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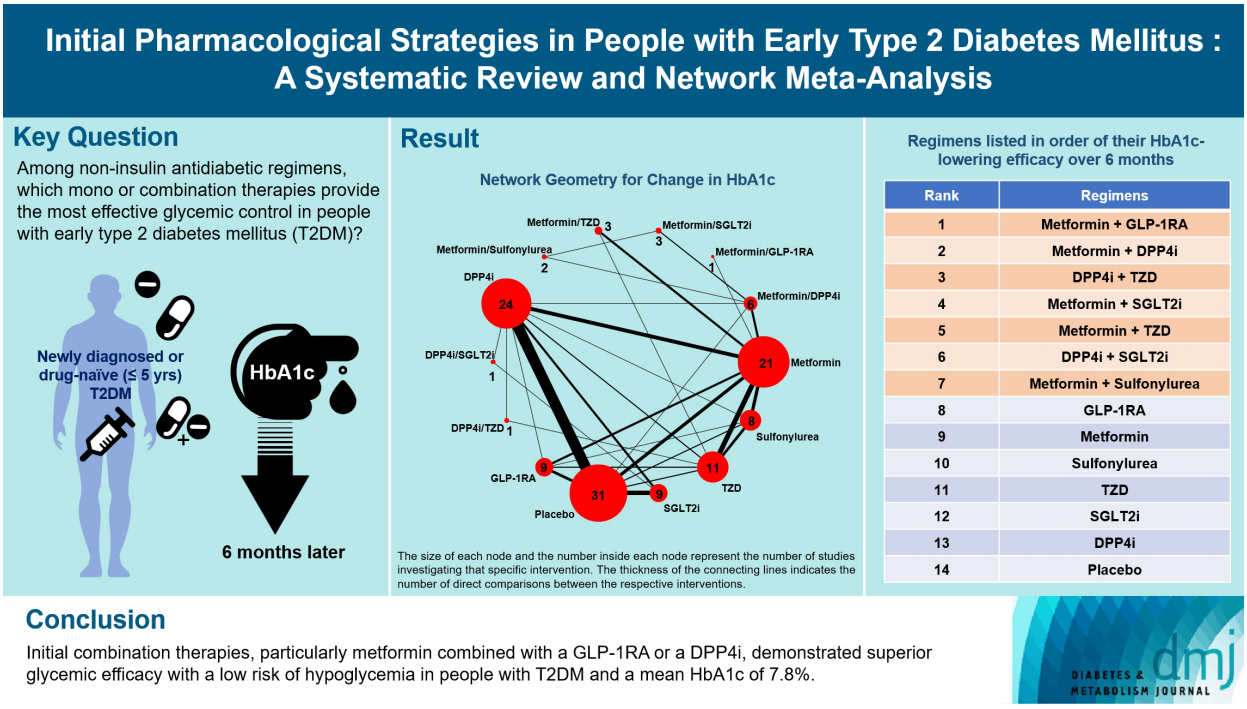

Highlights

- **This NMA assessed HbA1c-lowering efficacies of non-insulin therapies in early T2DM.**
- **Metformin plus GLP-1RA or DPP-4i showed the greatest glycemic control efficacy.**
- **Initial combination therapies outperformed monotherapies for HbA1c reduction.**
- **These findings support early dual therapy to optimize glycemic control in T2DM.**

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Initial Pharmacological Strategies in People with Early Type 2 Diabetes Mellitus: A Systematic Review and Network Meta-Analysis

Jong Han Choi[1], Bo Kyung Koo[2], Ye Seul Yang[3,4], Se Hee Min[5], Jong Suk Park[6], Sang Youl Rhee[7,8], Hyun Jung Kim[9], Min Kyong Moon[2]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea
[2]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Medicine, Seoul National University College of Medicine, Seoul, Korea
[4]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[5]Division of Endocrinology and Metabolism, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[6]Division of Endocrinology and Metabolism, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[7]Department of Endocrinology and Metabolism, College of Medicine, Kyung Hee University, Seoul, Korea
[8]Department of Digital Health, College of Medicine, Kyung Hee University, Seoul, Korea
[9]Institute for Evidence-based Medicine, Cochrane Korea, Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

Background: Type 2 diabetes mellitus (T2DM) requires stringent glycemic control from an early stage to prevent complications. The most effective treatment regimen for early T2DM remains unclear. The study aimed to compare the efficacy and safety of monotherapies and combination therapies for early T2DM.
Methods: A systematic review and network meta-analysis were conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Randomized controlled trials focused on glycemic control, body weight, and adverse events were included. The primary outcomes were changes in glycosylated hemoglobin (HbA1c) and odds of achieving the target HbA1c after 6 months.
Results: All combination therapies were more effective than monotherapy. Metformin+glucagon-like peptide-1 receptor agonists (GLP-1RA) (weighted mean difference [WMD] −1.50%; 95% confidence interval [CI] −2.04 to −0.96) and metformin+dipeptidyl peptidase-4 inhibitors (WMD −1.46%; 95% CI, −1.96 to −0.95) were the most effective for change in HbA1c. GLP-1RA and sodium-glucose cotransporter-2 inhibitors led to weight reduction. Apart from the increased risk of hypoglycemia with sulfonylureas, no significant differences in adverse events were observed across regimens.
Conclusion: Early combination therapy effectively improved glycemic control in patients with early T2DM without significantly increasing adverse risks. Future studies should explore new combinations, including potent GLP-1RA.

Keywords: Diabetes mellitus, type 2; Drug therapy, combination; Hypoglycemic agents; Glycemic control

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent chronic metabolic disorder characterized by progressive insulin resistance and β-cell dysfunction, leading to sustained hyperglycemia [1]. Early and effective glycemic control is critical for preventing long-term complications, including cardiovascular disease and microvascular complications, all of which significantly impair the quality of life and increase mortality rates [2]. As the pharmacological landscape for managing T2DM has expanded, the

Corresponding author: Min Kyong Moon https://orcid.org/0000-0002-5460-2846
Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea
E-mail: mkmoon@snu.ac.kr

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optimal initial therapy remains a topic of considerable debate. Traditionally, metformin has been widely recommended as a first-line therapy for patients with newly diagnosed T2DM [3]. The development of more effective and safer glucose-lowering agents with diverse characteristics has allowed for a more flexible, person-centered approach to drug selection [4,5]. As such, treatment decisions can consider various demographic, medical, and socioeconomic factors specific to each patient. In particular, thiazolidinedione (TZD), dipeptidyl peptidase-4 inhibitor (DPP4i), sodium-glucose cotransporter-2 inhibitor (SGLT2i), and glucagon-like peptide-1 receptor agonist (GLP-1RA) have demonstrated a low risk of hypoglycemia [4,5]. These agents have also been shown to reduce treatment failure rates when used in combination while maintaining a favorable safety profile [6]. Consequently, recent guidelines advocate for the early initiation of combination therapy for mild hyperglycemia, reflecting a shift toward more aggressive, tailored treatment strategies aimed at preventing disease progression and improving patient outcomes [4,5].

Although multiple network meta-analyses (NMA) have evaluated diabetes medications [7,8], few have focused specifically on early T2DM or comprehensively compared monotherapy and combination therapy, leaving an important knowledge gap for this population. Our study addresses this gap by being the first to conduct an NMA comparing the efficacy and safety of various therapeutic regimens, including monotherapy and combination therapy, in people with early T2DM. This study aimed to compare the glucose-lowering efficacy of various non-insulin diabetes therapies and their impact on body weight, blood pressure, lipid profiles, and incidence of adverse events through an NMA of randomized controlled trials (RCTs). Our findings will guide clinicians in selecting the most appropriate initial treatment strategy for people with early T2DM.

METHODS

Study design

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and was registered with PROSPERO (CRD42024511058), ensuring transparency and conformance with established standards for systematic reviews.

The eligibility criteria for selecting studies were specified using the Population, Intervention, Comparison, Outcomes, Time, Study design framework, as detailed in Supplementary Table 1. This framework was designed to determine the most effective pharmacological regimen for adults with early T2DM. The studies included adults newly diagnosed with T2DM or those with previously diagnosed T2DM who had never received pharmacological treatment. Studies were excluded if the mean duration of diabetes exceeded 5 years or if the mean glycosylated hemoglobin (HbA1c) level was >8.5%. These criteria were selected to ensure a focus on patients in the early period of diabetes, excluding cases where severe hyperglycemia might require insulin treatment [4,5]. The selected interventions were non-insulin antidiabetic agents currently used in Korea as of 2024 or expected to be available soon, including metformin, sulfonylurea (SU), TZD, DPP4i, SGLT2i, and GLP-1RA. Only RCTs with an intervention period of at least 24 weeks, during which the intervention was sustained without any crossover, were included. The primary outcomes were changes in HbA1c or odds of achieving target HbA1c (<7.0% or <6.5%) after 24 weeks (6 months). Secondary outcomes included changes in fasting blood glucose (FBG), body weight, blood pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and odds for the incidence of adverse events.

Search strategy and literature selection

The search strategy was refined through multiple iterations, incorporating both controlled vocabulary (MeSH terms) and free text to ensure comprehensive coverage of relevant studies. The final search strategy (Supplementary Table 2) was developed in consultation with a professional librarian and was executed on January 31, 2024, across PubMed, Embase, Cochrane, and KoreaMed databases. A total of 69,706 documents were retrieved from the four databases. After removing duplicates by screening the title twice, 44,721 documents were included. From February 1 to February 28, 2024, six diabetes experts (J.H.C., Y.S.Y., S.H.M., B.K.K., J.S.P., and S.Y.R.) from the Committee of Clinical Practice Guidelines of the Korean Diabetes Association screened the titles of these documents, resulting in the selection of 21,214 documents. Abstract screening further reduced the number to 529 documents, which were selected for full-text review. Two independent diabetes experts (J.H.C. and Y.S.Y.) thoroughly read the full texts and selected the final documents. Discrepancies were resolved through discussions between the two experts, and if needed, a consensus meeting with all the six experts and the corresponding author (M.K.M.) was held to resolve any disagreements.

