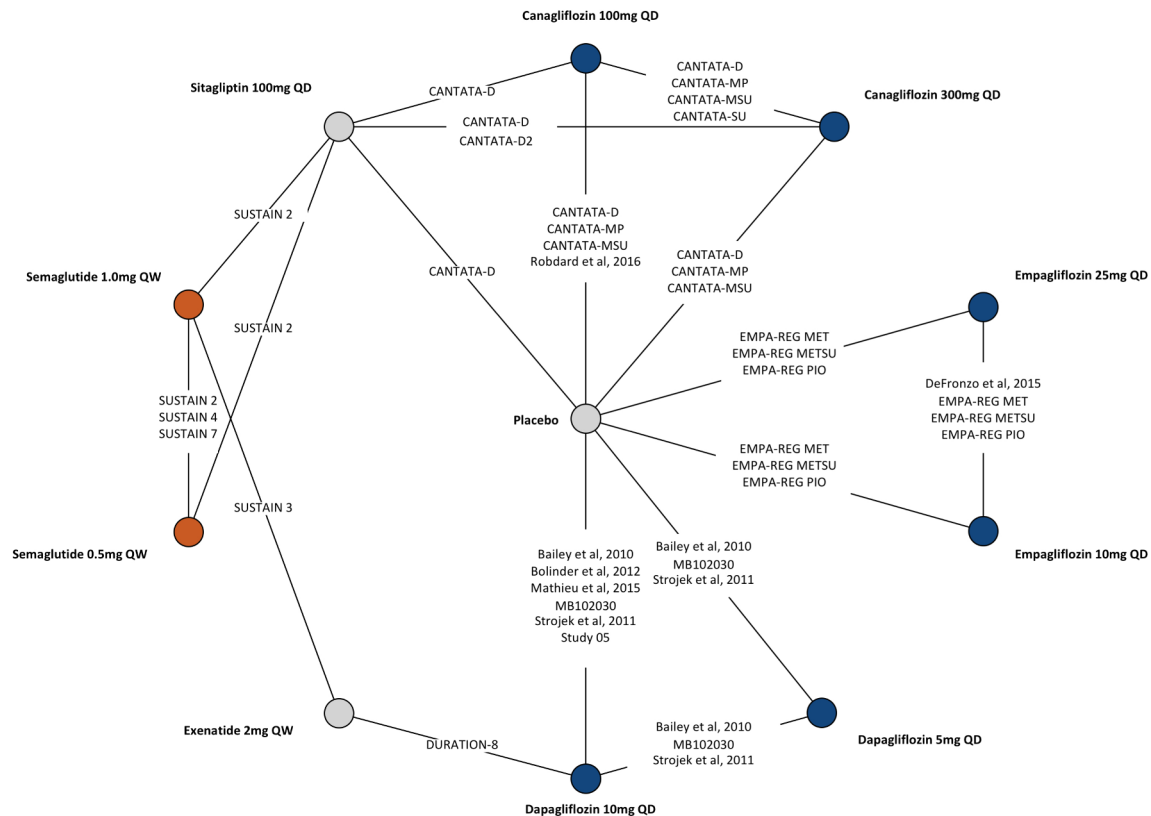
**Figure 2** Overall network of evidence of semaglutide, SGLT-2is and other treatments for type II diabetes that is uncontrolled using 1-2 oral antidiabetics.

$HbA_{1c}$ were also observed with once-weekly semaglutide 0.5 mg compared with all high-dose and low-dose SGLT-2is of interest, but with smaller effect sizes than those observed with once-weekly 1.0 mg dose. For all outcomes, modelled responses, rankings and the SUCRA scores are shown in the online supplementary appendix. Once-weekly semaglutide 1.0 mg had the highest probability of being ranked first with a SUCRA score of 1.

These results showed that while all therapies significantly reduced $HbA_{1c}$ compared with placebo, both once-weekly semaglutide doses demonstrated substantial clinical significance over the SGLT-2is comparators. A 0.3% $HbA_{1c}$ margin has been considered as threshold to assess clinical superiority between diabetes treatments by the FDA.[46] Considering this threshold, our results show that once-weekly semaglutide 0.5 mg had $HbA_{1c}$ reductions over other SGLT-2is of between 0.30% and 0.70%, and once-weekly semaglutide 1.0 mg showed reductions between 0.56% and 0.95%, suggesting that these results are clinically meaningful.

### Proportion of patients achieving <7% HbA1c
A total of 16 trials consisting of 8941 patients were included.[19–21 25 26 33–36 38 39 41–45] The DIC difference between the fixed-effect and random-effect models was less than three. The fixed-effect model was preferred (DIC: 64.62) because the majority of the connections in this network were supported by one or two trials and a random-effect model is not feasible in such cases.

Similar to the results obtained in the change from baseline for $HbA_{1c}$ analysis, once-weekly semaglutide was statistically significantly better than all SGLT-2is in achieving target $HbA_{1c}$ levels of <7% (table 4).

The OR for achieving target $HbA_{1c}$ <7% of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from 2.80 for empagliflozin 25 mg (95% CrI: 1.74 to 4.52) to 5.52 for canagliflozin 100 mg (95% CrI: 3.91 to 7.81). Again, relative to the same treatments, the OR for target $HbA_{1c}$ <7% of once-weekly semaglutide 0.5 mg versus SGLT-2is ranged from 2.06 for empagliflozin 25 mg (95% CrI: 1.27 to 3.39) to 4.07 for canagliflozin 100 mg (95% CrI: 2.86 to 5.83). A SUCRA score of 1 was achieved for once-weekly semaglutide 1.0 mg demonstrating that it was the best treatment compared with all other interventions.

