BMJ Open

Efficacy and safety of 11 sodium-glucose cotransporter-2 inhibitors at different dosages in type 2 diabetes mellitus patients inadequately controlled with metformin: a Bayesian network meta-analysis

Leqing Xu,[1] Yike Wu,[1] Jiyifan Li,[1] Yanan Ding,[1] Junwei Chow,[1] Longzhou Li,[1] Haiyang Liu,[1] Zihan Wang,[1] Tingting Gong,[1] Yue Li,[2] Guo Ma [1]

To cite: Xu L, Wu Y, Li J, *et al*. Efficacy and safety of 11 sodium-glucose cotransporter-2 inhibitors at different dosages in type 2 diabetes mellitus patients inadequately controlled with metformin: a Bayesian network meta-analysis. *BMJ Open* 2025;**15**:e088687. doi:10.1136/bmjopen-2024-088687

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-088687).

Received 13 May 2024
Accepted 07 February 2025

[1]Fudan University, Shanghai, Shanghai, China
[2]Shanghai Fifth People's Hospital, Fudan University, Shanghai, China

Correspondence to
Dr Guo Ma; mg0328@fudan.edu.cn and Dr Yue Li; liyuely1@126.com

ABSTRACT

Objectives Assess the efficacy and safety profiles of different sodium-glucose cotransporter-2 inhibitors (SGLT2is) as an add-on to metformin in type 2 diabetes mellitus (T2DM) patients.

Design Bayesian network meta-analysis.

Data sources PubMed, Embase, Cochrane Library, Web of Science and ClinicalTrials.gov were searched before 18 December 2024.

Eligibility criteria Randomised controlled trials (RCTs) evaluating T2DM patients taking one of 12 SGLT2is as add-on therapy to metformin. Efficacy outcomes focused on glycated haemoglobin (HbA1c) reduction, fasting plasma glucose (FPG) reduction and weight loss (WL). Safety outcomes included adverse events (AEs), serious AEs (SAEs), hypoglycaemia, urinary tract infections (UTI) and genital infections (GI).

Data extraction and synthesis Two investigators independently extracted data. The quality of the included studies was assessed using the Cochrane Risk of Bias Tool (V.2.0) for RCTs.

Results 23 RCTs involving 9144 patients and 11 SGLT2is were included. Compared with placebo, most SGLT2is reduced HbA1c (mean difference (MD), −0.45~−0.80%), FPG (MD, −0.78~−2.02 mmol/L) and body weight (MD, −0.88~−2.67 kg). Only 10 mg of henagliflozin increased the incidence of AEs, and none of the included interventions increased the risks of SAEs or UTIs. 50 mg of empagliflozin exhibited higher risks of hypoglycaemia. Only 10 mg of empagliflozin increased the risk of GI. According to the surface under the cumulative ranking values, SGLT2is with optimal efficacy and safety were 15 mg of ertugliflozin in HbA1c reduction, 300 mg of canagliflozin in FPG reduction, WL and hypoglycaemia, 400 mg of sotagliflozin in total AEs, 10 mg of ertugliflozin and 150 mg of ipragliflozin in SAEs, 12.5 mg of ipragliflozin in UTI and 1 mg of ertugliflozin in GI.

Conclusions As add-on therapy, SGLT2is demonstrated favourable antidiabetic efficacy and acceptable safety. 300 mg of canagliflozin was the best option among the included interventions considering favourable glucose control and WL. Some novel SGLT2is (eg, henagliflozin) exhibited promising efficacy and safety profiles, but more research is needed to validate the findings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A Bayesian network meta-analysis was conducted to comprehensively evaluate the efficacy and safety of 11 sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus inadequately controlled with metformin.
⇒ Minimal clinically important difference values were used to assess the clinical significance.
⇒ Most comparisons between different SGLT2is were based on indirect evidence due to the limited number of head-to-head studies.
⇒ Some studies included patients from specific regions or particular ethnic groups.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic diseases associated with relative lack of insulin and insulin resistance, characterised by high blood sugar. It can lead to severe complications including cardiovascular disease, chronic kidney disease and stroke. With rapidly increasing cases, T2DM has become a threat to global health. At present, there are approximately 537 million diabetes cases (20–79 years) worldwide, nearly 90% of whom are T2DM.[1 2]

Medication is crucial for glycaemic control. Metformin has been traditionally recommended as first-line therapy for T2DM patients due to its high efficacy, excellent safety and low cost.[3–6] However, T2DM is a progressive disease in many individuals. With the progression of T2DM, single antidiabetic

agents (eg, metformin) are usually insufficient to control blood glucose levels. Patients with T2DM inadequately controlled by metformin often require an additional antidiabetic agent, for example, a sodium-glucose cotransporter-2 inhibitor (SGLT2i).

SGLT2is are novel antidiabetic drugs lowering glucose by blocking the reabsorption of glucose in the proximal convoluted tubule of the kidneys and increasing urinary excretion of glucose. They demonstrate favourable efficacy in improving glycaemic control and reducing body weight (BW) of T2DM patients. SGLT2is are commonly coadministered with metformin in clinical practice. Combining SGLT2is with metformin is the dual first-line combination therapy approach for T2DM recommended by guidelines worldwide due to its efficacy in maintaining blood glucose control and multiple metabolic benefits.[7] In total, 12 SGLT2is have been launched in recent years. However, the efficacy and safety profiles of different SGLT2is as add-on therapy in T2DM patients have not been evaluated and compared, and the evidence-based basis on how to choose SGLT2is for T2DM patients inadequately controlled with metformin is also lacking up to now.

Network meta-analysis (NMA) is a well-established approach for generating quantitative estimates of relative effects among multiple interventions.[8] NMA integrates direct evidence from head-to-head comparisons and indirect evidence (estimated based on available direct evidence) to derive network estimates.[9 10] NMA facilitates the evaluation of comparative effectiveness for interventions that have not been directly compared.[9 10] Different from frequentist NMA, Bayesian NMA uses prior information and is free from the large sample assumption.[11] Although there are seldom important differences in the results of the two approaches, Bayesian NMA demonstrates smaller bias compared with frequentist approaches in scenarios with sparse networks (a large number of interventions but a few direct comparisons) and high heterogeneity.[12 13] Bayesian NMA is more flexible and provides more accurate estimates when data are limited.[14 15] Consequently, Bayesian NMA was employed to evaluate and compare the efficacy and safety of SGLT2is at different dosages for T2DM patients inadequately controlled with metformin. The study results will provide valuable evidence for the rational use of SGLT2is and clinical decision-making of T2DM medication.

MATERIAL AND METHODS

This Bayesian NMA was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension statement for NMA[16] (online supplemental table S1). The protocol was registered in the Prospective Register of Systematic Reviews (registration number: CRD42023471995).

Data sources and search strategy

PubMed, Embase, Cochrane Library, Web of Science and ClinicalTrials.gov databases were systematically searched for relevant studies. The initial search was conducted on 27 September 2023 and updated on 18 December 2024 to ensure the inclusion of the most recent evidence. The keywords for literature search were “type 2 diabetes mellitus, metformin, sodium-glucose cotransporter-2 inhibitor, canagliflozin, dapagliflozin, empagliflozin, luseogliflozin, tofogliflozin, ipragliflozin, ertugliflozin, enavogliflozin, henagliflozin, sotagliflozin, remogliflozin, bexagliflozin”. The detailed search strategy is shown in online supplemental table S2.

Selection criteria

The eligibility of studies was determined according to the participants, interventions, comparators, outcomes and study design (PICOS) criteria. Studies that met all of the following criteria were included: (1) Participants: patients aged over 18 with a diagnosis of T2DM as defined by any criteria, receiving a stable dose of metformin, glycated haemoglobin (HbA1c) ≥6.5%, with no gender restriction. (2) Interventions: one of 12 SGLT2is (ie, canagliflozin, dapagliflozin, empagliflozin, luseogliflozin, tofogliflozin, ipragliflozin, ertugliflozin, enavogliflozin, henagliflozin, sotagliflozin, remogliflozin, bexagliflozin), once daily (qd), as add-on therapy to continuing metformin, without any other antidiabetic drugs. Minimum intervention period of 12 weeks. (3) Comparators: placebo or another SGLT2i combined with metformin in the control group. (4) Outcomes: efficacy outcomes included HbA1c reduction, fasting plasma glucose (FPG) reduction and weight loss (WL). Safety outcomes included the proportion of patients with total adverse events (AEs), serious adverse events (SAEs), hypoglycaemia, urinary tract infections (UTI) and genital infections (GI). (5) Study design: the study type was randomised controlled trials (RCTs). It should be noted that placebo or SGLT2is as interventions and comparators in all the included studies were combined with metformin.

The exclusion criteria were as follows: (1) Incomplete data. (2) Case reports, reviews, conferences, animal studies, retrospective studies, phase I studies and articles not in English. (3) Secondary analyses. (4) Patients diagnosed with type 1 diabetes, aged <18, drug-naïve, with certain complications or comorbidities. (5) When RCTs consisted of a short-term period and an extension period, the extension period would be excluded due to high rate of loss to follow-up and heterogeneity.

After eliminating duplicates of articles with Note Express software and unrelated articles through title and abstract screening, two investigators (LX and YW) read full texts. Only the studies meeting the inclusion criteria were included. Any differences were resolved through discussion or consultation with a third independent investigator (JL).