Data extraction and risk of bias assessment for individual studies

Data extraction was initially performed by S.H.M., B.K.K., and Y.S.Y. Then, J.H.C. conducted a secondary review to verify the accuracy and completeness of the extracted data. The extracted data included both continuous and dichotomous variables relevant to the study outcomes. Continuous variables included HbA1c (%), FBG (mg/dL), body weight (kg), blood pressure (mm Hg), and lipid profiles (total cholesterol, HDL-C, LDL-C, and triglycerides) (mg/dL) after 24 weeks. For continuous variables, data were extracted for the mean difference with standard error (SE) of changes from baseline to 6 months. Dichotomous variables included the proportion of patients achieving target HbA1c (<7.0% or <6.5%) at 24 weeks and the incidence of adverse events. The data for dichotomous variables were reported as odds ratio (OR) with SE for each outcome. Data discrepancies were resolved by discussion among the initial extractors or through consultation with another reviewer, if necessary. The risk of bias in the included studies was assessed independently by two reviewers (J.H.C. and Y.S.Y.) using the Cochrane risk of bias 2.0 tool. This tool was selected for its ability to thoroughly evaluate key areas, including the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Any discrepancies in the risk of bias assessments were resolved through discussion or, when necessary, by consulting a third reviewer (M.K.M.) to reach consensus.

Data synthesis and analysis

The NMA was conducted by H.J.K. using STATA version 16.1 (StataCorp LP, College Station, TX, USA) to compare the efficacy and safety of the included interventions. A random-effects model was applied to account for potential heterogeneity across studies, incorporating both direct and indirect comparisons. Continuous outcomes are summarized as weighted mean difference (WMD) with 95% confidence interval (CI) and dichotomous outcomes as OR with 95% CI. Consistency between direct and indirect evidence was assessed using the node-splitting method, with a *P* value threshold of 0.1 used to evaluate statistical inconsistency. This threshold was chosen to account for potential complexities in the network structure and indirect comparisons in the analysis. Treatments were ranked based on the surface under the cumulative ranking (SUCRA) probabilities, estimating the likelihood of each intervention being the most effective. Additionally, a pairwise meta-analysis (PMA) was conducted using the same random-effects model in STATA to validate the NMA findings through direct comparisons between interventions. The integration of NMA and PMA allowed for cross-validation and comprehensive evaluation of therapeutic options for early-stage T2DM.

RESULTS

Sixty RCTs were included in the final analysis after a thorough full-text review based on predefined inclusion and exclusion criteria. The selection process, including the number of articles at each stage and reasons for exclusion, is detailed in Fig. 1. The key characteristics of the included studies are summarized in Supplementary Table 3. Among these, 47 studies (78.3%) involved intervention periods of 24 weeks, while the longest intervention period extended to 60 months. The mean age of participants ranged from 41.0 to 70.9 years, and the mean body mass index ranged from 22.5 to 39.8 kg/m^2. The mean HbA1c ranged from 6.6% to 8.5%, and the duration of diabetes varied from new diagnoses to a maximum of 5.0 years. The risk of bias assessment results for the primary outcome, change in HbA1c after 24 weeks, are provided in Supplementary Fig. 1. Supplementary Table 4 outlines the types of interventions, number of studies, participants, and baseline mean HbA1c values for each intervention. The number of studies, direct comparisons, and participants for each outcome variable are detailed in Supplementary Table 5.

Glucose-lowering efficacy

The network geometry for the change in HbA1c after six months is illustrated in Fig. 2. The global test for inconsistency showed a *P* value of 0.0724, suggesting a potential inconsistency in the network (Supplementary Table 6). The outcomes of the NMA and PMA are summarized in Table 1, and the ranking of treatments based on the network rank test is provided in Table 2. Data for glucose-lowering efficacy were available in 58 out of the 60 included studies, comprising 91 direct comparisons involving 20,161 participants. All dual combination therapies were ranked higher than monotherapies. Metformin+GLP-1RA was the most effective in lowering HbA1c (SUCRA: 85.8 vs. placebo WMD: –1.50%; 95% CI, –2.04 to –0.96), followed by metformin+DPP4i (SUCRA: 85.2 vs. placebo WMD: –1.46%; 95% CI, –1.96 to –0.95). Among the monotherapies, GLP-1RA (SUCRA: 47.4 vs. placebo WMD: –1.10%; 95% CI, –1.65 to –0.55) was the most effective. Metformin ranked sec-

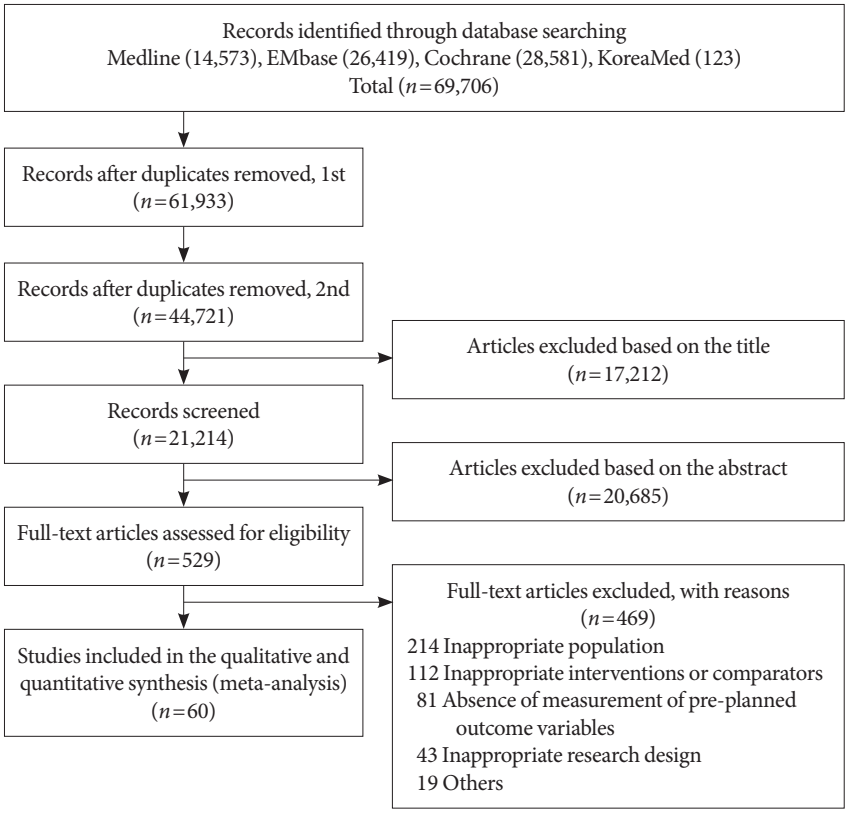

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow for literature selection and exclusion process.

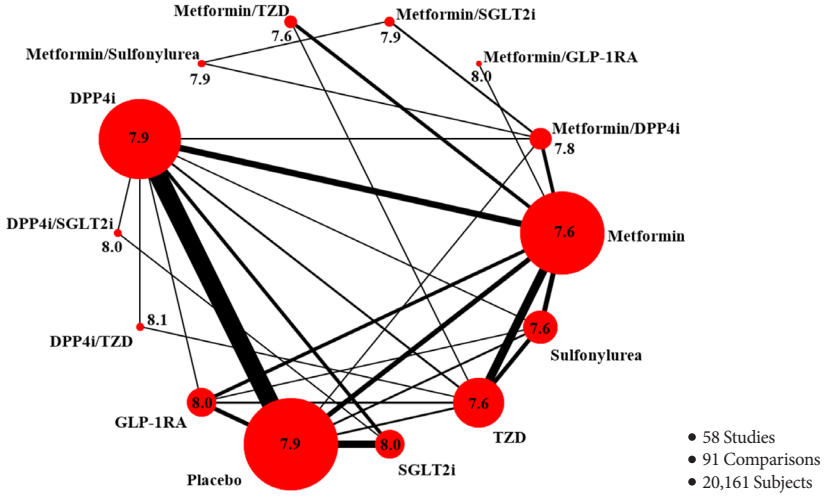

Fig. 2. Network geometry for glycosylated hemoglobin (HbA1c) reduction efficacy of anti-diabetic treatments after 24 weeks (6 months) in the network meta-analysis. Each circle represents an antidiabetic treatment that was included in the analysis, with the size of the circle proportional to the number of trials involving the treatment. The width of each connecting line is proportional to the number of individuals who participated in each pair of trials. The numbers inside or next to the circles indicate the baseline HbA1c levels for each treatment group. The global test for inconsistency yielded a *P* value of 0.0724, which suggests potential inconsistencies in the network of treatments. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor.