### Change in weight (kg)
Twenty trials comprising 10 829 patients were included in the NMA for change from baseline in weight.[19–21 25–28 30 33–39 41–45] The DIC difference between the fixed-effect and random-effect models was less than three. The fixed-effect model was chosen (DIC: 87.02) because the majority of the connections in this network were supported by one or two trials and a random-effect model is not feasible in such cases.

Once-weekly semaglutide displayed greater reductions in body weight compared with SGLT-2is. At 1.0 mg dose, once-weekly semaglutide leads to statistically significant weight reduction relative to all SGLT-2is. Specifically, the

**Table 1** Trial characteristics including treatment duration, trial phase, blinding, counties, number of study sites and study sponsor(s)

| Trial ID | Treatment duration, weeks | Trial Phase | Blinding | Country (s) | Study sites, n | Sponsor (s) |
|---|---|---|---|---|---|---|
| Bailey et al[35] | 102 | Phase 3 | Double blind | USA, Canada, Argentina, Mexico, Brazil | 80 | AstraZeneca and Bristol-Myers Squibb |
| Bolinder et al[32] | 102 | Phase 3 | Double blind | Bulgaria, Czech Republic, Hungary, Poland, Sweden | 40 | AstraZeneca and Bristol-Myers Squibb |
| CANTATA-D[36] | 52 | Phase 3 | Double blind | International | 169 | Janssen |
| CANTATA-D2[37] | 52 | Phase 3 | Double blind | International | 140 | Janssen |
| CANTATA-MP[38] | 52 | Phase 3 | Double blind | USA, Canada, Finland, France, Germany, Greece, India, Mexico, Spain, Thailand, UK | 74 | Janssen |
| CANTATA-MSU[39] | 52 | Phase 3 | Double blind | International | 85 | Janssen |
| CANTATA-SU[40] | 52 | Phase 3 | Double blind | International (19 countries) | 157 | Janssen |
| DeFronzo et al[41] | 52 | Phase 3 | Double blind | International (22 countries) | 197 | Boehringer Ingelheim |
| DURATION-8[42] | 52 | Phase 3 | Double blind | USA, Hungary, Poland, Romania, Slovakia, South Africa | 132 | AstraZeneca |
| EMPA-REG MET[20] and EMPA-REG EXTEND MET[29] | 24 | Phase 3 | Double blind | Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, USA | 148 | Boehringer Ingelheim |
| EMPA-REG METSU[19] and EMPA-REG EXTEND METSU[29] | 24 | Phase 3 | Double blind | USA, Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey | 148 | Boehringer Ingelheim |
| EMPA-REG PIO[21] and EMPA-REG EXTEND PIO[61] | 24 | Phase 3 | Double blind | Canada, China, Greece, India, Philippines, Thailand, Ukraine, USA | 69 | Boehringer Ingelheim and Eli Lilly |
| Mathieu et al[43] | 24 | Phase 3 | Double blind | USA, Czech Republic, Mexico, Poland, Puerto Rico, Romania, Russia, UK, India, Turkey | 67 | AstraZeneca and Bristol-Myers Squibb |
| MB102030[28] | 48 | Phase 3 | Double blind | Argentina, Canada, India, Mexico, Peru, Philippines, Taiwan,USA | 105 | AstraZeneca |
| Robdard et al[44] | 26 | Phase 3 | Double blind | International (five countries) | 47 | Janssen R&D |
| Strojek et al[45] | 48 | Phase 3 | Double blind | International | 84 | AstraZeneca and Bristol-Myers Squibb |
| Study 05[25] | 24 | Phase 3 | Double blind | Canada, Czech Republic, Germany, Poland, Slovakia, Spain | 46 | AstraZeneca |

Continued

| Trial ID | Treatment duration, weeks | Trial Phase | Blinding | Country (s) | Study sites, n | Sponsor (s) |
|---|---|---|---|---|---|---|
| SUSTAIN 2[33] | 56 | Phase 3 | Double blind | Argentina, Bulgaria, Czech Republic, Hong Kong, Hungary, India, Japan, Mexico, Norway, Portugal, Romania, Russia, South Africa, Spain, Sweden, Thailand, Turkey, Ukraine | 18 | Novo Nordisk |
| SUSTAIN 3[62] | 56 | Phase 3 | Open label | Argentina, Croatia, Finland, France, Germany, Greece, Italy, Netherlands, Serbia, Switzerland, UK, USA | 141 | Novo Nordisk |
| SUSTAIN 4[34] | 30 | Phase 3 | Open label | International (14 countries) | – | Novo Nordisk |
| SUSTAIN 7[63] | 40 | Phase 3 | Open label | Bulgaria, Croatia, Finland, Germany, Greece, Hong Kong, India, Ireland, Latvia, Lithuania, Portugal, Romania, Slovakia, Spain, UK, USA | 198 | Novo Nordisk |

**Table 1** Continued

–, not applicable.

MD of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from −1.35 kg for canagliflozin 300 mg (95% CrI: −1.89 to −0.79 kg) to −2.48 kg for dapagliflozin 5 mg (95% CrI: −3.13 to −1.82 kg) (table 5).

With the 0.5 mg dose of once-weekly semaglutide, the weight loss was comparable to the highest doses of canagliflozin (300 mg) and empagliflozin (25 mg), while the reductions were statistically significant in favour of once-weekly semaglutide 0.5 mg when compared with canagliflozin 100 mg, empagliflozin 10 mg and all doses of dapagliflozin (table 5). The results from the surface under the cumulative ranking curve demonstrated a SUCRA score of 1 for once-weekly semaglutide 1.0 mg indicating that it was ranked as the best treatment with highest certainty.