Data extraction and risk of bias assessment

For each eligible study, two investigators (LX and YW) independently extracted the following data: (1) Study

characteristics (trial name, first author, publication sources and year, registration number, phase of the trial, study sites, study design). (2) Population (sample size, number of patients lost to follow-up, mean age, sex, race, baseline HbA1c, baseline FPG, baseline BW, diagnostic criteria, duration of T2DM, mean dose of metformin). (3) Intervention (name of drugs, dose, cycle). (4) Efficacy outcomes (HbA1c reduction, FPG reduction, WL). (5) Safety outcomes (total AEs, SAEs, hypoglycaemia, UTI, GI). For all the outcomes, data for the modified intention-to-treat (mITT) population were extracted.

The quality of the included studies was assessed using the Cochrane Risk of Bias Tool (V.2.0)[17] for RCTs, which was based on five domains including random sequence generation, allocation concealment, blinding, missing outcome data and selective reporting of outcomes. Each item was rated as 'high risk', 'low risk' or 'unclear'.

Statistical analysis

The efficacy outcomes included HbA1c reduction (%), FPG reduction (mmol/L) and WL (kg). The safety outcomes included incidence (%) of total AEs, SAEs, hypoglycaemia, UTI and GI. The network plots were created with *Stata* (V.17) to visually represent the treatment network. Bayesian NMA was performed using *R* software (V.4.2.3) with package gemtc (V.1.0-2) and JAGS software (V.4.3.2). The mean difference (MD) value was used to calculate continuous variables. The OR value was used to calculate dichotomous variables. If the SD was not reported, it was obtained from the SE and CI for group means according to the Cochrane Handbook for Systematic Reviews of Interventions.[18]

The gemtc package will automatically assign uninformative prior distributions to all parameters in our model, which are commonly used in NMA.[14 19 20] For each outcome measure, a random-effect consistency model was used, and four independent Markov chains were established for running 20 000 burn-ins and 50 000 simulations. The surface under the cumulative ranking (SUCRA) was generated using *R* software with package multinma (V.0.5.1). The SUCRA value was used to estimate the probabilities of being the best for different interventions. Higher SUCRA values suggest better treatments. For continuous outcomes, the clinical significance of the findings was assessed by comparing the NMA results with the minimal clinically important difference (MCID) thresholds, which were extracted from previous studies.[21–23] Specifically, a change in HbA1c of 0.5% is considered a clinically significant change, while a 0.5% HbA1c change is associated with 2.0 mg/dL fasting glucose change in those taking antidiabetic drugs.[21–23] A 5% of WL is generally accepted as clinically significant; 4.4 kg was used as MCID for WL.[23]

For key assumptions of NMA, statistical heterogeneity was assessed with I^2. An I^2 value greater than 50% was defined as significant heterogeneity. We calculated the difference of deviance information criterion (DIC) between the consistent model and inconsistent model to check global consistency. A difference greater than 5 was considered to indicate inconsistency. A node-splitting model was used to detect local inconsistency if there were potentially inconsistent loops in the network. Additionally, Egger's regression test with a funnel plot was performed using *R* software with package netmeta (V.2.8-2) to evaluate publication bias, and p values of less than 0.05 were considered statistically significant. Sensitivity analyses were performed by (1) excluding studies that contributed to high heterogeneity and (2) excluding studies with high risks of bias. Placebo was used as the comparison in sensitivity analyses.

Patient and public involvement

Patients and the public were not involved.

RESULTS

Search results and study characteristics

The flowchart of study selection is shown in figure 1. A total of 2104 records were identified from the databases. After removing the duplicates, reading the abstract, title and full text, 23 studies[24–46] with 32 interventions were included in the Bayesian NMA. Two studies[47 48] considering extension periods were excluded to reduce the risk of bias caused by high rate of loss to follow-up and heterogeneity. A total of 9144 patients were enrolled in the study, receiving treatment regimens including metformin in combination with either placebo or one of the following 11 SGLT2is: dapagliflozin, canagliflozin, ipragliflozin, luseogliflozin, empagliflozin, ertugliflozin, sotagliflozin, henagliflozin, enavogliflozin, bexagliflozin and janagliflozin.

The network plots are shown in figures 2 and 3. The characteristics of all included studies are presented in online supplemental table S3. Among the included studies, 5 (21.7%) RCTs were phase II and 18 (78.3%) RCTs were phase III. The mean number of patients enrolled was 398 (165–918), and the mean age was 56.6 years (52.7–60.7). 4846 (53.0%) patients were male. 18 studies reported the mean duration since diabetes diagnosis, with an average of 6.6 years (4.9–9.1). The baseline mean HbA1c, FPG and BW of patients were 8.08% (7.17–8.62), 9.17 mmol/L (7.84–10.5) and 80.71 kg (68.2–91.7), respectively.

Quality assessments

As shown in figure 4 and online supplemental table S4, no studies had high risks of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. Overall, 11 (47.8%) RCTs had a low risk of bias, 8 (34.8%) RCTs were regarded as unclear risk and 4 (17.4%) RCTs were considered high risk. Among high-risk RCTs, two had incomplete outcome data, and two exhibited high risks of bias for selective reporting.

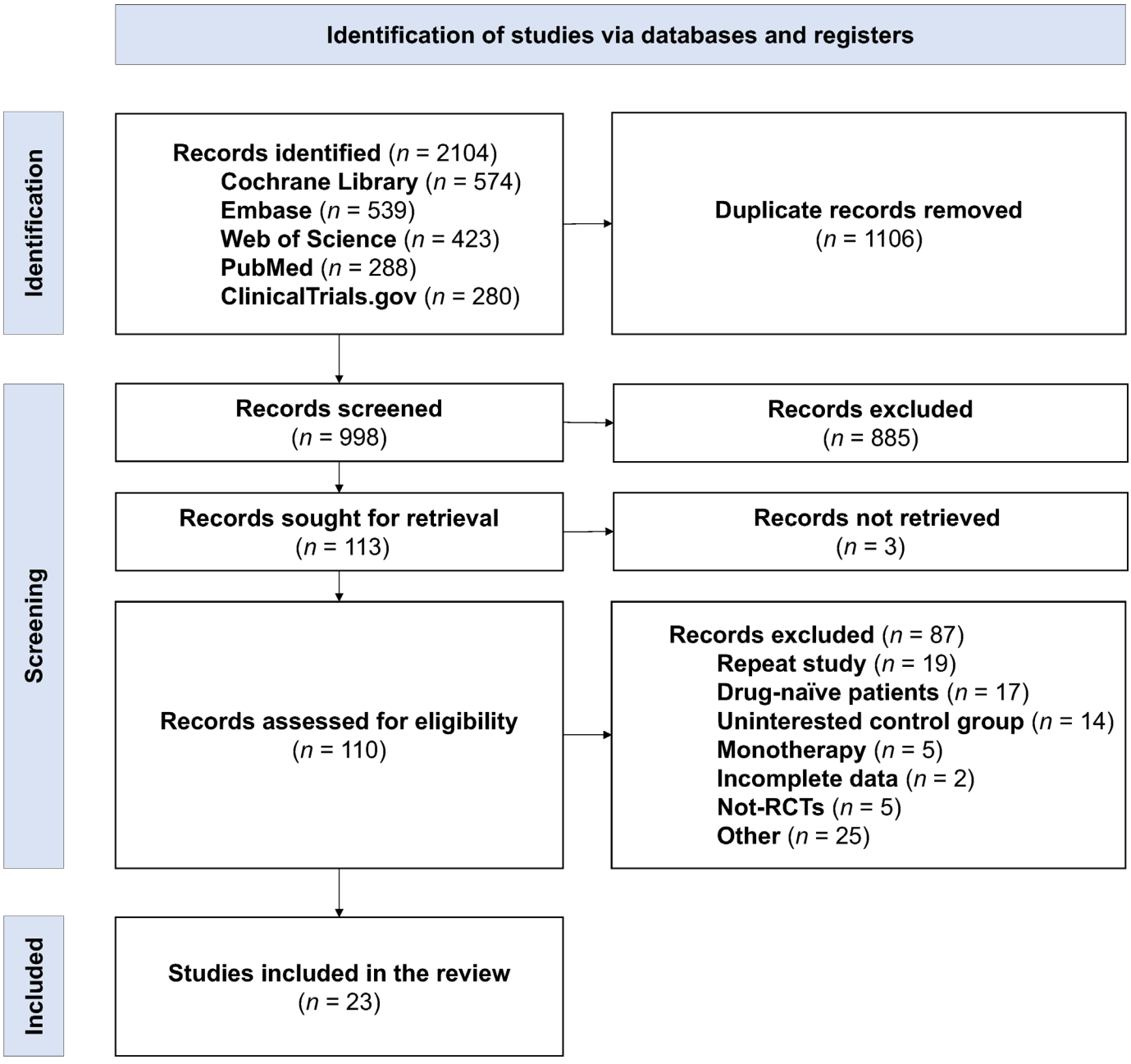


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 flow diagram. The process followed PRISMA guidelines. RCT, randomised controlled trial.

Outcomes of efficacy and safety

For each outcome, the statistical analysis was performed using a random-effect consistency model. League tables are shown in online supplemental table S5. SUCRA curves and values are shown in figures 5 and 6 and online supplemental table S6.