Table 1. Network and pairwise meta-analysis results for HbA1c reduction efficacy of anti-diabetic treatments after 6 months

	Placebo	DPP4i	SGLT2i	TZD	SU	Met	GLP-1RA	Met+SU	DPP4i+SGLT2i	Met+TZD	Met+SGLT2i	DPP4i+TZD	Met+DPP4i	Met+GLP-1RA
Placebo	Placebo	−0.70[a] (−1.09 to −0.31)	−0.90[a] (−1.44 to −0.36)	−1.00[a] (−1.58 to −0.42)	−1.00[a] (−1.59 to −0.41)	0.10 (−0.46 to 0.66)	−1.10[a] (−1.65 to −0.55)	−1.19[a] (−1.97 to −0.41)	−1.20[a] (−1.74 to −0.66)	−1.25[a] (−1.77 to −0.72)	−1.31[a] (−1.87 to −0.74)	−1.40[a] (−2.02 to −0.78)	−1.46[a] (−1.96 to −0.95)	−1.50[a] (−2.04 to −0.96)
DPP4i	0.49[a] (0.45 to 0.54) I^2=75.6% 17 studies	DPP4i	−0.20 (−0.57 to 0.17)	−0.30 (−0.87 to 0.27)	−0.30 (−0.88 to 0.28)	0.15 (−0.19 to 0.49)	−0.40 (−0.95 to 0.15)	−0.49 (−1.26 to 0.29)	−0.50[a] (−0.87 to −0.13)	−0.55[a] (−1.06 to −0.03 to)	−0.61[a] (−1.17 to −0.05)	−0.70[a] (−1.18 to −0.22)	−0.76[a] (−1.26 to −0.26)	−0.80[a] (−1.34 to −0.26)
SGLT2i	0.84[a] (0.77 to 0.92) I^2=35.3% 7 studies	0.08 (−0.02 to 0.17) I^2=63.4% 3 studies	SGLT2i	−0.10 (−0.78 to 0.58)	−0.10 (−0.79 to 0.59)	0.60 (0.06 to 1.14)	−0.20 (−0.86 to 0.46)	−0.29 (−1.15 to 0.57)	−0.30 (−0.66 to 0.06)	−0.35 (−0.98 to 0.29)	−0.41 (−1.08 to 0.26)	−0.5 (−1.11 to 0.11)	−0.56 (−1.18 to 0.06)	−0.6 (−1.25 to 0.05)
TZD	0.41[a] (0.15 to 0.68) I^2=85.4% 2 studies	0.37[a] (0.18 to 0.56) I^2=0.0% 2 studies		TZD	0.00 (−0.61 to 0.61)	−0.40[a] (−0.79 to −0.01)	−0.10 (−0.67 to 0.47)	−0.19 (−0.98 to 0.61)	−0.20 (−0.88 to 0.48)	−0.25 (−0.79 to 0.30)	−0.31 (−0.89 to 0.27)	−0.40 (−1.15 to 0.35)	−0.46 (−0.98 to 0.07)	−0.50 (−1.06 to 0.06)
SU	0.23[a] (0.01 to 0.46) I^2=78.1% 2 studies	−0.30[a] (−0.57 to −0.03) I^2=0.0% 1 study		0.29[a] (0.24 to 0.34) I^2=45.1% 4 studies	SU	0.10 (−0.44 to 0.64)	−0.10 (−0.68 to 0.48)	−0.19 (−0.99 to 0.61)	−0.20 (−0.89 to 0.49)	−0.25 (−0.80 to 0.31)	−0.31 (−0.90 to 0.28)	−0.40 (−1.16 to 0.36)	−0.46 (−0.99 to 0.08)	−0.50 (−1.07 to 0.07)
Met	0.53[a] (0.43 to 0.64) I^2=92.3% 5 studies	0.18[a] (0.12 to 0.23) I^2=81.6% 6 studies		0.08[a] (0.03 to 0.13) I^2=37.2% 8 studies	−0.18[a] (−0.23 to −0.13) I^2=44.0% 5 studies	Met	−0.24 (−0.69 to 0.22)	−0.15 (−0.70 to 0.39)	0.18 (−0.89 to 1.25)	−0.21 (−0.61 to 0.19)	−0.40[a] (−0.77 to −0.03)	−0.09 (−0.76 to 0.58)	−0.14 (−0.64 to 0.36)	−0.36[a] (−0.67 to −0.04)
GLP-1RA	1.03[a] (0.91 to 1.16) I^2=89.2% 4 studies	0.30[a] (0.09 to 0.51) I^2=0.0% 1 study		0.00 (−0.18 to 0.19) I^2=82.3% 2 studies	0.37 (−0.15 to 0.59) I^2=0.0% 1 study	0.15[a] (0.04 to 0.27) I^2=77.6% 3 studies	GLP-1RA	−0.09 (−0.86 to 0.69)	−0.10 (−0.76 to 0.56)	−0.15 (−0.66 to 0.37)	−0.21 (−0.77 to 0.35)	−0.30 (−1.03 to 0.43)	−0.36 (−0.86 to 0.14)	−0.40 (−0.94 to 0.14)
Met+SU							Met+SU	−0.01 (−0.87 to 0.85)	−0.06 (−0.81 to 0.69)	−0.12 (−0.77 to 0.52)	−0.21 (−1.13 to 0.70)	−0.27 (−0.86 to 0.32)	−0.31 (−1.08 to 0.46)	
DPP4i+SGLT2i		0.50[a] (0.36 to 0.65) I^2=0.0% 1 study	0.30[a] (0.18 to 0.42) I^2=0.0% 1 study						DPP4i+SGLT2i	−0.05 (−0.68 to 0.59)	−0.11 (−0.78 to 0.56)	−0.2 (−0.81 to 0.41)	−0.26 (−0.88 to 0.36)	−0.3 (−0.95 to 0.35)
Met+TZD				0.40[a] (0.15 to 0.65) I^2=0.0% 1 study		0.24[a] (0.07 to 0.41) I^2=29.2% 3 studies				Met+TZD	−0.06 (−0.59 to 0.47)	−0.15 (−0.86 to 0.55)	−0.21 (−0.68 to 0.25)	−0.25 (−0.76 to 0.25)
Met+SGLT2i								0.30 (−0.48 to 1.08) I^2=0.0% 1 study			Met+SGLT2i	−0.09 (−0.83 to 0.65)	−0.15 (−0.40 to 0.10)	−0.19 (−0.74 to 0.36)
DPP4i+TZD		0.70[a] (0.36 to 1.04) I^2=0.0% 1 study		0.40[a] (0.16 to 0.64) I^2=0.0% 1 study								DPP4i+TZD	−0.06 (−0.75 to 0.64)	−0.10 (−0.82 to 0.62)
Met+DPP4i	1.60[a] (1.40 to 1.80) I^2=0.0% 1 study	0.90[a] (0.72 to 1.09) I^2=0.0% 1 study				0.39[a] (0.27 to 0.50) I^2=31.4% 3 studies		0.27 (−0.22 to 0.76) I^2=0.0% 1 study			0.13[a] (0.07 to 0.20) I^2=46.6% 2 studies		Met+DPP4i	−0.04 (−0.53 to 0.45)
Met+GLP-1RA						0.40[a] (0.25 to 0.55) I^2=0.0% 1 study								Met+GLP-1RA

Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for HbA1c (%) reduction efficacy of antidiabetic treatments after 6 months. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in reverse order of the mean rank results.

HbA1c, glycosylated hemoglobin; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; SU, sulfonylurea; Met, metformin; GLP-1RA, glucagon-like peptide-1 receptor agonist.

[a]Results indicate statistical significance.

Table 2. Results of network rank test for HbA1c reduction efficacy of antidiabetic treatments after 6 months

Antidiabetic treatments	SUCRA	PrBest	Mean rank
Met+GLP-1RA	85.8	35.8	2.8
Met+DPP4i	85.2	17.7	2.9
DPP4i+TZD	75.2	23.6	4.2
Met+SGLT2i	67.4	3.7	5.2
Met+TZD	63.1	4.1	5.8
DPP4i+SGLT2i	58.4	4.2	6.4
Met+SU	53.6	8.0	7.0
GLP-1RA	47.4	1.3	7.8
Met	45.4	0.0	8.1
SU	39.0	0.8	8.9
TZD	37.5	0.8	9.1
SGLT2i	29.0	0.0	10.2
DPP4i	12.9	0.0	12.3
Placebo	0.0	0.0	14.0

HbA1c, glycosylated hemoglobin; SUCRA, surface under the cumulative ranking curve; PrBest, probability of being the best; Met, metformin; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinediones; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea.

ond in the rank test among monotherapies, but it was the only treatment among all therapies that did not show a statistically significant reduction in HbA1c compared to placebo (SUCRA: 45.4 vs. placebo WMD: 0.10%; 95% CI, –0.46 to 0.66). In contrast, on PMA, metformin significantly reduced HbA1c (vs. placebo WMD: –0.53%; 95% CI, –0.64 to –0.43).

The network geometry for the ORs of achieving target HbA1c at 24 weeks is illustrated in Supplementary Fig. 2. The global test indicated no evidence of inconsistency (P=0.9128). Data for this outcome were available from 30 of the 60 included studies, encompassing 48 direct comparisons with 15,018 participants. The detailed NMA and PMA results for this outcome are presented in Table 3, and the network rank test results are shown in Supplementary Fig. 2. Metformin+DPP4i emerged as the most effective combination (SUCRA: 89.9 vs. placebo OR: 34.31; 95% CI, 7.69 to 153.00), followed by DPP4i+TZD (SUCRA: 76.7 vs. placebo OR: 24.49; 95% CI, 5.20 to 115.44). Among monotherapies, GLP-1RA ranked the highest (SUCRA: 57.0 vs. placebo OR: 15.90; 95% CI, 3.48 to 72.69), followed by SU (SUCRA: 53.5 vs. placebo OR: 15.08; 95% CI, 3.16 to 71.97) and TZD (SUCRA: 52.7 vs. placebo OR: 14.63; 95% CI, 3.15 to 67.86). Despite minor changes in the ranking order among metformin, SU, and TZD, the overall rank test results were consistent with those observed for HbA1c reduction. Similar to the HbA1c reduction results, metformin was the only therapy with no statistically significant superiority over placebo in achieving target HbA1c (SUCRA: 38.4, OR: 0.58; 95% CI, 0.17 to 1.96). However, in PMA, metformin showed a significant improvement in achieving the HbA1c target compared to placebo (OR: 11.49; 95% CI, 4.07 to 32.26), indicating that metformin is also an effective therapy in direct comparisons.