### Change in SBP

Seventeen trials including 9541 patients were included in NMA for change from baseline in SBP.[19–21 26–28 30 33–36 38 39 42–45] The DIC difference between the fixed-effect and random-effect models was less than three. The fixed-effect model was chosen (DIC: 71.12) for base-case analysis because the majority of the connections in this network were supported by one or two trials and a random-effect model is not feasible in such cases. Once-weekly semaglutide performed better than all SGLT-2is in reducing SBP, although with only the results of once-weekly semaglutide 1.0 mg versus dapagliflozin 5 mg (MD: −3.12 mm Hg; 95% CrI: −5.64 to −0.60 mm Hg) and empagliflozin 10 mg (MD: −2.45 mm Hg; 95% CrI: −4.75 to −0.14 mm Hg) being statistically significant (table 5).

While exploring for between trial differences in patient characteristics, introducing covariate adjustments based on the number of prior OAD failures at baseline via metaregression yielded a better fitting model with lower DIC (67.92) compared with the base case (71.32). When adjusting for prior number of OADs received at baseline, the results were similar between once-weekly semaglutide and the SGLT-2i except for comparison of once-weekly semaglutide 1.0 mg with respect to empagliflozin 10 mg (MD: −2.26 mm Hg; 95% CrI: −4.56 to 0.04 mm Hg), where the results were not statistically significant anymore (see online supplementary appendix). Once-weekly semaglutide 1.0 mg achieved a SUCRA score of 0.96 which suggests that it has a 96% probability of being ranked as the best treatment compared with all other interventions.

### Change in FPG

Twenty-one trials including 11 790 patients were included in the NMA for change from baseline in FPG.[19–21 25–28 32–45] The DIC difference between the fixed-effect and random-effect models was less than three. The fixed-effect model was chosen (DIC: 93.09) because the majority of the connections in this network were supported by one or two trials, and a random-effect model is not feasible in such cases.