HbA1c reduction

21 studies involving 32 interventions were included in HbA1c reduction analysis (figure 2A). Pairwise comparisons (online supplemental table S5) revealed differences between SGLT2is. Compared with placebo, 22 interventions reduced HbA1c (MD ranging from −0.45 to −0.80%), with several exceeding the MCID of 0.5%. For instance, 10 mg and 5 mg of henagliflozin, 15 mg and 25 mg of ertugliflozin, and 300 mg of canagliflozin showed reductions of −0.80% (−1.26, −0.34), −0.76% (−1.22, −0.30), −0.78% (−1.10, −0.46), −0.74% (−1.22, −0.27) and −0.74% (−1.07, −0.40), respectively. Nine interventions did not show a significant difference, for example, 2.5 mg of dapagliflozin and 1 mg and 5 mg of empagliflozin (MD (95% CI), −0.37 (−0.78, 0.05), −0.16 (−0.58, 0.26) and −0.30 (−0.72, 0.12), respectively). As add-on therapy, some interventions were also superior to 1 mg of empagliflozin in decreasing HbA1c beyond the MCID threshold. These included 300 mg of canagliflozin, 5 mg and 15 mg of ertugliflozin, and 10 mg of henagliflozin (MD (95% CI),

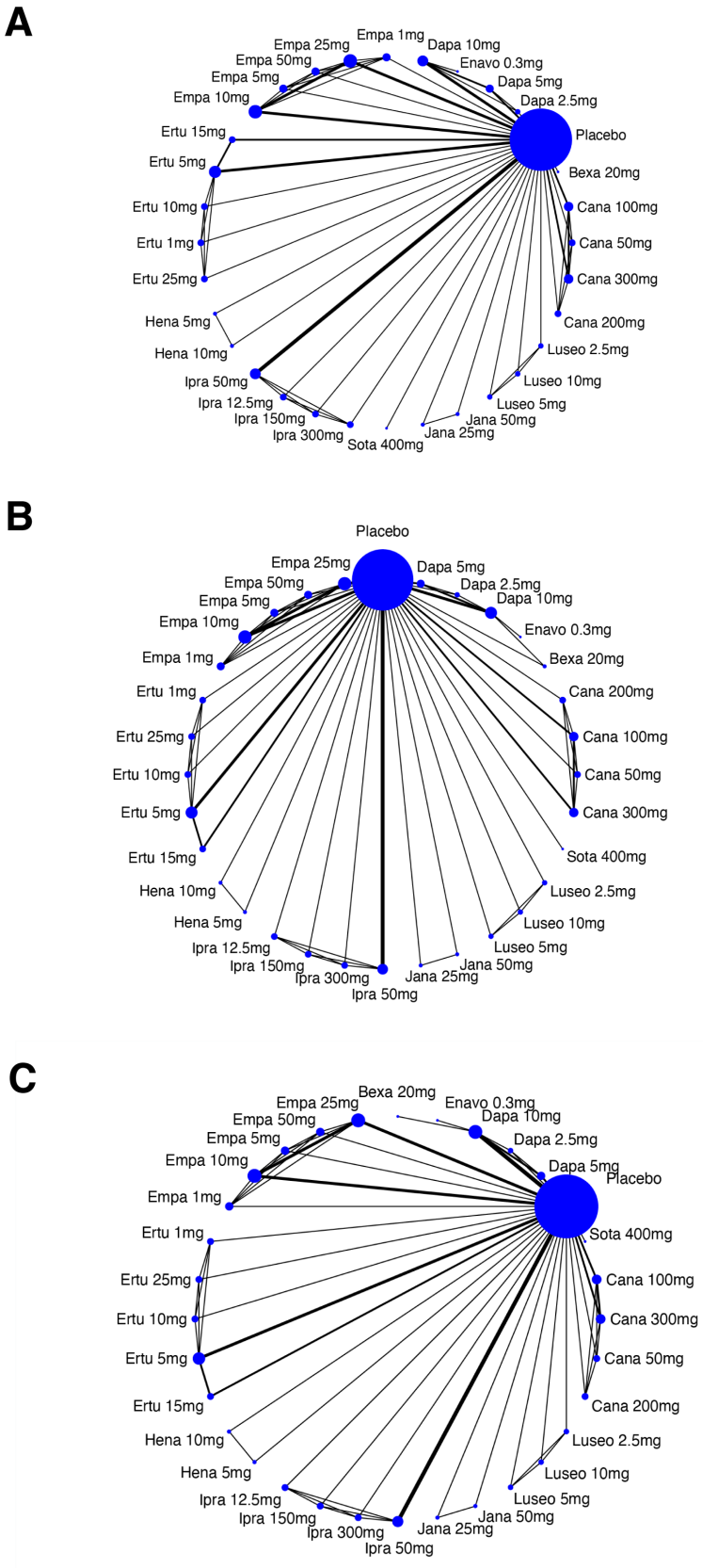


Figure 2 Network plots comparing included interventions for efficacy outcomes. (**A**) HbA1c reduction, (**B**) FPG reduction, (**C**) WL. Each node represented a certain intervention, and the node size represented the sample size. The line width represented the number of studies comparing every pair of treatments. Bexa, bexagliflozin; Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Enavo, enavogliflozin; Ertu, ertugliflozin; Hena, henagliflozin; Ipra, ipragliflozin; Jana, janagliflozin; Luseo, luseogliflozin; Sota, sotagliflozin; WL, weight loss.

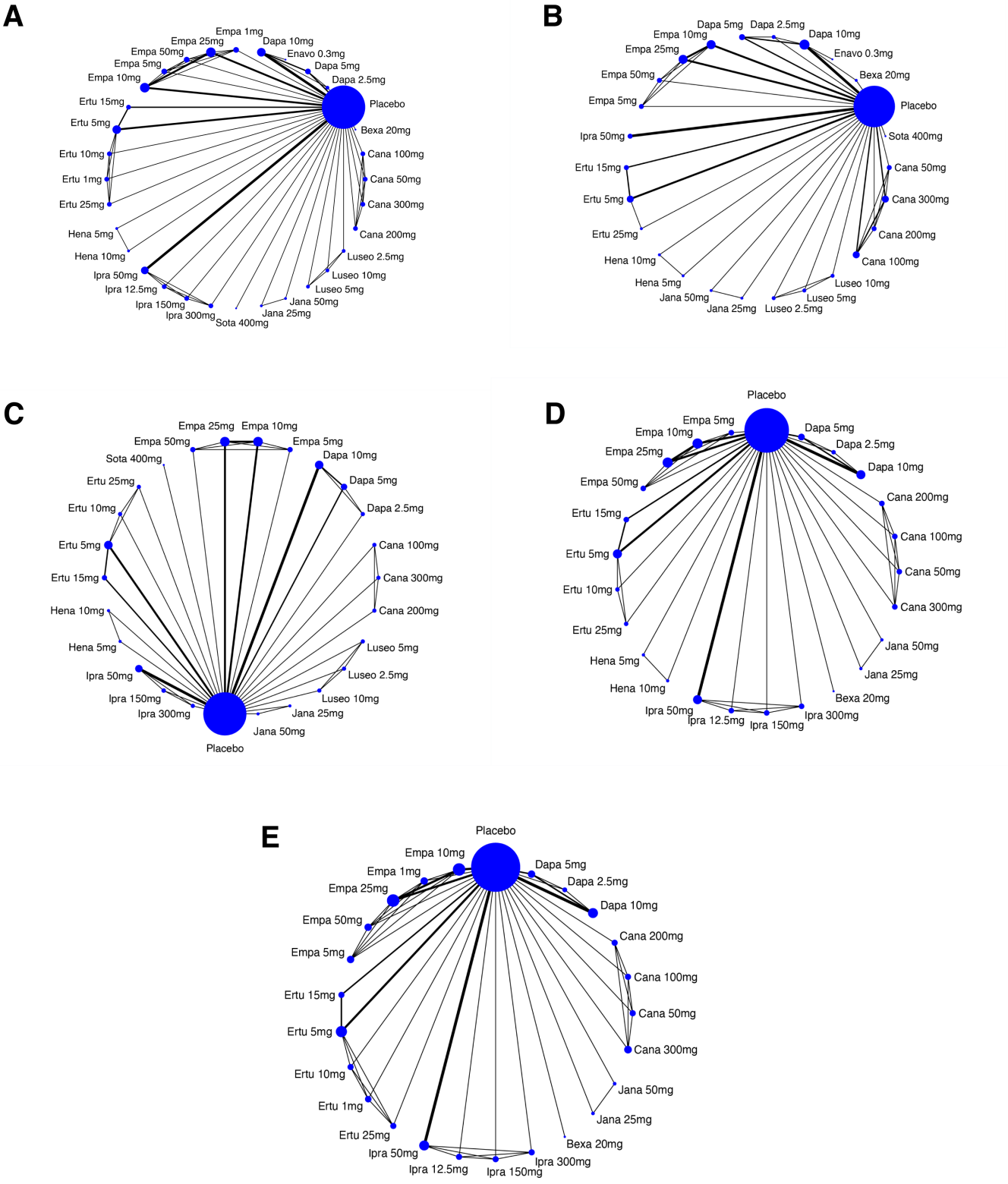
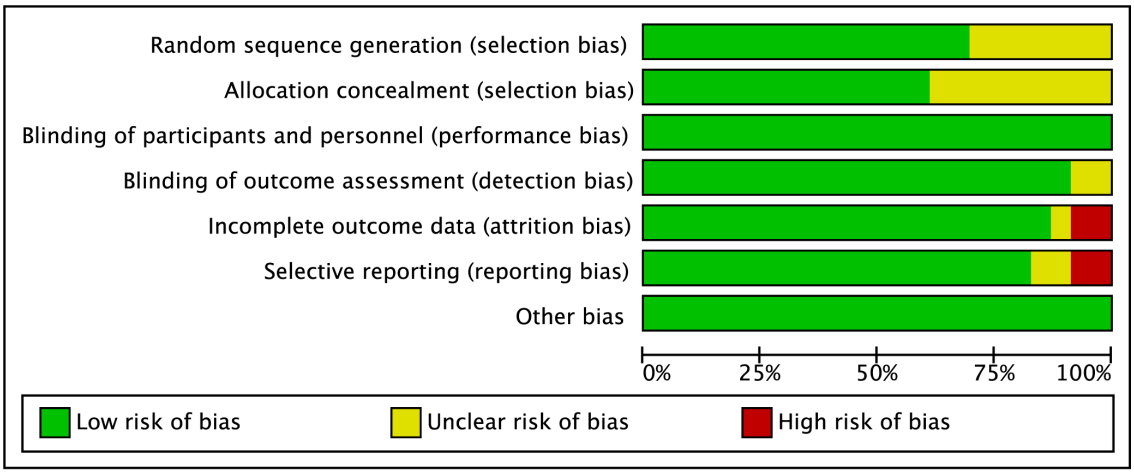


Figure 3 Network plots comparing included interventions for safety outcomes. (**A**) Total adverse events (AEs), (**B**) serious adverse events (SAEs), (**C**) hypoglycaemia, (**D**) urinary tract infections (UTI), (**E**) genital infections (GI). Each node represented a certain intervention, and the node size represented the sample size. The line width represented the number of studies comparing every pair of treatments. Bexa, bexagliflozin; Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Enavo, enavogliflozin; Ertu, ertugliflozin; Hena, henagliflozin; Ipra, ipragliflozin; Jana, janagliflozin; Luseo, luseogliflozin; Sota, sotagliflozin.