The NMA results for FBG are presented in Supplementary Fig. 3. The global test results indicated a potential for inconsistency (P=0.0545). Overall, combination therapies generally demonstrated better efficacy than monotherapies, although the results varied across treatments. Among the combination therapies, metformin+DPP4i combination was the most effective (SUCRA: 87.7 vs. placebo WMD: –48.0 mg/dL; 95% CI, –71.7 to –24.4). Among monotherapies, SGLT2i ranked the highest (SUCRA: 60.3 vs. placebo WMD: –36.9 mg/dL; 95% CI, –54.8 to –19.1). Similar to the HbA1c reduction findings, metformin showed the smallest effect size compared to placebo (WMD: –13.0 mg/dL; 95% CI, –25.4 to –0.7).

Body weight

The NMA and PMA results for body weight are presented in Supplementary Fig. 4. The global test results showed no evidence of inconsistency (P=0.1806). The rank test results indicated that GLP-1RA (SUCRA: 89.0), SGLT2i (SUCRA: 62.7), metformin (SUCRA: 55.6), and their combination therapies ranked higher, while TZD (SUCRA: 3.0), SU (SUCRA: 18.6), DPP4i (SUCRA: 29.0), and their combinations ranked lower in terms of weight reduction. GLP-1RA showed the best weight reduction result (SUCRA: 89.0 vs. TZD WMD: –3.50 kg; 95% CI, –4.60 to –2.40), while the combination of metformin+GLP-1RA had a similar SUCRA but showed the largest effect size (SUCRA: 88.5 vs. TZD WMD: –5.50 kg; 95% CI, –8.13 to –2.87). In the NMA, none of the drug regimens showed statistically significant weight reduction effects compared to placebo. However, in the PMA, both SGLT2i (WMD: –2.08 kg; 95% CI, –2.34 to –1.81) and GLP-1RA (WMD: –1.71 kg; 95% CI, –2.08 to –1.33) demonstrated significant weight reduction compared to placebo. In contrast, TZD (WMD: 3.34 kg; 95% CI, 1.79 to 4.89) and SU (WMD: 1.75 kg; 95% CI, 0.11 to 3.39) showed significant weight gain compared to placebo in the NMA.

Table 3. Network and pairwise meta-analysis results for odds ratios of HbA1c target achievement of antidiabetic treatments after 6 months

	Placebo	DPP4i	SGLT2i	Met	TZD	SU	GLP-1RA	DPP4i+SGLT2i	Met+SGLT2i	DPP4i+TZD	Met+DPP4i
Placebo	Placebo	6.56[a] (1.82–23.64)	9.23[a] (1.97–43.36)	0.58 (0.17–1.96)	14.63[a] (3.15–67.86)	15.08[a] (3.16–71.97)	15.90[a] (3.48–72.69)	19.67[a] (4.19–92.31)	21.33[a] (3.65–124.53)	24.49[a] (5.20–115.44)	34.31[a] (7.69–153.00)
DPP4i	0.38[a] (0.30–0.47) I^2=37.0% 11 studies	DPP4i	1.41 (0.59–3.34)	0.54 (0.16–1.82)	2.23 (0.67–7.48)	2.30 (0.66–8.00)	2.42 (0.74–7.99)	3.00[a] (1.26–7.11)	3.25[a] (0.73–14.45)	3.74[a] (1.56–8.93)	5.23[a] (1.64–16.69)
SGLT2i	0.33[a] (0.24–0.45) I^2=49.2% 5 studies	0.84 (0.63–1.10) I^2=0.0% 2 studies	SGLT2i	0.47 (0.14–1.58)	1.58 (0.36–7.01)	1.63 (0.36–7.44)	1.72 (0.39–7.51)	2.13 (0.94–4.84)	2.31 (0.41–12.95)	2.65 (0.78–9.05)	3.72 (0.87–15.79)
Met	0.09[a] (0.03–0.25) I^2=0.0% 1 study	0.65[a] (0.53–0.78) I^2=0.0% 4 studies		Met	1.02 (0.32–3.22)	0.29 (0.06–1.43)	0.57 (0.24–1.34)	1.16 (0.41–3.27)	3.00[a] (1.37–6.58)	1.07 (0.32–3.59)	0.87 (0.28–2.74)
TZD		0.44[a] (0.31–0.61) I^2=0.0% 2 studies		0.86 (0.63–1.17) I^2=0.0% 3 studies	SU	1.03 (0.30–3.60)	1.05 (0.31–3.61)	1.30 (0.29–5.94)	1.41 (0.31–6.49)	1.62 (0.36–7.43)	2.27 (0.68–7.56)
SU				0.76 (0.45–1.29) I^2=0.0% 1 study	1.31 (0.77–2.22) I^2=0.0% 1 study	TZD	1.09 (0.46–2.57)	1.34 (0.30–5.94)	1.46 (0.33–6.49)	1.67 (0.38–7.44)	2.34 (0.73–7.51)
GLP-1RA	0.22[a] (0.10–0.46) I^2=90.4% 4 studies	0.44[a] (0.29–0.69) I^2=0.0% 1 study		0.71[a] (0.56–0.90) I^2=0.0% 2 studies		0.92 (0.59–1.44) I^2=0.0% 1 study	GLP-1RA	1.24 (0.28–5.39)	1.34 (0.31–5.89)	1.54 (0.35–6.75)	2.16 (0.69–6.78)
DPP4i+SGLT2i		0.33[a] (0.21–0.52) I^2=0.0% 1 study	0.47[a] (0.33–0.68) I^2=0.0% 1 study					DPP4i+SGLT2i	1.08 (0.19–6.08)	1.25 (0.37–4.25)	1.74 (0.41–7.41)
Met+SGLT2i									Met+SGLT2i	1.15 (0.20–6.46)	1.61 (0.63–4.11)
DPP4i+TZD		0.27[a] (0.17–0.43) I^2=0.0% 1 study				0.67[a] (0.50–0.89) I^2=0.0% 1 study				DPP4i+TZD	1.40 (0.33–5.98)
Met+DPP4i	0.03[a] (0.01–0.09) I^2=0.0% 1 study	0.22[a] (0.14–0.33) I^2=0.0% 1 study		0.35[a] (0.28–0.44) I^2=0.0% 2 studies					0.62 (0.35–1.11) I^2=0.0% 1 study		Met+DPP4i

Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for odd ratios of HbA1c target achievement of antidiabetic treatments after 6 months. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in reverse order of the mean rank results. The American Diabetes Association guidelines recommend setting HbA1c targets at below 7.0%, and this was the primary target used in the analysis. When data on HbA1c targets below 7.0% were unavailable, targets below 6.5% were used instead.

HbA1c, glycosylated hemoglobin; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; Met, metformin; TZD, thiazolidinediones; GLP-1RA, glucagon-like peptide-1 receptor agonist.

[a]Results indicate statistical significance.

Adverse events and hypoglycemia

The NMA and PMA results for any and serious adverse events are presented in Supplementary Figs. 5 and 6, respectively. The global test results showed no evidence of inconsistency for any adverse event (P=0.8471) and serious adverse events (P=0.9773). In the rank test for any adverse events, placebo (SUCRA: 91.9), GLP-1RA (SUCRA: 77.9), and DPP4i (SUCRA: 51.1) ranked the highest, indicating a lower likelihood of adverse events. Conversely, SGLT2i (SUCRA: 34.2) and SU (SUCRA: 28.3) ranked the lowest, indicating a higher likelihood of adverse events. For serious adverse events, DPP4i (SUCRA: 63.6), SU (SUCRA: 60.7), and metformin+DPP4i (SUCRA: 58.3) ranked the highest, whereas DPP4i+SGLT2i (SUCRA: 33.8) and SGLT2i (SUCRA: 21.4) ranked the lowest, indicating more events. However, no statistically significant differences were observed in the occurrence of any or serious adverse events across treatment combinations in both NMA and PMA.

The NMA and PMA results for hypoglycemia are presented in Supplementary Fig. 7. The global test results showed no evidence of inconsistency (P=0.9385). In the NMA rank test, DPP4i+SGLT2i ranked higher than placebo, suggesting a lower likelihood of hypoglycemia, but the difference was not statistically significant (SUCRA: 92.4, OR: 0.20; 95% CI, 0.01 to 5.50), and no direct comparisons were available. Following DPP4i+SGLT2i, placebo (SUCRA: 77.8), DPP4i (SUCRA: 70.9), TZD (SUCRA: 55.9), and SGLT2i (SUCRA: 52.8) ranked higher, indicating a lower hypoglycemia risk. Conversely, SU (SUCRA: 10.1) ranked the lowest, indicating the highest risk of hypoglycemia. SU was significantly associated with a higher risk of hypoglycemia compared to placebo (OR: 17.2; 95% CI, 1.4 to 220.3). In the PMA, although SU did not have direct comparisons with placebo, it showed a significantly higher risk of hypoglycemia compared to TZD (OR: 5.13; 95% CI, 3.21 to 8.18), GLP-1RA (OR: 9.10; 95% CI, 5.69 to 14.55), and metformin (OR: 4.87; 95% CI, 4.03 to 5.89). No other treatments were associated with a statistically significant increase in the risk of hypoglycemia.

Other secondary outcomes

For systolic and diastolic blood pressure, data were available from 21 and 20 studies, respectively, out of the 60 included studies. The number of direct comparisons was 33 for systolic blood pressure and 32 for diastolic blood pressure, involving 6,350 and 6,313 participants, respectively. However, owing to the limited number of included studies and the fragmented network structure, a coherent network could not be established for these outcomes. As a result, NMA could not be performed.