**Table 2** Baseline patient characteristics of trials in the evidence base

| Trial ID | Treatment | Females, n (%) | Weight (kg) Mean (SD) | BMI (kg/m²) Mean (SD) | Disease duration (years) Mean (SD) | HbA1c (%) Mean (SD) | Fasting plasma glucose (mmol/L) Mean (SD) | Postprandial glucose (mmol/L) Mean (SD) | Systolic blood pressure (mm Hg) Mean (SD) |
|---|---|---|---|---|---|---|---|---|---|
| Bailey et al[35] | Placebo | 61 (45.0) | 87.7 (19.2) | 31.8 (5.3) | 5.8 (5.1) | 8.11 (1.0) | 9.19 (2.6) | – | 127.7 (14.6) |
| | Dapagliflozin 5 mg | 68 (50.0) | 84.7 (16.3) | 31.4 (5.0) | 6.4 (5.8) | 8.17 (1.0) | 9.39 (2.7) | – | 126.9 (14.3) |
| | Dapagliflozin 10 mg | 58 (43.0) | 86.3 (17.5) | 31.2 (5.1) | 6.1 (5.4) | 7.92 (0.8) | 8.66 (2.2) | – | 126.0 (15.9) |
| Bolinder et al[32] | Placebo | 40 (44.0) | 90.9 (13.7) | 31.7 (3.9) | 5.5 (5.3) | 7.16 (0.5) | 8.3 (1.4)* | – | 133.3 |
| | Dapagliflozin 10 mg | 40 (44.9) | 92.1 (14.1) | 32.1 (3.9) | 6.0 (4.5) | 7.19 (0.4) | 8.21 (1.4)* | – | 135.9 |
| CANTATA-D[36] | Placebo | 89 (48.6) | 86.6 (22.4) | 31.1 (6.1) | 6.8 (5.3) | 8 (0.9) | 9.1 (2.1) | 13.8 (3.6) | 128 (12.7) |
| | Sitagliptin 100 mg | 194 (53.0) | 87.7 (21.6) | 32 (6.1) | 6.8 (5.2) | 7.9 (0.9) | 9.4 (2.3) | 14.2 (3.6) | 128 (13.5) |
| | Canagliflozin 100 mg | 194 (52.7) | 88.7 (22.2) | 32.4 (6.4) | 6.7 (5.4) | 7.9 (0.9) | 9.3 (2.3) | 14.3 (3.8) | 128 (12.7) |
| | Canagliflozin 300 mg | 202 (55.0) | 85.4 (20.9) | 31.4 (6.3) | 7.1 (5.4) | 7.9 (0.9) | 9.6 (2.5) | 14.5 (4.1) | 128.7 (13) |
| CANTATA-D2[37] | Sitagliptin 100 mg | 163 (43.1) | 89.1 (23.2) | 31.7 (6.9) | 9.7 (6.3) | 8.1 (0.9) | 9.2 (2.5) | 16 (5.1) | 130.1 (14) |
| | Canagliflozin 300 mg | 170 (45.1) | 87.4 (23.2) | 31.5 (6.9) | 9.4 (6.1) | 8.1 (0.9) | 9.4 (2.6) | 16.4 (5.1) | 131.2 (13.2) |
| CANTATA-MP[38] | Placebo | 39 (33.9) | 93.8 (22.4) | 32.5 (6.4) | 10.1 (6.6) | 8 (1) | 9.1 (2.2) | – | 128.2 (12.3) |
| | Canagliflozin 100 mg | 36 (31.9) | 94.2 (22.2) | 32.3 (6.2) | 10.5 (6.6) | 8 (0.9) | 9.4 (2.2) | – | 126.4 (12.3) |
| | Canagliflozin 300 mg | 51 (44.7) | 94.4 (25.9) | 32.8 (7.7) | 11 (7.6) | 7.9 (0.9) | 9.1 (2.3) | – | 126.7 (12) |
| CANTATA-MSU[39] | Placebo | 80 (51.3) | 91.2 (22.6) | 32.7 (6.8) | 10.3 (6.7) | 8.1 (0.9) | 9.4 (2.2) | 15.5 (3.4) | 130.1 (13.7) |
| | Canagliflozin 100 mg | 81 (51.6) | 93.8 (22.6) | 33.3 (6.3) | 9 (5.7) | 8.1 (0.9) | 9.6 (2.3) | 16.5 (3.7) | 130.4 (13.5) |
| | Canagliflozin 300 mg | 69 (44.2) | 93.5 (22) | 33.2 (6.3) | 9.4 (6.4) | 8.1 (0.9) | 9.3 (2.1) | 16 (4) | 130.8 (12.8) |
| CANTATA-SU[40] | Canagliflozin 100 mg | 231 (48.0) | 86.9 (20.1) | 31 (5.3) | 6.5 (5.5) | 7.8 (0.8) | 9.2 (2.1) | – | 130 (12.4) |
| | Canagliflozin 300 mg | 244 (50.0) | 86.6 (19.5) | 31.2 (5.4) | 6.7 (5.5) | 7.8 (0.8) | 9.1 (2) | – | 130 (13.8) |
| DeFronzo et al[41] | Empagliflozin 10 mg | 59 (43.1) | 86.1 (18.2) | 30.9 (5.4) | – | 8 (0.9) | 9 (1.9)* | – | 131.6 (14.4) |
| | Empagliflozin 25 mg | 75 (53.6) | 87.7 (17.6) | 31.8 (5.3) | – | 8.02 (0.8) | 8.9 (2.1)* | – | 129.2 (13.4) |
| DURATION-8[42] | Exenatide 2 mg | 111 (48.9) | 89.8 (20.2) | 32 (5.9) | 7.4 (5.5) | 9.3 (1.1) | 10.8 (2.4)* | 14.9 (3.7)* | 129.1 (13.1) |
| | Dapagliflozin 10 mg | 120 (52.2) | 91.1 (19.7) | 33 (6.1) | 7.1 (5.5) | 9.3 (1) | 10.9 (2.3)* | 14.6 (3.4)* | 130 (12.9) |
| EMPA-REG MET[20] and EMPA-REG EXTEND MET[29] | Placebo | 91 (44.0) | 79.7 (18.6) | 28.7 (5.2) | – | 7.9 (0.9) | 8.7 (1.8) | – | 128.6 (14.7) |
| | Empagliflozin 10 mg | 92 (42.4) | 81.6 (18.5) | 29.1 (5.5) | – | 7.94 (0.8) | 8.6 (2) | – | 129.6 (14.1) |
| | Empagliflozin 25 mg | 93 (43.7) | 82.2 (19.3) | 29.7 (5.7) | – | 7.86 (0.9) | 8.3 (1.7) | – | 130 (15.1) |
| EMPA-REG METSU[19] and EMPA-REG EXTEND METSU[29] | Placebo | 113 (50.0) | 76.2 (16.9) | 27.9 (4.9) | – | 8.15 (0.8) | 8.42 (2) | – | 128.8 (14.3) |
| | Empagliflozin 10 mg | 112 (50.0) | 77.1 (18.3) | 28.3 (5.4) | – | 8.07 (0.8) | 8.38 (1.8) | – | 128.7 (13.9) |
| | Empagliflozin 25 mg | 102 (47.0) | 77.5 (18.8) | 28.3 (5.5) | – | 8.1 (0.8) | 8.69 (1.9) | – | 129.3 (14.2) |
| EMPA-REG PIO[21] and EMPA-REG EXTEND PIO[61] | Placebo | 92 (55.8) | 78.1 (20.1) | 29.3 (5.4) | – | 8.2 (0.9) | 8.4 (2.2) | – | 125.7 (12.1) |
| | Empagliflozin 10 mg | 82 (49.7) | 78 (19.1) | 29.2 (5.6) | – | 8.1 (0.9) | 8.4 (2.1) | – | 126.5 (13.7) |
| | Empagliflozin 25 mg | 83 (49.4) | 78.9 (19.9) | 29.1 (5.5) | – | 8.1 (0.8) | 8.4 (2.1) | – | 125.9 (13.9) |
| Mathieu et al[43] | Placebo | 84 (52.5) | – | 32.2 (5.3) | 8 (6.6) | 8.17 (1) | 9.8 (2.6)* | 13.5 (3.2)* | – |
| | Dapagliflozin 10 mg | 90 (56.3) | – | 31.2 (4.7) | 7.2 (5.7) | 8.24 (1) | 9.9 (2.7)* | 13.4 (3.4)* | – |