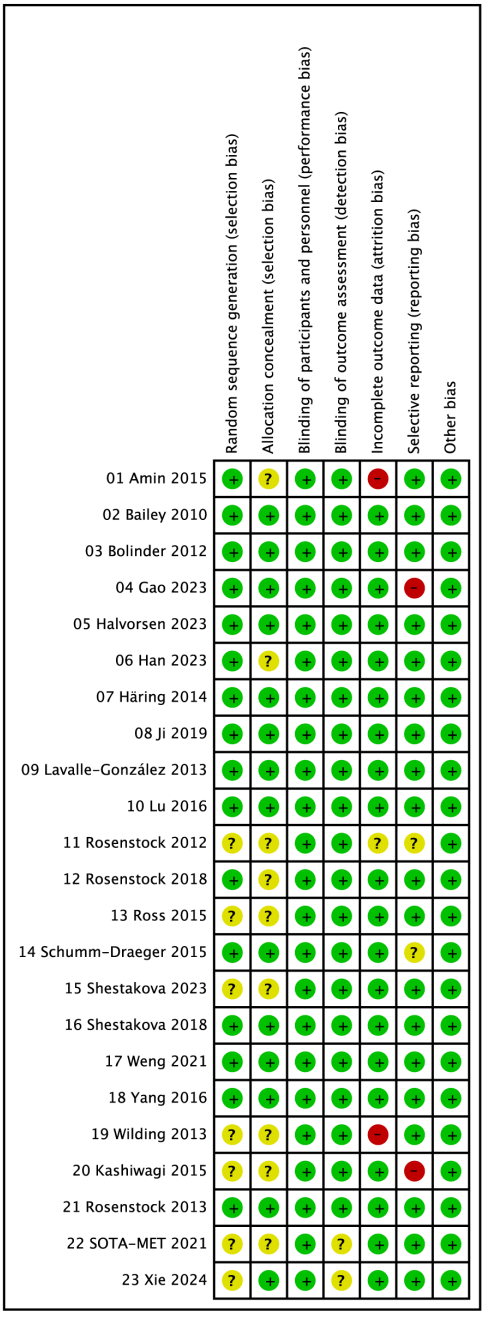


Figure 4 Assessment of risk of bias.

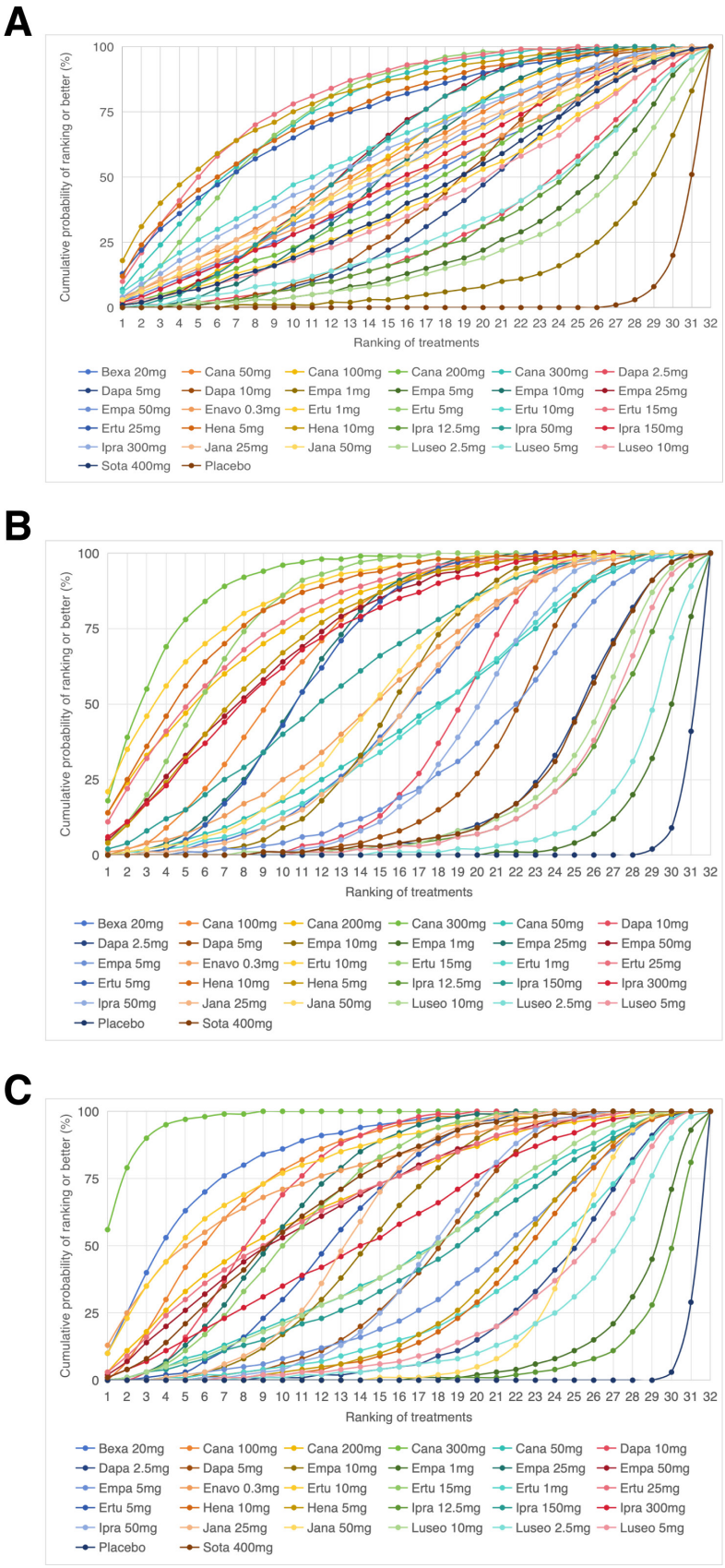


Figure 5 Plots of SUCRA for efficacy outcomes. (**A**) HbA1c reduction, (**B**) FPG reduction, (**C**) WL. The graph shows the cumulative probability of each intervention ranking. Different colours represented different interventions. The interventions with higher SUCRA values had better efficacy. SUCRA, surface under the cumulative ranking curve; Bexa, bexagliflozin; Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Enavo, enavogliflozin; Ertu, ertugliflozin; Hena, henagliflozin; Ipra, ipragliflozin; Jana, janagliflozin; Luseo, luseogliflozin; Sota, sotagliflozin; WL, weight loss.