Regarding lipid profiles, data for LDL-C, HDL-C, and triglycerides were available from 27, 28, and 27 studies, respectively, of the 60 included studies. The NMA and PMA results for these outcomes are presented in Supplementary Figs. 8-10. The global test results indicated significant inconsistencies, with P<0.0001 for LDL-C, P<0.0001 for HDL-C, and P=0.0038 for triglycerides. While some treatment combinations showed statistically significant differences in either NMA or PMA, the results varied across drug classes and were inconsistent. Notably, the PMA for SGLT2i revealed a slight but statistically significant increase in LDL-C (WMD: 4.5 mg/dL; 95% CI, 1.9 to 7.0), a significant increase in HDL-C (WMD: 2.7 mg/dL; 95% CI, 1.9 to 3.4), and a significant decrease in triglycerides (WMD: –11.7 mg/dL; 95% CI, –18.7 to –4.8) compared to placebo.

DISCUSSION

This study represents the first systematic review and NMA to compare not only monotherapies but also various combination therapies in people with early T2DM and non-severe hyperglycemia (HbA1c ≤8.5%), who have minimal prior exposure to pharmacotherapy. The findings offer a comprehensive comparison of glycemic control efficacies and other outcomes across diverse therapeutic strategies in this specific patient population.

Regarding glycemic control, all dual combination therapies consistently demonstrated superior glycemic control compared to monotherapies. Among them, metformin+GLP-1RA (HbA1c reduction: vs. placebo WMD: –1.50%; 95% CI, –2.04 to –0.96) and metformin+DPP4i (HbA1c reduction: vs. placebo WMD: –1.46%; 95% CI, –1.96 to –0.95; HbA1c target achievement: vs. placebo OR: 34.33; 95% CI, 7.70 to 153.16) were the most effective combinations. In terms of the rank test results for HbA1c reduction and target achievement, the order was consistent across therapies, except for the minimal reversal in the ranking of metformin, SU, and TZD in monotherapies. Apart from the therapies not included in the analysis, all other therapies showed concordance between the two outcomes. Interestingly, metformin was the only therapy that failed to show statistically significant superiority over the placebo in both HbA1c reduction and target achievement (HbA1c reduction: vs. placebo WMD: 0.10%; 95% CI, –0.46 to 0.66; HbA1c target achievement: vs. placebo OR: 1.08; 95% CI, 0.19 to 6.08), which contradicts common clinical expectations. This discrep-

ancy is likely due to the relatively small proportion of placebo-controlled comparisons involving metformin (14.7%, five of 34 comparisons), which may have underestimated its effect on NMA. In contrast, DPP4i had a higher proportion of placebo comparisons (51.5%, 17 of 33 comparisons), which may have provided a more accurate estimate of its efficacy. In the PMA, metformin showed statistically significant effects compared to placebo (HbA1c reduction: WMD: –0.53%; 95% CI, –0.64 to –0.43; HbA1c target achievement: OR: 11.49; 95% CI, 4.07 to 32.26). This finding reinforces the existing knowledge that metformin is an effective glucose-lowering therapy when analyzed using direct evidence, despite the NMA results. The glycemic control effects of various drug regimens in adults with early T2DM observed in this study are consistent with findings from general studies conducted in overall T2DM populations [8], further supporting the consistency of these therapeutic approaches.

In terms of weight reduction, GLP-1RA, SGLT2i, metformin, and their combination therapies were more effective than the placebo, whereas TZD, SU, and DPP4i ranked lower. Regarding any and serious adverse events, no significant differences were observed among the various agents and their combinations. Notably, and as expected, SU was the only therapy that significantly increased the risk of hypoglycemia compared to other treatments (vs. placebo OR: 17.2; 95% CI, 1.34 to 220.3). Regarding lipid profiles, including LDL-C, HDL-C, and triglycerides, the results were characterized by substantial heterogeneity and limited study comparisons, leading to inconsistent findings (global test $P<0.01$). In the PMA, despite the superior cardiovascular outcomes of SGLT2i, they slightly increased the LDL-C levels (vs. placebo WMD: 4.5 mg/dL; 95% CI, 1.9 to 7.0). SGLT2i also increased HDL-C (vs. placebo WMD: 2.7 mg/dL; 95% CI, 1.9 to 3.4) and decreased triglycerides (vs. placebo WMD: –11.7 mg/dL; 95% CI, –18.7 to –4.8). These results are consistent with recent reports [9], reflecting their complex effects on lipid metabolism. This pattern suggests that while SGLT2i improve certain cardiovascular outcomes, their impact on the lipid profile, particularly the increase in LDL-C, should be considered in the context of overall patient management.

This study has several limitations that should be considered when interpreting the results. First, our findings are only applicable to people with early T2DM. However, our thorough analysis confirmed that the effects of drug regimens in patients with early T2DM are consistent with those observed in the overall T2DM population. Second, the selection of studies focusing on early T2DM led to a high level of inconsistencies in each outcome, particularly when certain drug combinations were overly represented in placebo-controlled or active-controlled trials. This could still result in the overestimation or underestimation of drug efficacy, despite our mitigation efforts through PMA. As recent guidelines increasingly emphasize early combination therapy, the accumulation of results from RCTs focusing on various combination therapies in people with early T2DM who meet our study criteria, followed by NMA, could help overcome heterogeneity and further reduce the potential for interpretative errors. In our study, GLP-1RA showed a lower-than-expected effect on glycemic control and weight reduction. This outcome may be attributed to the varied efficacy of GLP-1RA agents, as the study included only one trial with subcutaneous semaglutide, two with oral semaglutide, one with liraglutide, two with dulaglutide, one with once-weekly exenatide, and three with once-daily exenatide. The relatively small number of studies involving more potent GLP-1RA agents could have contributed to the observed results. Therefore, in the future, additional RCTs involving more potent GLP-1RAs, such as subcutaneous semaglutide, in early T2DM will be necessary, and further integrated analyses of these studies may be required.

In conclusion, our NMA results demonstrated superior glycemic control with initial combination therapies compared to monotherapies without an increased risk of adverse events in early T2DM. However, the heterogeneity of the included studies and the specific focus on early T2DM may have over- or underestimated the effects. Therefore, future RCTs involving potent GLP-1RAs, novel antidiabetic agents, and various combination therapies, even in people with early T2DM, are crucial for establishing more effective and individualized treatment strategies within clinical guidelines.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0660.

CONFLICTS OF INTEREST

Sang Youl Rhee has been an associate editor of the *Diabetes & Metabolism Journal* since 2022. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception or design: M.K.M.
Acquisition, analysis, or interpretation of data: all authors.
Drafting the work or revising: J.H.C., M.K.M.
Final approval of the manuscript: J.H.C., Y.S.Y., M.K.M.

ORCID

Jong Han Choi *https://orcid.org/0000-0002-2667-4332*
Min Kyong Moon *https://orcid.org/0000-0002-5460-2846*

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Supplementary Table 1. Population, Intervention, Comparison, Outcomes, Time, Study design (PICOTS) table

Category	Details
Population	- Adults with newly diagnosed type 2 diabetes mellitus or
	- Adults with previously diagnosed type 2 diabetes mellitus but who have never received pharmacological treatment
	Exclusion criteria for studies
	- Studies with participants having a mean disease duration of >5 years
	- Studies with participants having a mean baseline HbA1c >8.5%
Interventions and comparators	Medications
	1) Placebo: placebo, non-pharmacological therapy (e.g., lifestyle intervention)
	2) Metformin
	3) Sulfonylureas: glibenclamide, gliclazide, glimepiride
	4) Thiazolidinediones: rosiglitazone, pioglitazone, lobeglitazone
	5) Dipeptidyl peptidase-4 inhibitors: sitagliptin, vildagliptin, linagliptin, saxagliptin, alogliptin, anagliptin, teneligliptin, gemigliptin, evogliptin
	6) Sodium-glucose cotransporter-2 inhibitors: dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipragliflozin, enavogliflozin
	7) Glucagon-like peptide-1 receptor agonists: exenatide, lixisenatide, dulaglutide, liraglutide, semaglutide
	8) Combination therapy of two or more drugs listed in 2) to 7)
Outcomes	Primary outcomes
	- Change in HbA1c
	- Odd ratios (ORs) for achievement of target HbA1c levels (<7.0% or <6.5%)
	Secondary outcomes
	- Change in fasting blood glucose, body weight, blood pressure
	- Change in total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides
	- ORs for incidence of adverse events
Time	≥24 weeks
Study design	Randomized controlled study with an intervention period of more than 24 weeks

HbA1c, glycosylated hemoglobin.