Continued

**Table 2** Continued

| Trial ID | Treatment | Females, n (%) | Weight (kg) Mean (SD) | BMI (kg/m²) Mean (SD) | Disease duration (years) Mean (SD) | HbA1c (%) Mean (SD) | Fasting plasma glucose (mmol/L) Mean (SD) | Postprandial glucose (mmol/L) Mean (SD) | Systolic blood pressure (mm Hg) Mean (SD) |
|---|---|---|---|---|---|---|---|---|---|
| MB102030[28] | Placebo | 68 (48.9) | 86.4 (21.3) | – | 5.07 (5) | 8.34 (1) | 8.92 (2.6) | 16.3 (4.5) | – |
| | Dapagliflozin 10 mg | 81 (57.9) | 84.8 (22.2) | – | 5.75 (6.4) | 8.37 (1) | 9.15 (2.6) | 17.1 (5.2) | – |
| | Dapagliflozin 5 mg | 63 (44.7) | 87.8 (20.7) | – | 5.64 (5.4) | 8.4 (1) | 9.36 (2.9) | 15.8 (5.5) | – |
| Robdard et al[44] | Canagliflozin 100 mg | 51 (48.1) | 94.1 (21.8) | 32.3 (5.8) | 9.8 (5.4) | 8.5 (0.9) | 10.3 (2.6) | – | – |
| | Placebo | 41 (38.3) | 90 (19.3) | 31.7 (5.5) | 10.1 (5.9) | 8.4 (0.8) | 10 (2.1) | – | – |
| Strojek et al[45] | Placebo | 74 (51.0) | 80.94 (–) | 29.74 (4.6) | 7.4 (5.7) | 8.15 (0.7) | 9.58 (2.1) | 8.73 (–) | 133.3 (–) |
| | Dapagliflozin 5 mg | 71 (50.0) | 81 (–) | 29.84 (5.2) | 7.4 (5.7) | 8.12 (0.8) | 9.68 (2.1) | 8.8 (–) | 130.9 (–) |
| | Dapagliflozin 10 mg | 85 (56.3) | 80.56 (–) | 29.75 (5.6) | 7.2 (5.5) | 8.07 (0.8) | 9.55 (2) | 7.79 (–) | 132.4 (–) |
| Study 05[25] | Placebo | 48 (44.4) | 90.1 (16.2) | 32 (4.6) | 9.6 (6.2) | 8.24 (0.9) | 10.02 (2.4) | – | – |
| | Dapagliflozin 10 mg | 62 (57.4) | 88.6 (17.6) | 31.9 (4.8) | 9.3 (6.5) | 8.08 (0.9) | 9.29 (2.4) | – | – |
| SUSTAIN 2[33] | Semaglutide 0.5 mg | 202 (49.4) | 89.93 (20.4) | 32.43 (6.2) | 6.44 (4.7) | 8.01 (0.9) | 9.3 (2.4)* | – | 132.73 (16.1) |
| | Semaglutide 1.0 mg | 204 (49.9) | 89.21 (20.7) | 32.5 (6.6) | 6.7 (5.6) | 8.04 (0.9) | 9.3 (2.2)* | – | 132.56 (13.9) |
| | Sitagliptin 100 mg | 199 (48.9) | 89.29 (19.7) | 32.45 (5.8) | 6.6 (5.1) | 8.17 (0.9) | 9.6 (2.2)* | – | 132.66 (14.6) |
| SUSTAIN 3[62] | Semaglutide 1.0 mg | 185 (45.8) | 96.21 (22.5) | 33.97 (7.2) | 9.02 (6) | 8.36 (1) | 10.6 (2.7)* | – | 133.35 (14.9) |
| | Exenatide 2 mg | 177 (43.7) | 95.37 (20.5) | 33.57 (6.2) | 9.4 (6.7) | 8.33 (1) | 10.4 (2.7)* | – | 133.66 (14.2) |
| SUSTAIN 4[34] | Semaglutide 0.5 mg | 165 (45.6) | 93.73 (21.4) | 33.11 (6.4) | 7.77 (5.1) | 8.13 (0.8) | 9.56 (2.8) | – | 131.57 (14.1) |
| | Semaglutide 1.0 mg | 178 (49.4) | 94 (22.5) | 32.96 (6.5) | 9.34 (7.2) | 8.25 (0.9) | 9.95 (3) | – | 132.21 (16.1) |
| SUSTAIN 7[63] | Semaglutide 0.5 mg | 132 (43.9) | 96.4 (24.4) | 33.7 (7.1) | 7.7 (5.9) | 8.3 (1) | 9.8 (2.5) | – | 134 (14.8) |
| | Semaglutide 1.0 mg | 138 (46.0) | 95.5 (20.9) | 33.6 (6.5) | 7.3 (5.7) | 8.2 (0.9) | 9.8 (2.6) | – | 133 (14.5) |

*Converted from mg/dL to mmol/L.

**Table 3** Risk of bias assessment of included trials

| Trial ID | Was randomisation carried out appropriately? | Was concealment of treatment allocation adequate? | Were the groups similar at the outset of the study in terms of prognostic factors? | Were the care providers, participants and outcome assessors blind to treatment allocation? | Were there any unexpected imbalances in drop-outs between groups? | Is there any evidence to suggest that the authors measured more outcomes than they reported? | Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Other sources of bias |
|---|---|---|---|---|---|---|---|---|
| Bailey et al[35] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| Bolinder et al[32] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| CANTATA-D[36] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| CANTATA-D2[37] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| CANTATA-MP[38] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| CANTATA-MSU[39] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| CANTATA-SU[40] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| DeFronzo et al[41] | Yes | Not clear | Yes | Yes | No | No | Yes | Yes |
| DURATION-8[42] | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| EMPA-REG MET[20] | Yes | Yes | Yes | Yes | No | No | No | Yes |
| EMPA-REG EXTEND MET[29] | Yes | Yes | Yes | Yes | No | Yes | No | Yes |
| EMPA-REG METSU[19] | Yes | Not clear | Yes | Yes | No | No | Yes | Yes |
| EMPA-REG EXTEND METSU[29] | Yes | Not clear | Yes | Yes | No | No | Yes | Yes |
| EMPA-REG PIO[21] | Yes | Yes | Yes | Yes | No | Yes | No | Yes |
| EMPA-REG EXTEND PIO[61] | Yes | Yes | Yes | Yes | No | Yes | No | Yes |
| Mathieu et al[43] | Yes | Yes | Yes | Yes | No | Yes | No | Yes |
| MB102030[64] | Not clear | Not clear | Yes | Yes | No | No | Not clear | Yes |
| Robdard et al[65] | Yes | Yes | Yes | Yes | Yes | No | No | Yes |
| Strojek et al[45] | Yes | Yes | Yes | Yes | No | No | No | Yes |
| Study 05[66] | Yes | Yes | Yes | Yes | Not clear | No | Yes | Yes |
| SUSTAIN 2[67] | Yes | Yes | Yes | Yes | No | No | No | Yes |
| SUSTAIN 3[62] | Yes | No | Yes | No | No | No | No | Yes |
| SUSTAIN 4[34] | Yes | No | Yes | No | No | No | No | Yes |
| SUSTAIN 7[67] | Yes | No | Yes | No | No | No | No | Yes |