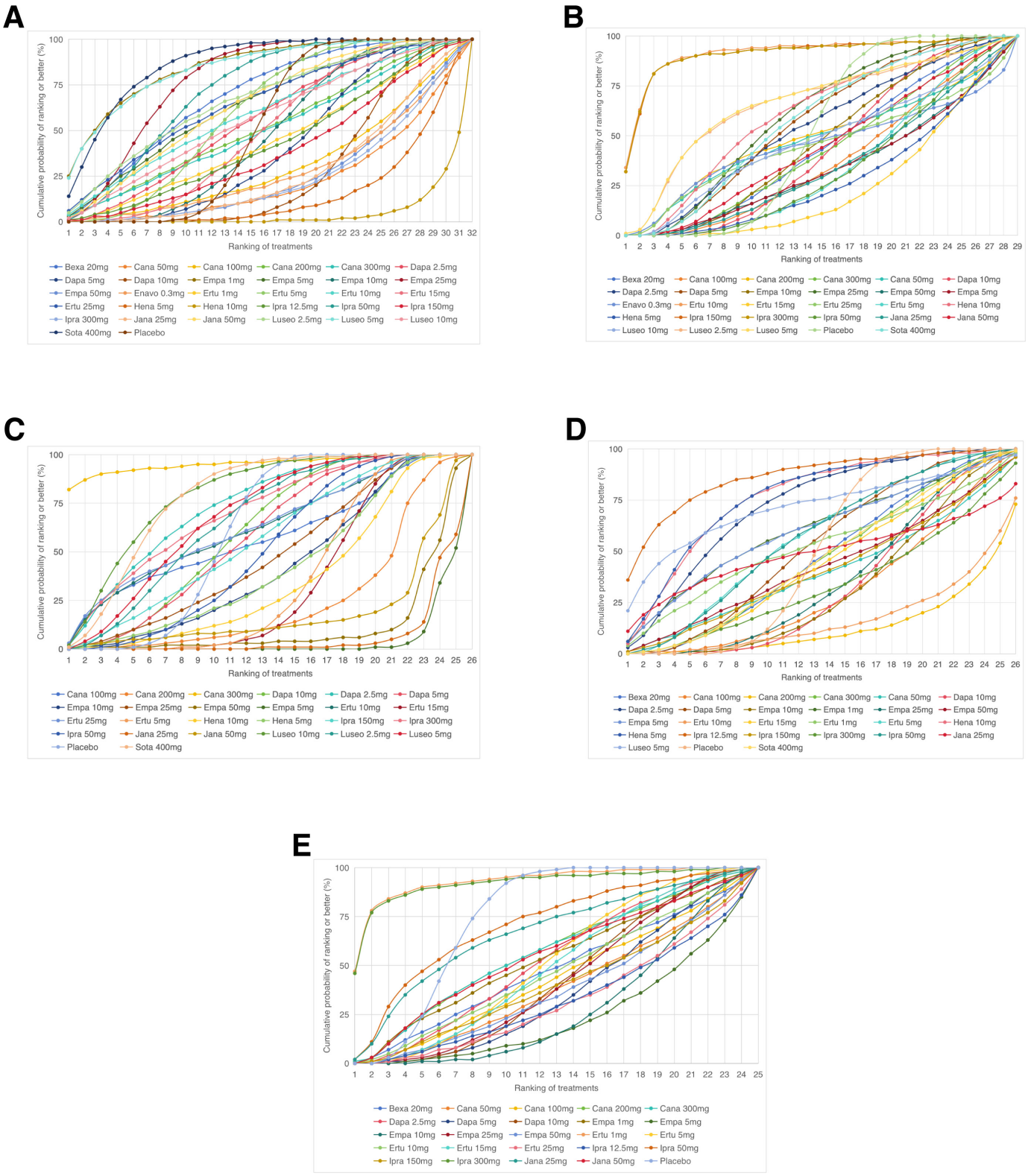


Figure 6 Plots for SUCRA of safety outcomes. (**A**) Total adverse events (AEs), (**B**) serious adverse events (SAEs), (**C**) hypoglycaemia, (**D**) urinary tract infections (UTI), (**E**) genital infections (GI). The graph shows the cumulative probability of each intervention ranking. Different colours represented different interventions. The interventions with higher SUCRA values had better safety. SUCRA, surface under the cumulative ranking curve; Bexa, bexagliflozin; Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Enavo, enavogliflozin; Ertu, ertugliflozin; Hena, henagliflozin; Ipra, ipragliflozin; Jana, janagliflozin; Luseo, luseogliflozin; Sota, sotagliflozin.

−0.58% (−1.12, −0.04), −0.57% (−1.08, −0.06), −0.62% (−1.15, −0.09) and −0.64% (−1.27, −0.02), respectively). There were no significant differences among the other included interventions. According to the SUCRA values (figure 5A, and online supplemental table S6A), 15 mg of ertugliflozin (81%) ranked the highest in reducing HbA1c, followed by 10 mg of henagliflozin (80%), 300 mg of canagliflozin (77%), 5 mg of ertugliflozin (76%) and 5 mg of henagliflozin (76%). The interventions ranking last were placebo (3%), followed by 1 mg of empagliflozin (13%), 2.5 mg of luseogliflozin (21%) and 5 mg of empagliflozin (24%).

FPG reduction

22 studies involving 32 interventions were included in FPG reduction analysis (figure 2B). As shown in online supplemental table S5, compared with placebo, most of the combination therapies reduced FPG (MD ranging from −0.78 to −2.02 mmol/L), for example, 300 mg and 200 mg of canagliflozin, 10 mg and 25 mg of ertugliflozin, and 10 mg of henagliflozin (MD (95% CI), −2.02 (−2.50, −1.50), −1.83 (−2.63, −1.04), −1.96 (−2.69, −1.23), −1.84 (−2.57, −1.11), −1.89 (−2.54, −1.23), respectively). However, only 300 mg of canagliflozin demonstrated clinical significance by surpassing the MCID (2.0 mmol/L). Five interventions did not show significant difference, including 1 mg of empagliflozin, 12.5 mg of ipragliflozin, and 2.5 mg, 5 mg and 10 mg of luseogliflozin (MD (95% CI), −0.23 (−0.89, 0.44), −0.61 (−1.32, 0.12), −0.38 (−1.11, 0.34), −0.63 (−1.35, 0.09), −0.67 (−1.39, 0.05), respectively). As for the SUCRA values (figure 5B and online supplemental table S6A), 300 mg of canagliflozin (90%) was the best option for FPG reduction, followed by 10 mg of ertugliflozin (86%), 10 mg of henagliflozin (84%), 15 mg of ertugliflozin (82%) and 25 mg of ertugliflozin (80%). The interventions ranking last were 2.5 mg of luseogliflozin (10%), 1 mg of empagliflozin (7%) and placebo (2%).

Weight loss (WL)

22 studies involving 32 interventions were included in WL analysis. The network plot is shown in figure 2C. According to the results of pairwise comparisons (online supplemental table S5), only two interventions showed no significant difference in WL compared with placebo, encompassing 1 mg of empagliflozin and 12.5 mg of ipragliflozin (MD (95% CI), −0.57 (−1.38, 0.23), −0.40 (−1.27, 0.48), respectively). The majority of SGLT2is as an add-on to metformin showed greater reduction in BW (MD ranging from −0.88 to −2.67 kg). 300 mg of canagliflozin was greater than most of the other SGLT2is in WL (MD ranging from −0.74 to −2.26 kg). However, no differences between any two interventions reached the MCID threshold of 4.4 kg. The results of SUCRA (figure 5C and online supplemental table S6A) indicated that 300 mg of canagliflozin (97%) demonstrated best efficacy in WL, followed by 20 mg of bexagliflozin (85%), 10 mg of ertugliflozin (80%), 100 mg of canagliflozin (79%) and 0.3 mg of enavogliflozin (77%). 1 mg of empagliflozin (10%), 12.5 mg of ipragliflozin (7%) and placebo (1%) ranked last among 32 interventions.

Total adverse events (AEs)

The NMA for AEs included 32 interventions, and the network plot is shown in figure 3A. Most interventions did not increase the risk of AEs. Only 10 mg of henagliflozin was associated with increased AEs (OR (95% CI), 2.29 (1.29, 4.14)). Compared with 10 mg of henagliflozin, most of the SGLT2is had lower incidence of AEs (OR ranging from 0.27 to 0.49) (online supplemental table S5). The SUCRA values (figure 6A and online supplemental table S6B) showed that 400 mg of sotagliflozin (87%) exhibited the lowest incidence of AEs, followed by 1 mg of empagliflozin (85%), 5 mg of luseogliflozin (85%), 25 mg of empagliflozin (78%) and 50 mg of ipragliflozin (73%). 10 mg of henagliflozin (4%) showed the highest incidence of AEs, followed by 5 mg of henagliflozin (15%) and 50 mg of canagliflozin (23%).

Serious adverse events (SAEs)

To ensure model convergence, treatment groups with sparse data (1 mg and 10 mg of ertugliflozin; 12.5 mg, 150 mg and 300 mg of ipragliflozin; 1 mg of empagliflozin) were removed from the analysis. As shown in figure 3B, 29 interventions were included in NMA for the incidence of SAEs. None of the included interventions increased the incidence of SAEs. Compared with placebo, 300 mg of ipragliflozin had lower incidence of SAEs (OR (95% CI), 3.29×10^{-8} (6.93×10^{-26}, 0.81)) (online supplemental table S5). According to the SUCRA values (figure 6B and online supplemental table S6B), 10 mg of ertugliflozin and 150 mg and 300 mg of ipragliflozin (91%) exhibited the lowest incidence of SAEs, followed by 2.5 mg and 5 mg of luseogliflozin (66%). 15 mg of ertugliflozin (24%) exhibited the highest incidence, followed by 5 mg of henagliflozin (28%).

Hypoglycaemia

Study 9[32] was excluded for not reporting the number of hypoglycaemia. To address issues affecting model convergence, 1 mg of ertugliflozin, 12.5 mg of ipragliflozin, 1 mg of empagliflozin, 0.3 mg of enavogliflozin and 50 mg of canagliflozin were removed from the analysis. 20 mg of bexagliflozin was removed for causing inconsistency (online supplemental table S8B). Finally, 26 interventions were included (figure 3C). Compared with placebo, 5 mg and 50 mg of empagliflozin, 5 mg and 15 mg of ertugliflozin, and 25 mg of janagliflozin exhibited higher incidence of hypoglycaemia (OR (95% CI), 6.00×10^{6} (16.54, 7.12×10^{15}), 1.36×10^{6} (2.35, 1.55×10^{15}), 2.29 (1.02, 6.18), 2.56 (1.09, 7.18), 2.50×10^{6} (6.38, 1.88×10^{22}) respectively). There were significant differences in the incidence of hypoglycaemia among 25 interventions comprising SGLT2is and metformin (figure 6C and online supplemental table S6B). According to the SUCRA values, 300 mg of canagliflozin (95%) showed

the lowest incidence of hypoglycaemia, followed by 10 mg of luseogliflozin (80%), 400 mg of sotagliflozin (79%), 2.5 mg of dapagliflozin (73%) and 300 mg of ipragliflozin (70%). By contrast, 5 mg of empagliflozin (4%), 25 mg of janagliflozin (6%) and 50 mg of empagliflozin (11%) displayed the highest incidence of hypoglycaemia.