Supplementary Table 2. Search strategy in MEDLINE through PubMed

1.	Metformin[Mesh:NoExp] OR metformin[TW] OR metformine[TW] OR LA-6023[TW] OR LA6023[TW]
2.	Sulfonylurea Compounds [Mesh:NoExp] OR sulfonylurea[TW]
3.	glimepiride[NM] OR glimepiride[TW] OR HOE-490[TW] OR HOE490[TW]
4.	Gliclazide[MH] OR gliclazide[TW] OR S-1702[TW] OR S1702[TW] OR S-852[TW] OR S852[TW]
5.	Glipizide[MH] OR glipizide[TW] OR K-4024[TW] OR K4024[TW]
6.	Glyburide[MH] OR glybenclamide[TW] OR glyburide[TW] OR HB-419[TW] OR HB419[TW] OR HB-420[TW] OR HB420[TW]
7.	Thiazolidinediones[Mesh:NoExp] OR thiazolidinediones[TW]
8.	Pioglitazone[MH] OR pioglitazone[TW] OR U-72107A[TW] OR U72107A[TW] OR AD-4833[TW] OR AD4833[TW]
9.	Rosiglitazone[MH] OR rosiglitazone[TW] OR BRL-49653[TW] OR BRL49653[TW]
10.	lobeglitazone[NM] OR lobeglitazone[TW] OR CKD-501[TW] OR CKD501[TW]
11.	Dipeptidyl-Peptidase IV Inhibitors [MH] OR "dipeptidyl-peptidase IV inhibitor*"[TW] OR "DPP-4 Inhibitor*"[TW]
12.	Sitagliptin Phosphate[MH] OR sitagliptin[TW] OR sitagliptine[TW] OR MK-0431[TW] OR MK0431[TW]
13.	Vildagliptin[MH] OR vildagliptin[TW] OR NVP-LAF237[TW] OR NVPLAF237[TW]
14.	Linagliptin[MH] OR linagliptin[TW] OR BI-1356[TW] OR BI1356[TW]
15.	saxagliptin[NM] OR saxagliptin[TW] OR BMS-477118[TW] OR BMS477118[TW]
16.	alogliptin[NM] OR alogliptin[TW] OR SYR-322[TW] OR SYR322[TW]
17.	anagliptin[NM] OR anagliptin[TW] OR SK-0403[TW] OR SK0403[TW]
18.	LC15-0444[NM] OR gemigliptin[TW] OR LC15-0444[TW] OR LC150444[TW]
19.	"4-(3-amino-4-(2,4,5-trifluorophenyl)butanoyl)-3-(tert-butoxymethyl)piperazin-2-one" [Supplementary Concept] OR evogliptin[TW] OR DA-1229[TW] OR DA1229[TW]
20.	"3-(4-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)pyrrolidin-2-ylcarbonyl)thiazolidine" [Supplementary Concept] OR teneligliptin[TW] OR mp-513[TW] OR mp513[TW]
21.	Glucagon-Like Peptide 1 [Mesh:NoExp] "glucagon-like peptide-1"[TW] OR GLP-1[TW] OR GLP1[TW]
22.	Exenatide[MH] OR exenatide[TW] OR AC-2993[TW] OR AC2993[TW] OR ITCA-650[TW] OR ITCA650[TW]
23.	dulaglutide[NM] OR dulaglutide[TW] OR LY-2189265[TW] OR LY2189265[TW]
24.	lixisenatide[TW] OR AVE-010[TW] OR AVE010[TW] OR AVE-0010[TW] OR AVE0010[TW] OR AQVE-10010[TW] OR AQVE10010[TW] OR ZP-10[TW] OR ZP10[TW]
25.	Liraglutide[MH] OR liraglutide[TW] OR NN-2211[TW] OR NN2211[TW]
26.	semaglutide[TW] OR NN-9535[TW] OR NN9535[TW] OR NN-9924[TW] OR NN9924[TW]
27.	Sodium-Glucose Transporter 2 Inhibitors [MH] OR "sodium-glucose transporter 2 inhibitor*"[TW] OR "SGLT2 Inhibitor*"[TW] OR "SGLT2 Inhibitor*"[TW]
28.	dapagliflozin[NM] OR dapagliflozin[TW] OR BMS-512148[TW] OR BMS512148[TW]
29.	Canagliflozin[MH] OR canagliflozin[TW] OR JNJ-28431754[TW] OR JNJ28431754[TW] OR TA-7284[TW] OR TA7284[TW]
30.	empagliflozin[NM] OR empagliflozin[TW] OR BI-10773[TW] OR BI10773[TW]
31.	ertugliflozin[NM] OR ertugliflozin[TW] OR PF-04971729[TW] OR PF04971729[TW]
32.	Ipragliflozin[NM] OR Ipragliflozin[TW] OR ASP-1941[TW] OR ASP1941[TW]
33.	Enavogliflozin[Supplementary Concept] OR enavogliflozin[TW] OR DWP-16001[TW] OR DWP16001[TW]
34.	1-33/OR
35.	33 AND (Randomized Controlled Trial[PT] OR Controlled Clinical Trial[PT:NoExp] OR randomised[TIAB] OR randomized[TIAB] OR placebo*[TIAB] OR Clinical Trials as Topic[Mesh:NoExp] OR randomly[TIAB] OR trial*[TI]) NOT (Case Reports[PT] OR case report*[TI] OR Comment[PT] OR comment*[TI] OR Letter[PT] OR letter[TI] OR Editorial[PT] OR (Animals[MeSH] NOT Humans[MeSH]))
36.	34 NOT Meta-Analysis[PT] OR metaanalys*[TI] OR meta-analys*[TI] OR Systematic Review[PT] OR systematic-review*[TI]

Supplementary Table 3. Main characteristics of randomized controlled trials included in systematic literature review and network meta-analysis

Study	Acronym	Clinical trial registration no.	Duration of intervention, mo	No. of randomized patients	Baseline HbA1c, %	Duration of diabetes, yr	Male sex, %	Age, yr	BMI, kg/m^2 (BW^a, kg)	Intervention (change in HbA1c after 6 months, %)			
										1st	2nd	3rd	4th
Abdullah et al. (2021) [1]		NA	6	220	NA	New	NA	51.6	30.6	M+D	M+S		
										(only HbA1c target achievement rates are available)			
Aroda et al. (2019) [2]	PIONEER-1	NCT02906930	6	703	8.0	3.5	50.8	55.0	31.8	P (–0.3)	G (–1.2)		
Aschner et al. (2010) [3]		NCT00449930	6	1,050	7.2	2.4	46.0	56.0	30.8	M (–0.6)	D (–0.4)		
Bailey et al. (2012) [4]		NA	6	136	7.9	1.4	50.1	53.0	31.8	P (0.0)	S (–0.8)		
Birkeland et al. (1994) [5]		NA	15	46	8.0	3.5	NA	59.0	26.4	P (0.1)	U (–0.6)		
Bi et al. (2013) [6]		ChiCTRTRC 10000941	6	138	8.1	New	NA	54.3	24.9	M (–1.7)	U (–2.0)		
Chen et al. (2018) [7]		NCT01644500	6	737	8.0	3.7	54.3	52.8	25.9	U (–0.6)	G (–1.0)		
de Boer et al. (2017) [8]	RELEASE	NCT02015299	6	45	6.3	1.0	61.4	63.0	30.4	P (0.1)	D (–0.3)		
Defronzo et al. (2008) [9]		NCT00286455	6	195	7.9	Drug naïve	53.2	53.4	NA	P (0.0)	D (–0.6)		
Dejager et al. (2007) [10]		NCT00099905	6	594	8.4	2.0	47.3	54.0	32.8	P (–0.3)	D (–0.8)		
Del Prato et al. (2011) [11]		NCT00621140	6	503	8.0	Drug naïve	48.3	55.7	29.1	P (0.3)	D (–0.4)		
Deng et al. (2017) [12]		NA	6	72	7.4	<2	75.0	63.9	22.5	P (–0.4)	D (–0.7)		
Derosa et al. (2013) [13]		NA	12	171	8.0	0.6	NA	57.1	31.9	M (–0.2)	M+G (–0.6)		
Erem et al. (2014) [14]		NA	12	57	8.3	New	31.6	53.2	32.5	M (–1.2)	U (–1.3)	T (–1.2)	
Esposito et al. (2011) [15]		NA	6	110	8.1	New	52.7	54.6	29.0	M (–0.9)	T (–0.9)		
Ferrannini et al. (2010) [16]		NCT00528372	6	485	7.9	0.5	51.2	52.5	32.5	P (–0.2)	S (–0.8)		
Frederich et al. (2012) [17]		NCT00316082	6	365	8.0	1.7	46.1	55.0	30.5	P (–0.3)	D (–0.7)		
Gautam et al. (2023) [18]		CTRI/ 2020/12/030147	6	114	8.3	New	51.8	41.0	NA	M+D (–1.3)	M+S (–1.2)		
Hallsten et al. (2002) [19]		NA	6	41	6.6	New	68.1	58.0	29.8	P (–0.2)	M (–0.7)	T (–0.3)	
Ishii et al. (2020) [20]	J-BOND	jRCTs 051180165	6	253	7.9	3.3	59.7	54.3	28.4	D (–1.0)	S (–0.9)		
Ishtiaque et al. (2022) [21]		NA	6	180	7.6	New	NA	47.0	29.4	M+D (–1.2)	M+S (–1.0)		
Jianfang et al. (2023) [22]		NCT03796975	6	120	8.2	New	71.7	59.0	26.0	M (–1.7)	M+T (–1.8)		
Kadoglou et al. (2011) [23]		NA	6	136	7.6	2.3	27.2	62.4	29.9	M (–0.7)	M+T (–1.0)		
Kahn et al. (2006) [24]		NCT00279045	60	4,360	7.4	Drug naïve	57.7	56.9	32.2	M (–0.7)	U (–0.9)	T (–0.6)	
Kawazu et al. (2017) [25]	JEDIS	NA	36	95	6.6	New	64.4	59.4	23.8	P (0.0)	M (–0.2)	U (–0.1)	D (–0.4)
Kiyici et al. (2009) [26]		NA	12	50	6.7	Drug naïve	44.0	51.7	31.0	P (0.1)	M (–0.3)	T (–0.7)	
Lambadiari et al. (2018) [27]		NCT03010683	6	60	8.5	New	66.7	51.0	30.3	M (–0.7)	G (–1.6)		
Lee et al. (1998) [28]		NA	6	48	8.4	3.5	0.0	60.0	39.8	P (–0.1)	M (–1.0)		
Lewin et al. (2015) [29]		NCT01422876	12	667	8.0	Drug naïve	53.8	54.6	31.6	D (–0.7)	S (–0.9)	D+S (–1.2)	
Linong et al. (2014) [30]		NCT01095653	6	393	8.3	1.4	65.4	51.4	25.6	P (–0.3)	S (–1.1)		
Li et al. (2021) [31]		NA	6	326	7.4	New	51.8	49.8	24.5	M (–2.0)	M+D (–2.3)		
Matthews et al. (2019) [32]	VERIFY	NCT01528254	60	2,001	6.7	3.4	47.0	54.4	31.1	M	M+D		
										(only HbA1c target achievement rates are available)			