The high degree of 'Yes' status for the Other sources of bias are due to industry sponsoring. In modern pharmacological research, randomised controlled trials are typically industry sponsored. Nonetheless, there have been studies in the past that have indicated a tendency for higher effect sizes to be reported in such trials. As such, these have been identified as unclear with respect to risk of bias.

Once-weekly semaglutide performed better than all SGLT-2is; there was strong evidence of improved FPG relative to SGLT-2is for both doses of once-weekly semaglutide. Specifically, the MD of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from −0.41 mmol/L for canagliflozin 300 mg (95% CrI: −0.72 to −0.10 mmol/L) to −1.37 mmol/L for dapagliflozin 5 mg (95% CrI: −1.76 to −0.97 mmol/L) (table 5). Once-weekly semaglutide 1.0 mg achieved a full probability of being ranked as the best treatment as evident from the SUCRA score of 1, which was consistent with most other efficacy outcomes.

### Sensitivity analyses and metaregressions

Sensitivity analyses were conducted by: (i) removing three trials having a population composed of >40% Asian patients[19–21]; and (ii) removing one trial with high cardiovascular risk.[25] The results of these sensitivity analyses showed that whether or not Asian populations were

**Table 4** Relative efficacy with 95% credible intervals comparing HbA$_{1c}$ (%) in once-weekly semaglutide versus SGLT-2is

| | Mean difference for HbA$_{1c}$ (%) random-effect NMA | | | OR of patients achieving HbA$_{1c}$ <7.0% from fixed-effect NMA | | |
|---|---|---|---|---|---|---|
| | Placebo | Once-weekly semaglutide 0.5mg | Once-weekly semaglutide 1.0mg | Placebo | Once-weekly semaglutide 0.5mg | Once-weekly semaglutide 1.0mg |
| Placebo | – | −1.12 (−1.35 to −0.89) | −1.38 (−1.59 to −1.16) | – | 9.45 (6.57 to 13.52) | 12.80 (9.05 to 18.11) |
| Once-weekly semaglutide 0.5mg | 1.12 (0.89 to 1.35) | – | −0.26 (−0.38 to −0.13) | 0.11 (0.07 to 0.15) | – | 1.35 (1.09 to 1.68) |
| Once-weekly semaglutide 1.0mg | 1.38 (1.16 to 1.59) | 0.26 (0.13 to 0.38) | – | 0.08 (0.06 to 0.11) | 0.74 (0.60 to 0.92) | – |
| Canagliflozin 100mg once daily | 0.67 (0.55 to 0.80) | −0.45 (−0.68 to −0.21) | −0.71 (−0.92 to −0.48) | 0.43 (0.34 to 0.55) | 4.07 (2.86 to 5.83) | 5.52 (3.91 to 7.81) |
| Canagliflozin 300mg once daily | 0.82 (0.69 to 0.95) | −0.30 (−0.52 to −0.07) | −0.56 (−0.76 to −0.33) | 0.25 (0.20 to 0.32) | 2.38 (1.66 to 3.41) | 3.22 (2.27 to 4.56) |
| Dapagliflozin 5mg once daily | 0.43 (0.29 to 0.57) | −0.70 (−0.96 to −0.43) | −0.95 (−1.20 to −0.69) | 0.40 (0.27 to 0.57) | 3.74 (2.33 to 6.08) | 5.08 (3.21 to 8.09) |
| Dapagliflozin 10mg once daily | 0.58 (0.48 to 0.68) | −0.55 (−0.78 to −0.29) | −0.80 (−1.02 to −0.57) | 0.29 (0.22 to 0.37) | 2.70 (1.83 to 4.02) | 3.66 (2.53 to 5.30) |
| Empagliflozin 10mg once daily | 0.59 (0.45 to 0.71) | −0.53 (−0.80 to −0.27) | −0.79 (−1.04 to −0.53) | 0.27 (0.19 to 0.37) | 2.53 (1.57 to 4.09) | 3.43 (2.13 to 5.49) |
| Empagliflozin 25mg once daily | 0.61 (0.48 to 0.74) | −0.51 (−0.78 to −0.25) | −0.77 (−1.02 to −0.51) | 0.22 (0.16 to 0.30) | 2.06 (1.27 to 3.39) | 2.80 (1.74 to 4.52) |

Each cell represents the comparison (mean difference and 95% CrI) of the column treatment versus the row treatment. All bolded values are statistically meaningful at the 0.05 significance level.
NMA, network meta-analysis; SGLT-2is, sodium-glucose cotransporter 2 inhibitors.