Urinary tract infections (UTI)

After excluding treatment groups (0.3 mg of enavogliflozin, 25 mg of ertugliflozin, 50 mg of janagliflozin, 2.5 mg and 10 mg of luseogliflozin) undermining the convergence of the model, 27 interventions were included in Bayesian NMA for UTI (figure 3D). Compared with placebo, none of the included SGLT2is increased the risk of UTI (online supplemental table S5). Meanwhile, there was no significant difference in the risk of UTI among the different combinations of SGLT2is and metformin. The SUCRA values showed that (figure 6D and online supplemental table S6B) 12.5 mg of ipragliflozin (86%) exhibited the lowest incidence of UTI among included interventions, followed by 5 mg and 10 mg of henagliflozin (77%, 77%, respectively), 2.5 mg of dapagliflozin (73%) and 5 mg of luseogliflozin (72%). On the contrary, 200 mg of canagliflozin (15%) showed the highest risk of UTI, followed by 10 mg of ertugliflozin (18%) and 100 mg of canagliflozin (32%).

Genital infections (GI)

After eliminating the studies not reporting the cases of GI (study 9[32], 22[45] and 23[46]) and decreasing the convergence of the model (study 6,[29] 15,[38] 17[40]), Bayesian NMA included 25 interventions (figure 3E). As shown in the league table (online supplemental table S5), compared with placebo, only 10 mg of empagliflozin increased the incidence of GI (OR (95% CI), 12.73 (1.37, 437.17)), while 1 mg of ertugliflozin decreased the incidence (OR (95% CI), 2.39×10^{-15} (5.86×10^{-49}, 0.52)). According to the SUCRA values (figure 6E and online supplemental table S6B), 1 mg of ertugliflozin (93%) and 300 mg of ipragliflozin (92%) exhibited the lowest incidence of GI. In contrary, 5 mg and 10 mg of empagliflozin (25%, 28%, respectively) exhibited relatively high probability of causing GI. It is worth noting that metformin monotherapy (74%) ranked third.

Consistency and heterogeneity

For each outcome, the difference of DIC between the consistent model and inconsistent model was less than 5 (online supplemental table S8A), indicating favourable global consistency among the included RCTs. The node-splitting model analysis suggested that, in the networks for HbA1c reduction, WL, AE and GI analysis, there were no comparisons available for assessing inconsistency. For FPG reduction, SAE and UTI, the p values were greater than 0.05 (online supplemental table S8B), indicating favourable local consistency. Local inconsistency was identified in some comparisons in the network for hypoglycaemic events, which were 20 mg of bexagliflozin versus placebo (p=0.0057) and 10 mg of dapagliflozin versus 20 mg of bexagliflozin (p=0.014). The direct and indirect estimates of these comparisons are presented in online supplemental table S8B. As for heterogeneity, the results of I^2 test are shown in online supplemental table S7. A degree of heterogeneity (I^2>50%) was observed in some comparisons.

Sensitivity analysis

After excluding studies contributing to heterogeneity for HbA1c reduction (studies 14[37] and 20[43]) and FPG reduction (study 20[43]) analysis, a total of 19 studies were included in the sensitivity analysis for HbA1c reduction, and 21 studies were included in the sensitivity analysis for FPG reduction. The results are shown in online supplemental table S9A. Compared with placebo, 2.5 mg of dapagliflozin, 5 mg of empagliflozin, 0.3 mg of enavogliflozin, 1 mg of ertugliflozin, and 5 mg and 10 mg of luseogliflozin showed greater efficacy in reducing HbA1c in the sensitivity analysis. 5 mg and 10 mg of luseogliflozin exhibited greater efficacy in reducing FPG in the sensitivity analysis. Overall, the sensitivity analysis results were consistent with those of the main analysis for most interventions.

After removing studies with high risks of bias (studies 1,[24] 4,[27] 19[42] and 20[43]), the following numbers of studies were included in the sensitivity analyses: 17 studies for HbA1c reduction; 18 studies for FPG reduction, WL, AEs and SAEs; 15 studies for hypoglycaemia; 19 studies for UTI; and 13 studies for GI. The sensitivity analysis excluding studies with high risks of bias revealed no significant statistical changes for most interventions (online supplemental table S9B). Exceptions included 2.5 mg of dapagliflozin, 0.3 mg of enavogliflozin, and 5 mg and 10 mg of luseogliflozin in HbA1c reduction; 2.5 mg of luseogliflozin in WL; 5 mg and 15 mg of ertugliflozin in hypoglycaemic events; and 5 mg and 10 mg of dapagliflozin, 25 mg of empagliflozin and 300 mg of ipragliflozin in GI.

Publication bias

The funnel plots and results of Egger's regression test are shown in online supplemental figure S1 and table S10. For most indicators, comparison-adjusted funnel plots were approximately symmetric and p values were greater than 0.05, suggesting the absence of small-study effects in the NMA. However, there was evidence of publication bias for GI (p=0.0025).

DISCUSSION

This Bayesian NMA was conducted based on 23 RCTs, involving 11 SGLT2is, 32 interventions and 9144 individuals. This study compared the efficacy and safety of SGLT2is in patients with T2DM inadequately controlled with metformin monotherapy.

Principal findings

The findings indicated that, compared with metformin monotherapy, the addition of most SGLT2is to metformin

showed favourable antidiabetic efficacy in reducing HbA1c, FPG and total BW, and acceptable safety regarding the incidence of AEs, SAEs, hypoglycaemia, UTI and GI. Combined SGLT2is could be an ideal option for T2DM patients inadequately controlled with metformin.

Regarding efficacy, 15 mg of ertugliflozin demonstrated the best efficacy in HbA1c reduction, while 300 mg of canagliflozin is the best option for FPG reduction and WL. The addition of some SGLT2is to metformin might be related to inferior safety outcomes, increasing the incidence of total AEs (eg, 10 mg of henagliflozin), hypoglycaemia (eg, 15 mg of ertugliflozin) and GI (eg, 10 mg of empagliflozin). According to the SUCRA values (online supplemental table S6), the interventions displaying the best safety were 400 mg of sotagliflozin in total AEs, 10 mg of ertugliflozin and 150 mg of ipragliflozin in SAEs, 300 mg of canaglilflozin in hypoglycaemia, 12.5 mg of ipraglilflozin in UTI and 25 mg of ertugliflozin in GI. Generally, the included SGLT2i exhibited significant difference in the incidence of AEs, SAEs, hypoglycaemia and GI. Among them, 5 mg of luseoglilfozin showed the greatest safety considering the incidence of total AEs, SAEs, hypoglycaemic events and UTI (ranked second, fourth, sixth, fifth, respectively). 300 mg of canagliflozin appeared to exhibit superior efficacy, since it ranked first in FPG reduction and WL and third in HbA1c reduction. Among the dual therapy regimens, 300 mg of canagliflozin demonstrated acceptable incidence of hypoglycaemia and GI, but was simultaneously related to high risks of AEs and SAEs. By contrast, 5 mg of luseogliflozin was relatively safe while being significantly inferior in glucose control.

Previous studies[49–51] assessed the efficacy and safety of SGLT2is in adults with T2DM. Shyangdan *et al*[49] reported that canagliflozin and empagliflozin as an add-on to metformin were significantly more effective than placebo combined with metformin in HbA1c reduction and WL, which is consistent with our findings. This could be attributed to the dual action arising from combination therapy in suppressing hepatic glucose output and promoting renal glycosuria.[52] Meanwhile, they also found that 300 mg of canagliflozin showed the greatest efficacy in reducing HbA1c and BW among the four interventions (ie, 100 mg and 300 mg of canagliflozin, 10 mg and 25 mg of empagliflozin). Zaccardi *et al*[50] indicated that the highest dose (ie, 300 mg) of canagliflozin reduced HbA1c and FPG to a greater extent than dapagliflozin and empagliflozin at any doses. Our study found that there was significant difference among SGLT2is as add-on therapy in WL. However, Zaccardi *et al*[50] and Tsapas *et al*[51] arrived at a similar conclusion that no differences of efficacy in WL were found between individual SGLT2is. This discrepancy may arise from variations in study design, since their studies included both SGLT2is monotherapy and combination therapies, while ours only included combination therapies. Additionally, only 3 and 4 SGLT2is were involved in their studies, respectively, but 11 SGLT2is were included in ours. Meanwhile, the differences between our study and previous studies may also be related to disparities in the racial composition of the included patients, as efficacy of SGLT2is in WL may be different between Asians and non-Asians.[53]

In terms of safety, there was no significant difference in the incidence of total AEs between most of SGLT2is and placebo. The difference across SGLT2is was also not significant. It is worth noting that sotagliflozin, a dual inhibitor of SGLT2 and SGLT1,[54] showed relatively greater safety considering total AEs. As for hypoglycaemia, we found that the addition of most of the SGLT2is did not increase the risk compared with placebo. This could be attributed to the fact that the glucosuric effect of SGLT2is is bound to the filtered glucose load. When the filtered load is less than 80 g/d, SGLT2is become ineffective at further lowering blood glucose.[55] However, our findings indicated that different SGLT2is exhibited varying degrees of risks of hypoglycaemia, for example, 5 mg and 50 mg of empagliflozin and 25 mg janagliflozin were observed to have higher risks, while 12.5 mg of ipragliflozin and 50 mg and 300 mg of canagliflozin were relatively safe.