(*Continued to the next page*)

Supplementary Table 3. Continued

Study	Acronym	Clinical trial registration no.	Duration of intervention, mo	No. of randomized patients	Baseline HbA1c, %	Duration of diabetes, yr	Male sex, %	Age, yr	BMI, kg/m^2 (BW[a], kg)	Intervention (change in HbA1c after 6 months, %)			
										1st	2nd	3rd	4th
Mita et al. (2019) [33]		UMIN 000022953	6	43	7.3	3.4	60.5	59.2	26.0	M (−0.5)	D (−0.5)		
Moretto et al. (2008) [34]		NCT00381342	6	233	7.8	1.3	56.3	54.0	31.7	P (−0.2)	G (−0.8)		
Nauck et al. (2016) [35]		NCT01183013	6	936	8.1	Drug naïve	54.8	57.1	32.6	D (−0.4)	T (−0.7)	D+T (−1.1)	
Nie et al. (2017) [36]		NA	6	240	7.1	1.0	70.0	50.5	28.5	M (−0.6)	T (−0.5)	M+T (−0.9)	
Pan et al. (2012) [37]		NCT00698932	6	568	8.2	1.0	55.5	51.4	25.9	P (−0.3)	D (−0.8)		
Park et al. (2017) [38]		NCT02946541	6	160	7.2	4.5	53.1	57.2	25.5	P (0.0)	D (−0.2)		
Pi-Sunyer et al. (2007) [39]		NCT00120536	6	354	8.4	2.2	55.1	51.2	32.2	P (−0.1)	D (−0.8)		
Pratley et al. (2014) [40]		NCT 01023581	6	784	NA	2.4	47.7	53.5	30.7	P (0.2)	M (−0.9)	D (−0.5)	M+D (−1.4)
Roden et al. (2013) [41]	EMPA-MONO	NCT01289990	18	899	7.9	Drug naïve	63.3	55.0	28.4	P (0.1)	D (−0.7)	S (−0.7)	
Rosenstock et al. (2009) [42]		NCT00121641	6	401	8.0	2.6	50.3	53.5	31.7	P (0.2)	D (−0.5)		
Russell-Jones et al. (2012) [43]	DURATION-4	NCT00676338	6	820	8.5	2.7	59.0	54.0	(87.0*)	M (−1.5)	T (−1.6)	D (−1.2)	G (−1.5)
Scherbaum et al. (2008) [44]		NCT00101712	12	306	6.8	2.6	59.5	63.1	30.2	P (0.0)	D (−0.3)		
Schweizer et al. (2009) [45]		NCT00246619	6	335	7.7	3.0	48.7	70.9	29.6	M (−0.8)	D (−0.6)		
Sorli et al. (2017) [46]	SUSTAIN-1	NCT02054897	6	388	8.1	4.2	54.0	53.7	32.9	P (0.0)	G (−1.5)		
Stenlof et al. (2013) [47]		NCT01081834	6	587	8.0	4.3	46.2	55.4	31.6	P (0.1)	S (−0.9)		
Teramoto et al. (2007) [48]		NA	6	92	8.2	Drug naïve	73.9	56.7	25.0	U (−1.4)	T (−0.8)		
Terra et al. (2017) [49]	VERTIS-MONO	NCT01958671	6	461	8.2	5.0	56.6	56.4	33.0	P (−0.1)	S (−0.9)		
Umpierrez et al. (2014) [50]	AWARD-3	NCT01126580	12	807	7.6	3.0	43.7	55.3	33.3	M (−0.6)	G (−0.8)		
Wang et al. (2024) [51]	PIONEER-11	NCT04109547	6	521	8.0	2.2	63.7	52.0	28.3	P (−0.2)	G (−1.5)		
Wang et al. (2016) [52]		NA	6	28	8.2	New	40.5	60.2	NA	P (−0.7)	S (−1.4)		
Wu et al. (2015) [53]		NA	6	57	8.0	New	57.9	51.9	24.2	P (−0.4)	D (−1.2)		
Xiao et al. (2016) [54]		NA	6	41	7.3	New	52.9	62.1	28.1	M+U (−0.8)	M+D (−1.1)		
Xu et al. (2015) [55]	CONFIDENCE	NCT01147627	12	278	8.0	New	61.3	<50	25.9	T (−1.3)	G (−1.8)		
Yang et al. (2015) [56]		NA	6	109	7.1	3.6	54.3	56.2	25.0	P (0.2)	D (−0.5)		
Yang et al. (2013) [57]		NA	6	182	8.3	3.1	58.0	53	26.1	P (−0.1)	D (−0.7)		
Yoon et al. (2011) [58]	PEAM	NA	12	349	7.8	Drug naïve	55.3	50.9	25.6	M (−1.0)	U (−1.0)	T (−0.9)	
Zhang et al. (2023) [59]		ChiCTR 2000037951	6	64	8.3	New	56.4	47.0	26.4	M+U (−1.2)	M+S (−1.5)		
Zografou et al. (2015) [60]		NA	6	64	8.1	Drug naïve	59.4	54.4	31.9	M (−1.2)	M+D (−1.7)		

HbA1c, glycosylated hemoglobin; BMI, body mass index; BW, body weight; NA, not available; M, metformin; D, dipeptidyl peptidase-4 inhibitor; S, sodium-glucose cotransporter-2 inhibitor; P, placebo or lifestyle management only; G, glucagon-like peptide-1 receptor agonist; U, sulfonylureas; T, thiazolidinedione.

[a]In cases where BMI was unavailable in the literature and only BW was provided, BW was indicated, with the value presented in parentheses.

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Supplementary Table 4. Characteristics of included studies for HbA1c reduction efficacy of antidiabetic treatments after 6 months

Treatment	Number of studies	Number of subjects	Mean baseline HbA1c
Placebo	31	2,844	7.9
Met	22	3,486	7.6
SU	8	1,743	7.6
TZD	11	2,225	7.6
DPP4i	24	3,531	7.9
SGLT2i	9	1,992	8.0
GLP-1RA	9	2,590	8.0
Met+SU	2	49	7.9
Met+TZD	3	207	7.6
Met+DPP4i	6	591	7.8
Met+SGLT2i	3	179	7.9
Met+GLP-1RA	1	84	8.0
DPP4i+TZD	1	371	8.1
DPP4i+SGLT2i	1	269	8.0
Total	58	20,161	7.8

HbA1c, glycosylated hemoglobin; Met, metformin; SU, sulfonylurea; TZD, thiazolidinedione; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Supplementary Table 5. Number of studies, direct comparisons, and participants by outcome variables

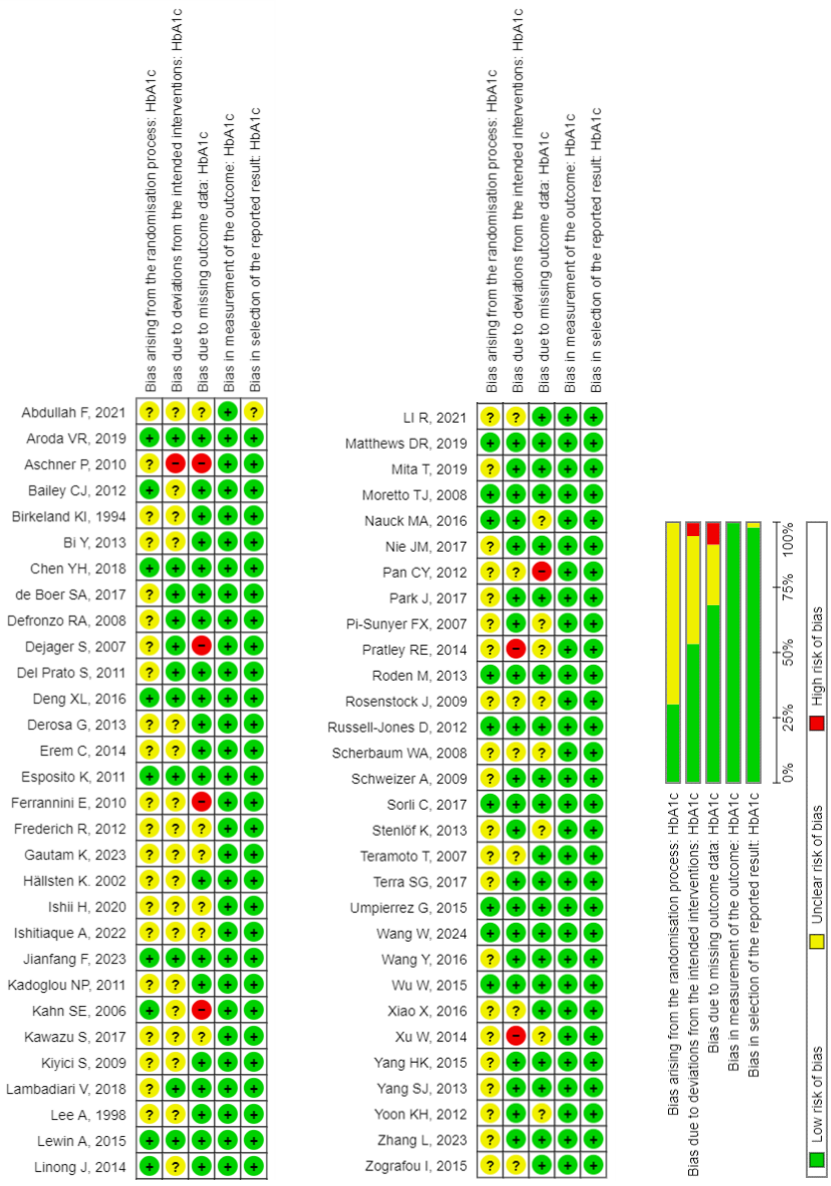
Outcome variables	Studies	Direct comparisons	Subjects
HbA1c	58	91	20,161
Proportion of achievement of target HbA1c	30	48	15,018
Fasting blood glucose	51	81	18,333
Body weight	42	66	18,706
Systolic blood pressure	21	33	6,350
Diastolic blood pressure	20	32	6,313
Low-density lipoprotein cholesterol	27	44	10,716
High-density lipoprotein cholesterol	28	45	10,984
Triglyceride	27	44	10,751
Any adverse event	31	46	17,592
Serious adverse event	27	42	16,288
Hypoglycemia	22	30	13,359
Total	60	93	22,291

HbA1c, glycosylated hemoglobin.