**Table 5** Mean differences of change from baseline with 95% credible intervals comparing the relative efficacy of once-weekly semaglutide versus SGLT-2is using fixed-effect NMA

| | Mean difference for weight (kg) | | | Mean difference for SBP (mm HG) | | | Mean difference for FPG (mmol/L) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo | Once-weekly semaglutide 0.5mg | Once-weekly semaglutide 1.0mg | Placebo | Once-weekly semaglutide 0.5mg | Once-weekly semaglutide 1.0mg | Placebo | Once-weekly semaglutide 0.5mg | Once-weekly semaglutide 1.0mg |
| Placebo | – | −2.62 (−3.21 to −2.03) | −3.98 (−4.54 to −3.43) | – | −5.12 (−7.20 to −3.07) | −5.94 (−7.89 to −4.02) | – | −1.96 (−2.31 to −1.62) | −2.40 (−2.72 to −2.07) |
| Once-weekly semaglutide 0.5mg | 2.62 (2.03 to 3.21) | – | −1.36 (−1.71 to −1.02) | 5.12 (3.07 to 7.20) | – | −0.83 (−2.04 to 0.39) | 1.96 (1.62 to 2.31) | – | −0.43 (−0.63 to −0.24) |
| Once-weekly semaglutide 1.0mg | 3.98 (3.43 to 4.54) | 1.36 (1.02 to 1.71) | – | 5.94 (4.02 to 7.89) | 0.83 (−0.39 to 2.04) | – | 2.40 (2.07 to 2.72) | 0.43 (0.24 to 0.63) | – |
| Canagliflozin 100mg once daily | 2.00 (1.66 to 2.34) | −0.62 (−1.22 to −0.01) | −1.98 (−2.56 to −1.40) | 4.31 (3.07 to 5.56) | −0.82 (−2.90 to 1.25) | −1.63 (−3.65 to 0.35) | 1.61 (1.40 to 1.83) | −0.35 (−0.68 to −0.01) | −0.78 (−1.10 to −0.46) |
| Canagliflozin 300mg once daily | 2.64 (2.26 to 3.01) | 0.02 (−0.54 to 0.58) | −1.35 (−1.89 to −0.79) | 4.67 (3.38 to 5.98) | −0.45 (−2.55 to 1.64) | −1.27 (−3.29 to 0.76) | 1.99 (1.76 to 2.21) | 0.03 (−0.30 to 0.35) | −0.41 (−0.72 to −0.10) |
| Dapagliflozin 5mg once daily | 1.51 (1.14 to 1.87) | −1.11 (−1.79 to −0.43) | −2.48 (−3.13 to −1.82) | 2.84 (1.11 to 4.55) | −2.31 (−4.91 to 0.34) | −3.12 (−5.64 to −0.60) | 1.03 (0.79 to 1.27) | −0.93 (−1.35 to −0.52) | −1.37 (−1.76 to −0.97) |
| Dapagliflozin 10mg once daily | 1.82 (1.54 to 2.09) | −0.80 (−1.42 to −0.18) | −2.17 (−2.75 to −1.57) | 4.16 (2.85 to 5.46) | −0.97 (−3.16 to 1.23) | −1.78 (−3.87 to 0.24) | 1.32 (1.15 to 1.49) | −0.64 (−1.01 to −0.28) | −1.08 (−1.42 to −0.73) |
| Empagliflozin 10mg once daily | 1.74 (1.47 to 2.02) | −0.88 (−1.53 to −0.23) | −2.24 (−2.86 to −1.61) | 3.48 (2.30 to 4.71) | −1.64 (−3.99 to 0.75) | −2.45 (−4.75 to −0.14) | 1.50 (1.32 to 1.68) | −0.46 (−0.86 to −0.07) | −0.90 (−1.27 to −0.53) |
| Empagliflozin 25mg once daily | 1.98 (1.71 to 2.26) | −0.63 (−1.29 to 0.01) | −2.00 (−2.62 to −1.38) | 3.77 (2.60 to 4.95) | −1.36 (−3.71 to 1.00) | −2.18 (−4.45 to 0.05) | 1.57 (1.39 to 1.75) | −0.39 (−0.78 to −0.00) | −0.83 (−1.20 to −0.45) |

Each cell represents the comparison (mean difference and 95% CrI) of the column treatment versus the row treatment. All bolded values are statistically meaningful at the 0.05 significance level.
FPG, fasting plasma glucose; NMA, network meta-analysis; SBP, systolic blood pressure; SGLT-2is, sodium-glucose cotransporter 2 inhibitors.

included, or if one trial with high cardiovascular risk was excluded, the effect estimates did not change in significance or direction for any of the outcomes of interest (online supplementary appendix). Similarly, metaregression did not lead to any meaningful change in estimate magnitudes or statistical significance, with the exception of SBP results (as shown above). Finally, safety analyses were not feasible as the safety results for SGLT-2is and semaglutide were reported at separate time points, namely 26 and 52 weeks. As such, safety analyses were not conducted.

## DISCUSSION

Using an SLR and NMA, this study provided evidence in support of improved efficacy using once-weekly semaglutide relative to SGLT-2is licensed in Europe and North America for the treatment of patients with inadequate glycaemic control using 1–2 OADs. The SLR identified a rich evidence base via comprehensive literature searches. Results of the NMA demonstrated that across most efficacy outcomes (HbA$_{1c}$, target HbA1c<7%, weight loss and FPG), once-weekly semaglutide had the highest estimated efficacy. There was very strong evidence that once-weekly semaglutide led to larger decreases in both HbA$_{1c}$ and weight. Specifically, the magnitude of the differences was large and clinically meaningful. With respect to SBP, SGLT-2is were also quite effective relative to placebo and though once-weekly semaglutide had the largest estimated beneficial effect, it could not quite be distinguished statistically from the SGLT-2is. There was also strong evidence of improved FPG relative to SGLT-2is for both doses of once-weekly semaglutide. Once-weekly semaglutide 0.5 mg had the second best estimated relative efficacy for HbA$_{1c}$ and weight.