The present Bayesian NMA showed that none of the combination therapies increased the risk of UTI compared with placebo (online supplemental table S5). Our findings differed from a previous meta-analysis,[56] but were consistent with a recent real-world study.[57] Moreover, the association between SGLT2is and the risk of UTI is not clear, with prior studies reporting conflicting findings.[56–58] It should be noted that the safety profiles of SGLT2is may depend on races/ethnicities. For example, a meta-analysis found that, compared with placebo, the risk of UTI with SGLT2is treatment was not increased in Asians, but was significantly increased in non-Asians.[53]

SGLT2i-induced glucosuria plays a facilitating role in elevating the risk of GI.[59] Accordingly, SGLT2is appear to easily lead to GI in T2DM patients.[60–63] Nevertheless, in the current study, most of SGLT2is did not increase the risk of GI compared with placebo (online supplemental table S5). Moreover, the SUCRA values (online supplemental table S6) showed that 1 mg of ertugliflozin (93%) and 300 mg of ipragliflozin (92%) were safe, with significantly fewer GI. It is important to note that the data regarding the two interventions were obtained from individual studies, with a relatively small number of patients receiving these interventions (54 and 72, respectively). Therefore, the results should be interpreted with caution. The subgroup analysis of a previous research found that ipragliflozin was not associated with an increased risk of reproductive tract infections in either drug-naïve or metformin-based patients.[64] Similarly, we also found that ipragliflozin at any doses combined with metformin was not related to a higher risk of GI (online supplemental table S5). Besides, 300 mg of ipragliflozin was safer than most of the other SGLT2is (online supplemental table S6). A real-world retrospective cohort study[61] reported that, although the use of SGLT2is was associated with an increased risk of GI, no meaningful difference among individual SGLT2is was identified. Two studies[65 66]

suggested that SGLT2is may increase the risk of diabetic ketoacidosis (DKA). However, only a few cases of DKA were reported in the included studies. Accordingly, the risk of DKA was not assessed in this study.

The differences in efficacy and safety among SGLT2is may be attributed to population, study design, doses, outcome definition and/or pharmacological selectivity. Two studies[67 68] investigated the impact of pharmacological selectivity of SGLT2is on efficacy and safety outcomes and found that the extent of selectivity of SGLT2is to SGLT2 over SGLT1 might be clinically relevant.

Implications

The present study systematically evaluated the safety and efficacy of 11 marketed SGLT2is and 32 interventions, including both newer agents (eg, henagliflozin) and relatively older ones (eg, canagliflozin) by synthesising evidence from RCTs. The results of the current study can provide clinicians with a reference to assess the advantages and weaknesses of SGLT2is comprehensively for T2DM patients inadequately controlled with metformin and also serve as valuable evidence for updating clinical practice guidelines. Our findings indicated that, among the dual therapy regimens, 300 mg of canagliflozin demonstrated optimal efficacy and acceptable incidence of hypoglycaemia and GI, but simultaneously increased the risks of AEs and SAEs. 5 mg of luseogliflozin was relatively safe while being significantly inferior in glucose control. Clinical decisions often involve multiple relevant outcomes and should take into account patient-specific factors such as comorbidities, tolerability and individual treatment goals. For example, for patients prioritising WL, 300 mg of canagliflozin might be an ideal option, but the high risk of AEs should be noted. The American Diabetes Association guideline emphasises the risks of GI when using SGLT2is.[69] Based on the results of the present study, for patients at a high risk of GI, 300 mg of ipragliflozin may be a more suitable choice.

Some new SGLT2is (eg, 5 mg and 10 mg of henagliflozin) also showed promising efficacy and acceptable safety profiles. However, the evaluation of novel SGLT2is was limited by the availability of data, and some evidence included in this study exhibited moderate quality. Additionally, most of the included RCTs were placebo-controlled, and only two RCTs were a head-to-head study. Therefore, more large-scale, high-quality and active-controlled RCTs are needed to further validate our conclusions.

SUCRA rankings provide some guidance in clinical practice but come with certain limitations in their interpretation and application.[70] For instance, differences in relative treatment effects might not be clinically meaningful.[71] Therefore, in this study, to avoid the potential misinterpretation of SUCRA rankings, we used the MCID value for continuous outcomes.[72] Nevertheless, although some differences among SGLT2is were statistically significant, many differences did not surpass MCID threshold, which may limit their practical impact in clinical practice.

Limitations

We should acknowledge several limitations of this study. First, most of the data for novel drugs each were derived from only one trial with a limited sample size, which could introduce bias. Second, characteristics of placebo, races of included participants, baseline glycaemic control, dose of metformin and diabetes duration differ across RCTs. The variation in metformin dosage, baseline glycaemic control and diabetes duration could potentially influence the efficacy and safety outcomes. Some of the included studies involved patients from specific countries or regions, which may limit the generalisability of our findings to broader T2DM populations. Third, a degree of statistical heterogeneity was found in the NMA for some outcome measures (eg, GI). Hence, a sensitivity analysis was conducted and the results did not change substantially when excluding studies significantly influenced the heterogeneity of the model. Despite conducting a comprehensive literature search and including unpublished reports from ClinicalTrials.gov, the results still indicated the presence of publication bias in the analysis of GI probably due to missing data. The limited number of studies available for each comparison restricted our ability to investigate potential sources of publication bias, which could lead to highly misleading of the safety of competing interventions.[73] Besides, local inconsistency was identified in the network for hypoglycaemia analysis, which may be attributed to differences in participant characteristics, such as ethnicity, across the included studies. We provided results of direct and indirect comparisons and excluded these studies in the main analysis. Considering these limitations, the results of the study should be interpreted cautiously.

CONCLUSIONS

Overall, SGLT2is as add-on therapy to metformin displayed favourable efficacy and acceptable safety in antidiabetic therapy, which was suitable for T2DM patients inadequately controlled by metformin. Among the included interventions, 300 mg of canagliflozin exhibited the greatest efficacy in reducing FPG and WL, followed by HbA1c reduction, while it was associated with increased risks of AEs and SAEs. Although some SGLT2is demonstrated statistically significant differences in efficacy and safety outcomes, many of these differences did not surpass the MCID threshold, which may limit their real-world clinical relevance. Besides, novel SGLT2is like henagliflozin demonstrated promising efficacy and safety. However, the limited data calls for further investigation, particularly through large-scale, well-designed RCTs. The findings of this Bayesian NMA provide clinicians with a comprehensive assessment of the relative efficacy and safety of SGLT2is as an add-on to metformin.

Contributors LX: conceptualisation, methodology, software, validation, formal analysis, investigation, writing—original draft, writing—review and editing, visualisation, project administration. YW: methodology, validation, formal analysis, investigation, visualisation, writing—review and editing. JL: methodology,

validation, visualisation, formal analysis, writing—review and editing. YD: methodology, validation, formal analysis, visualisation. JC: methodology, validation, formal analysis, writing—review and editing. LL: methodology, validation, formal analysis, writing—review and editing. HL: methodology, validation, formal analysis, writing—review and editing. ZW: methodology, validation, formal analysis, writing—review and editing. TG: validation, formal analysis, writing—review and editing. YL: writing—review and editing, project administration, supervision. GM: conceptualisation, methodology, validation, formal analysis, writing—review and editing, project administration, supervision. GM is the guarantor.

Funding This work was supported by the National Natural Science Foundation of China (grant numbers 82374133, 82074109, 81873078 and 81374051) and the Minhang District Natural Science Foundation of Shanghai in China (2021MHZ028).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was not required for this study as it involved only publicly available data and did not involve human or animal subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