Approximately 80% of patients with T2D are either overweight or obese, with associated issues for insulin resistance, glycaemic control and cardiovascular risk factors[4]; as a result, therapies which can lead to weight reduction or maintenance are desirable for the prevention of these complications. Although there is no universal standard as to a clinically relevant degree of weight reduction, weight loss above 2.3 kg is associated with improved comorbid outcomes.[47 48] Every intervention included in the NMA was associated with weight reduction; however, only the results for the comparison of once-weekly semaglutide doses and canagliflozin 300 mg to placebo were considered clinically meaningful. These results are consistent with the class-effects of GLP-1 receptor agonists compared with insulin or sulfonylureas.[4] A study conducted by McIntosh et al evaluated second-line treatment after metformin observed an increase in weight for patients treated with sulfonylureas, meglitinides and thiazolidinediones compared with placebo and GLP-1 receptor agonists.[49]

All of the interventions had statistically significant reductions in SBP compared with placebo. A decrease of at least 5 mm Hg in SBP is defined as clinically meaningful

reduction[50];compared with placebo, only once-weekly semaglutide and canagliflozin 300 and 100 mg met this threshold. The results for SGLT-2is being associated with reductions in SBP are consistent with those from previously published meta-analyses.[51–53]

Choosing between treatment options requires a full consideration of the differences between treatments as well as patient preferences. This study has demonstrated that there are important advantages to once-weekly semaglutide relative to SGLT-2is with respect to clinical efficacy. These measures of efficacy include HbA$_{1c}$, FPG and weight, which are both impactful on a number of known comorbidities, such as cardiovascular disease.

The strengths of this study include the use of highly sensitive searches in the peer-reviewed literature; this was supplemented with hand searches of leading diabetes research conferences. The review processes were determined by the predefined eligibility criteria established in the review protocol. Data quality was held at a high standard by the involvement of two independent researchers for the study selection and data extraction phases of the review; any discrepancies were managed by a third reviewer in the event of any disagreement. Additionally, a large number of sensitivity analyses (adjusted and restricted analyses) were conducted, demonstrating the robustness of the analytical results.

This study also has some limitations. The SLR is limited by the use of published data, leading to a risk of publication bias. Some clinical trials do not get published and others are only published in abstract form presenting limited information. The current study included an extensive search of conference abstracts to help mitigate the impact on the SLR results. Another limitation was the reliance on fixed-effect models, which may have underestimated the uncertainty around estimates. The choice of fixed-effect models were in accordance with NICE guidelines; however, for some outcomes network sparseness rather than lack of between study heterogeneity may have driven this choice. Therefore, results should be interpreted with care. Finally, with respect to the SLR, the search and selection process was restricted to trials published in the English language.

There were also several limitations to the analyses. First, while the population of interest was patients with inadequate glycaemic control using 1–2 OADs, a large number of studies only included patients on OAD monotherapy while others only included patients on dual therapy, which may have affected the homogeneity of the population. The pooling of such populations was required to ensure network connectivity, and models adjusting for these differences through metaregression suggest minimal impact from these differences. Second, there was a lack of direct comparisons due to a deficiency of reported comparisons in the literature. This placed a greater weight on the hypothesis of consistency between direct and indirect evidences. Nonetheless, despite longer pathways between the treatments of interest, the analysis still provided strong evidence of higher efficacy for

once-weekly semaglutide and did not hint any evidence of inconsistency. Third, analyses of safety outcomes were not feasible; however, it should be noted that safety concerns are known to be different between these two drugs classes. SGLT-2is are known to have concerns over urinary and genital tract infections, volume depletion, ketoacidosis and thromboembolic events.[54 55] Semaglutide has more concerns with gastrointestinal adverse events, hypoglycaemia, and amylase and lipase increases.[56] Additionally, some studies have found that incretin-based drugs are more effective in Asian patients.[57–59] Therefore, the results of the present NMA may not be extrapolated from European and North American populations directly to Asian populations. However, in the scope of the current study, sensitivity analyses around the proportion of Asian patients included in trials had negligible impact on results. Finally, these analyses only speak to the differences between these treatments with respect to clinical efficacy. Further research, including cost-effectiveness studies, may be informed by the current study estimates of relative efficacy, to assess impact on cost and quality of life. Whereas treatments may be compared on their relative efficacy using network meta-analysis, the long-term modelling of the outcomes for T2D and associated costs and health-related quality of life impact is needed in order to understand the benefits of antidiabetic drugs.[55] Health economic evaluations of these treatments are currently underway, but for the sake of timeliness and interpretability, the current study focuses on clinical outcomes.

Once-weekly semaglutide demonstrated clinically meaningful reductions in $HbA_{1c}$ and body weight in T2D patients inadequately controlled by 1–2 OADs, compared with all SGLT-2is licensed in Europe and North America, and was comparable to them in improving SBP. The evidence supports once-weekly semaglutide as a potential treatment option for patients inadequately controlled by 1–2 OADs. Given the lack of head-to-head evidence, this analysis provides valuable insight into the comparative outcomes of once-weekly semaglutide versus SGLT-2is. Nonetheless, these results do not preclude the need for more head-to-head studies investigating the comparative efficacy and safety of these therapies, as well as the benefits of their combination.[31 60]

**Data sharing statement** All data used for these analyses are publicly available. Given the use of clinical Study Reports, data are not available. For further questions regarding data, please reach out to the corresponding author.

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