ORCID iD

Guo Ma http://orcid.org/0000-0001-5524-7172

REFERENCES

1 Home, Resources, diabetes L with. IDF diabetes Atlas. Available: https://diabetesatlas.org/ [Accessed 31 Jan 2024].
2 Ahmad E, Lim S, Lamptey R, *et al*. Type 2 diabetes. *The Lancet* 2022;400:1803–20.
3 Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in China. *Int J Endocrinol Metab* 2021;41:482–548.
4 Davies MJ, Aroda VR, Collins BS, *et al*. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022;45:2753–86.
5 American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2024. *Diabetes Care* 2024;47:S158–78.
6 Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2018;42:S1–325.
7 Expert Group for Expert Consensus on Sodium-Glucose Cotransporter-2 Inhibitors with Metformin in Patients with Type 2 Diabetes Mellitus (姓). *Int J Endocrinol Metab* 2023;43:437–48.
8 Laws A, Tao R, Wang S, *et al*. A Comparison of National Guidelines for Network Meta-Analysis. *Value Health* 2019;22:1178–86.
9 Christofilos SI, Tsikopoulos K, Tsikopoulos A, *et al*. Network meta-analyses: Methodological prerequisites and clinical usefulness. *World J Methodol* 2022;12:92–8.
10 Florez ID, De La Cruz-Mena JE, Veroniki AA. Network meta-analysis: a powerful tool for clinicians, decision-makers, and methodologists. *J Clin Epidemiol* 2024;176:111537.
11 Shim SR, Kim SJ, Lee J, *et al*. Network meta-analysis: application and practice using R software. *Epidemiol Health* 2019;41:e2019013.
12 Seide SE, Jensen K, Kieser M. A comparison of Bayesian and frequentist methods in random-effects network meta-analysis of binary data. *Res Synth Methods* 2020;11:363–78.
13 Sadeghirad B, Foroutan F, Zoratti MJ, *et al*. Theory and practice of Bayesian and frequentist frameworks for network meta-analysis. *BMJ Evid Based Med* 2023;28:204–9.
14 van Valkenhoef G, Lu G, de Brock B, *et al*. Automating network meta-analysis. *Res Synth Methods* 2012;3:285–99.
15 Harvey R, Charokopou M, Arteaga Duarte C, *et al*. PNS22 Network Meta-Analysis: A Comparison of Bayesian and Frequentist Approaches to Synthesis, and Evaluation of Their Suitability for Decision-Making. *Value Health* 2020;23:S647.
16 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
17 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
18 *Cochrane handbook for systematic reviews of interventions version 6.4*. 2023.
19 Huhn M, Nikolakopoulou A, Schneider-Thoma J, *et al*. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *The Lancet* 2019;394:939–51.
20 M.ScMH, Cuijpers PDP, Furukawa PDTA. 11.2 Bayesian network meta-analysis. Doing Meta-Analysis in R. Available: https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/bayesnma.html [Accessed 7 Jan 2025].
21 American Diabetes Association. Standards of medical care in diabetes--2009. *Diabetes Care* 2009;32:S13–61.
22 Ramachandran A, Riddle MC, Kabali C, *et al*. Relationship Between A1C and Fasting Plasma Glucose in Dysglycemia or Type 2 Diabetes. *Diabetes Care* 2012;35:749–53.
23 Goldenberg JZ, Day A, Brinkworth GD, *et al*. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. *BMJ* 2021;372:m4743.
24 Amin NB, Wang X, Jain SM, *et al*. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. *Diabetes Obes Metab* 2015;17:591–8.
25 Bailey CJ, Gross JL, Pieters A, *et al*. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2010;375:2223–33.
26 Bolinder J, Ljunggren Ö, Kullberg J, *et al*. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab* 2012;97:1020–31.
27 Gao L, Cheng Z, Su B, *et al*. Efficacy and safety of janagliflozin as add-on therapy to metformin in Chinese patients with type 2 diabetes inadequately controlled with metformin alone: A multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Obes Metab* 2023;25:785–95.
28 Halvorsen YD, Conery AL, Lock JP, *et al*. Bexagliflozin as an adjunct to metformin for the treatment of type 2 diabetes in adults: A 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2023;25:2954–62.
29 Han KA, Kim YH, Kim DM, *et al*. Efficacy and Safety of Enavogliflozin versus Dapagliflozin as Add-on to Metformin in Patients with Type 2 Diabetes Mellitus: A 24-Week, Double-Blind, Randomized Trial. *Diabetes Metab J* 2023;47:796–807.
30 Häring HU, Merker L, Seewaldt-Becker E, *et al*. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2014;37:1650–9.
31 Ji L, Liu Y, Miao H, *et al*. Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia. *Diabetes Obes Metab* 2019;21:1474–82.
32 Lavalle-González FJ, Januszewicz A, Davidson J, *et al*. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013;56:2582–92.
33 Lu CH, Min KW, Chuang LM, *et al*. Efficacy, safety, and tolerability of ipragliflozin in Asian patients with type 2 diabetes mellitus and

inadequate glycemic control with metformin: Results of a phase 3 randomized, placebo-controlled, double-blind, multicenter trial. *J Diabetes Investig* 2016;7:366–73.
34 Rosenstock J, Aggarwal N, Polidori D, *et al*. Dose-Ranging Effects of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-On to Metformin in Subjects With Type 2 Diabetes. *Diabetes Care* 2012;35:1232–8.
35 Rosenstock J, Frias J, Páll D, *et al*. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). *Diabetes Obes Metab* 2018;20:520–9.
36 Ross S, Thamer C, Cescutti J, *et al*. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. *Diabetes Obes Metab* 2015;17:699–702.
37 Schumm-Draeger PM, Burgess L, Korányi L, *et al*. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. *Diabetes Obes Metab* 2015;17:42–51.
38 Shestakova M, Kvasnikov B, Erina E, *et al*. Efficacy and safety of luseogliflozin in Caucasian patients with type 2 diabetes: results from a phase III, randomized, placebo-controlled, clinical trial. *BMJ Open Diabetes Res Care* 2023;11:e003290.
39 Shestakova MV, Wilding JPH, Wilpshaar W, *et al*. A phase 3 randomized placebo-controlled trial to assess the efficacy and safety of ipragliflozin as an add-on therapy to metformin in Russian patients with inadequately controlled type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2018;146:240–50.
40 Weng J, Zeng L, Zhang Y, *et al*. Henagliflozin as add-on therapy to metformin in patients with type 2 diabetes inadequately controlled with metformin: A multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Obes Metab* 2021;23:1754–64.
41 Yang W, Han P, Min KW, *et al*. Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: A randomized controlled trial. *J Diabetes* 2016;8:796–808.
42 Wilding JPH, Ferrannini E, Fonseca VA, *et al*. Efficacy and safety of ipragliflozin in patients with type 2 diabetes inadequately controlled on metformin: a dose-finding study. *Diabetes Obes Metab* 2013;15:403–9.
43 Kashiwagi A, Kazuta K, Goto K, *et al*. Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab* 2015;17:304–8.
44 Rosenstock J, Seman LJ, Jelaska A, *et al*. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. *Diabetes Obes Metab* 2013;15:1154–60.
45 ClinicalTrials.gov. 2000 feb 29 -. identifier nct02926950, efficacy and safety of sotagliflozin versus placebo in patients with type 2 diabetes mellitus on background of metformin. Bethesda (MD): National Library of Medicine (US). Available: https://clinicaltrials.gov/study/NCT02926950 [Accessed 1 Oct 2023].
46 Xie L, Han J, Cheng Z, *et al*. Efficacy and safety of bexagliflozin compared with dapagliflozin as an adjunct to metformin in Chinese patients with type 2 diabetes mellitus: A 24-week, randomized, double-blind, active-controlled, phase 3 trial. *J Diabetes* 2024;16:e13526.
47 Bailey CJ, Morales Villegas EC, Woo V, *et al*. Efficacy and safety of dapagliflozin monotherapy in people with Type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. *Diabet Med* 2015;32:531–41.
48 Bolinder J, Ljunggren Ö, Johansson L, *et al*. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab* 2014;16:159–69.
49 Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *BMJ Open* 2016;6:e009417.
50 Zaccardi F, Webb DR, Htike ZZ, *et al*. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab* 2016;18:783–94.
51 Tsapas A, Karagiannis T, Kakotrichi P, *et al*. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetes Obes Metab* 2021;23:2116–24.
52 Donnan K, Segar L. SGLT2 inhibitors and metformin: Dual antihyperglycemic therapy and the risk of metabolic acidosis in type 2 diabetes. *Eur J Pharmacol* 2019;846:23–9.
53 Cai X, Gao X, Yang W, *et al*. No disparity of the efficacy and all-cause mortality between Asian and non-Asian type 2 diabetes patients with sodium-glucose cotransporter 2 inhibitors treatment: A meta-analysis. *J Diabetes Investig* 2018;9:850–61.
54 Cefalo CMA, Cinti F, Moffa S, *et al*. Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives. *Cardiovasc Diabetol* 2019;18:20.
55 Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia* 2017;60:215–25.
56 Vasilakou D, Karagiannis T, Athanasiadou E, *et al*. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013;159:262–74.
57 Dave CV, Schneeweiss S, Kim D, *et al*. Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections. *Ann Intern Med* 2019;171:248–56.
58 Puckrin R, Saltiel MP, Reynier P, *et al*. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol* 2018;55:503–14.
59 Geerlings S, Fonseca V, Castro-Diaz D, *et al*. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. *Diabetes Res Clin Pract* 2014;103:373–81.
60 Li D, Wang T, Shen S, *et al*. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2017;19:348–55.
61 Dave CV, Schneeweiss S, Patorno E. Comparative risk of genital infections associated with SGLT2 inhibitors: A real-world retrospective cohort study. *Diabetes Obes Metab* 2019;21:434–8.
62 Shi Q, Nong K, Vandvik PO, *et al*. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2023;381:e074068.
63 Maruthur NM, Tseng E, Hutfless S, *et al*. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016;164:740–51.
64 Li CX, Liu LY, Zhang CX, *et al*. Comparative safety of different sodium-glucose transporter 2 inhibitors in patients with type 2 diabetes: a systematic review and network meta-analysis of randomized controlled trials. *Front Endocrinol* 2023;14:1238399.
65 Douros A, Lix LM, Fralick M, *et al*. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Diabetic Ketoacidosis : A Multicenter Cohort Study. *Ann Intern Med* 2020;173:417–25.
66 Liu J, Li L, Li S, *et al*. Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2020;22:1619–27.
67 Sayour AA, Oláh A, Ruppert M, *et al*. Effect of pharmacological selectivity of SGLT2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes: a meta-analysis. *Sci Rep* 2024;14:2188.
68 Täger T, Frankenstein L, Atar D, *et al*. Influence of receptor selectivity on benefits from SGLT2 inhibitors in patients with heart failure: a systematic review and head-to-head comparative efficacy network meta-analysis. *Clin Res Cardiol* 2022;111:428–39.
69 American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care* 2024;48:S181–206.
70 Mbuagbaw L, Rochwerg B, Jaeschke R, *et al*. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Syst Rev* 2017;6:79.
71 Mavridis D, Porcher R, Nikolakopoulou A, *et al*. Extensions of the probabilistic ranking metrics of competing treatments in network meta-analysis to reflect clinically important relative differences on many outcomes. *Biom J* 2020;62:375–85.
72 Cook CE. Clinimetrics Corner: The Minimal Clinically Important Change Score (MCID): A Necessary Pretense. *J Man Manip Ther* 2008;16:E82–3.
73 Trinquart L, Abbé A, Ravaud P. Impact of reporting bias in network meta-analysis of antidepressant placebo-controlled trials. *PLoS One* 2012;7:e35219.