Supplementary Table 6. Inconsistency test between direct and indirect treatment comparisons in mixed treatment comparison for HbA1c reduction efficacy after 6 months

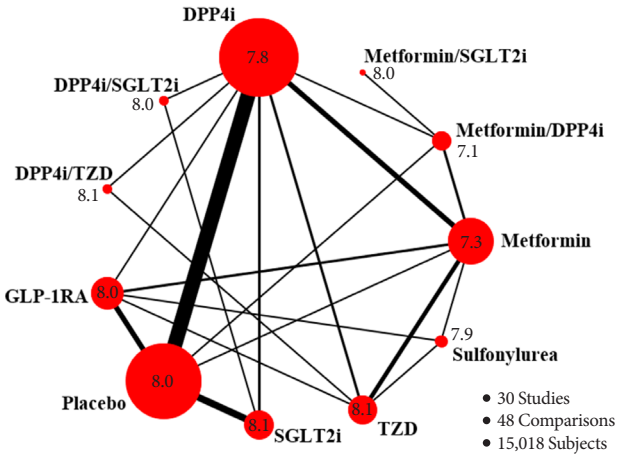
Side	Direct		Indirect		Difference		*P*>z
	Coef.	SE	Coef.	SE	Coef.	SE	
AB	0.159809	0.096023	0.046737	0.117675	0.113072	0.151779	0.456
AC	–0.228511	0.146051	–0.389340	0.121102	0.160830	0.189562	0.396
AE	0.590234	0.117408	0.715752	0.097522	–0.125518	0.153276	0.413
AG	0.030598	0.090634	0.132780	0.172981	–0.102182	0.195292	0.601
AJ	–0.106250	0.118338	0.030689	0.159489	–0.136940	0.197027	0.487
AK	–0.285494	0.235497	–0.469041	0.104630	0.183547	0.257946	0.477
AM	0.547967	0.059793	0.556625	0.116407	–0.008658	0.130917	0.947
AN	–0.044040	0.129344	–0.306142	0.111332	0.262102	0.170595	0.124
BD	–0.358439	0.173931	0.045395	0.105277	–0.403835	0.203336	0.047
BF	0.259628	0.241107	–0.264171	0.113369	0.523798	0.263660	0.047
BG	1.048282	0.122272	0.919986	0.130626	0.128296	0.178848	0.473
BK	0.112258	0.182119	0.497600	0.124553	–0.385343	0.220336	0.080
DF	0.370000	0.237240	0.234272	0.131814	0.135728	0.271399	0.617
EM	–0.807707	0.089433	–0.535640	0.162116	–0.272066	0.185248	0.142
GH	–0.432758	0.197061	–0.660952	0.103278	0.228195	0.222343	0.305
GI	–0.315314	0.184481	–0.874559	0.114245	0.559245	0.214100	0.009
GJ	–0.271204	0.128789	0.120366	0.154070	–0.391569	0.200603	0.051
GK	0.159809	0.096023	0.046737	0.117675	0.113072	0.151779	0.456
GL	–0.228511	0.146051	–0.389340	0.121102	0.160830	0.189562	0.396
GM	0.590234	0.117408	0.715752	0.097522	–0.125518	0.153276	0.413
GN	0.030598	0.090634	0.132780	0.172981	–0.102182	0.195292	0.601
HL	–0.106250	0.118338	0.030689	0.159489	–0.136940	0.197027	0.487
IM	–0.285494	0.235497	–0.469041	0.104630	0.183547	0.257946	0.477
JK	0.547967	0.059793	0.556625	0.116407	–0.008658	0.130917	0.947
JM	–0.044040	0.129344	–0.306142	0.111332	0.262102	0.170595	0.124
KL	–0.358439	0.173931	0.045395	0.105277	–0.403835	0.203336	0.047
KM	0.259628	0.241107	–0.264171	0.113369	0.523798	0.263660	0.047
KN	1.048282	0.122272	0.919986	0.130626	0.128296	0.178848	0.473
LN	0.112258	0.182119	0.497600	0.124553	–0.385343	0.220336	0.080
MN	0.370000	0.237240	0.234272	0.131814	0.135728	0.271399	0.617

HbA1c, glycosylated hemoglobin; SE, standard error; A, metformin; B, metformin+dipeptidyl peptidase-4 inhibitor (DPP4i); C, metformin+glucagon-like peptide-1 receptor agonist (GLP-1RA); E, metformin+thiazolidinedione; G, DPP4i; J, GLP-1RA; K, placebo; L, sodium-glucose cotransporter-2 inhibitor (SGLT2i); M, thiazolidinedione; N, sulfonylurea; D, metformin+SGLT2i; F, metformin+sulfonylurea; H, DPP4i+SGLT2i; I, DPP4i+thiazolidinedione.



Supplementary Fig. 1. Risk of bias assessment of all studies using the Cochrane risk of bias 2.0 for outcome of glycosylated hemoglobin (HbA1c) after 6 months.

A

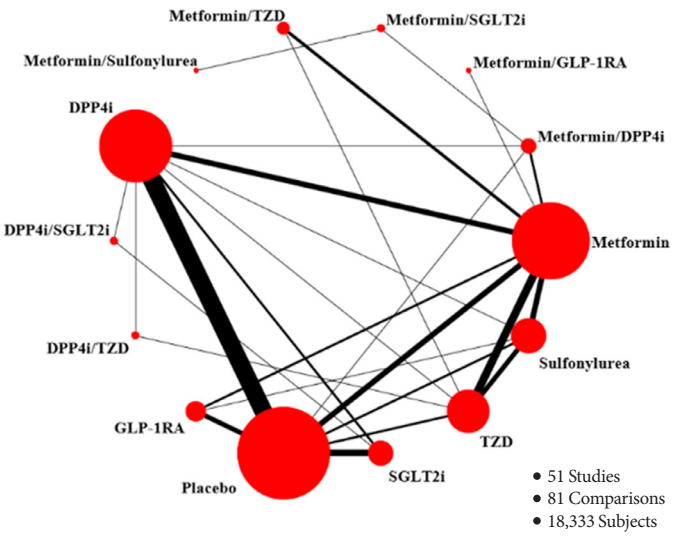


B

Treatment	SUCRA	PrBest	Mean rank
Met+DPP4i	89.9	45.6	2
DPP4i+TZD	76.7	23.1	3.3
Met+SGLT2i	66.7	11.7	4.3
DPP4i+SGLT2i	66.6	10.3	4.3
GLP-1RA	57.0	3.3	5.3
SU	53.5	3.9	5.7
TZD	52.7	2	5.7
Met	38.4	0	7.2
SGLT2i	31.7	0.1	7.8
DPP4i	16.8	0	9.3
Placebo	0.1	0	11

Supplementary Fig. 2. Network geometry (A), and the results of rank test (B) for odds ratios of glycosylated hemoglobin (HbA1c) target achievement of antidiabetic treatments after 6 months. Each circle represents an antidiabetic treatment that was included in the analysis, with the size of the circle proportional to the number of trials involving the treatment. The width of each connecting line is proportional to the number of individuals who participated in each pair of trials. The numbers inside or next to the circles indicate the baseline glycosylated hemoglobin (HbA1c) levels for each treatment group. The American Diabetes Association guidelines recommend setting HbA1c targets at below 7.0%, and this was the primary target used in the analysis. When data on HbA1c targets below 7.0% were unavailable, targets below 6.5% were used instead. The global test for inconsistency yielded a *P* value of 0.9128, indicating no evidence of inconsistency in the network. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; GLP-1RA, glucagon-like peptide-1 receptor agonist; SU, sulfonylurea.

A



B

Treatment	SUCRA	PrBest	Mean rank
Met+DPP4i	87.7	40.5	2.6
DPP4i+TZD	82.2	26.8	3.3
DPP4i+SGLT2i	76.4	11.3	4.1
Met+GLP-1RA	75.7	9.4	4.2
Met+SGLT2i	69.8	5.4	4.9
SGLT2i	60.3	1.9	6.2
Met	49.5	0.0	7.6
Met+SU	47.0	4.2	7.9
TZD	44.3	0.2	8.2
Met+TZD	33.5	0.1	9.7
SU	30.5	0.1	10.0
GLP-1RA	25.8	0.1	10.6
DPP4i	16.7	0.0	11.8
Placebo	0.4	0.0	13.9

Supplementary Fig. 3. Network geometry (A), and the results of rank test (B) for efficacy of antidiabetic treatments on fasting blood glucose after 6 months. (A) Each circle represents an antidiabetic treatment that was included in the analysis, with the size of the circle proportional to the number of trials involving the treatment. The width of each connecting line is proportional to the number of subjects who participated in each pair of trials. The global test for inconsistency yielded a *P* value of 0.0545, which suggests that there may be inconsistencies present in the network of treatments. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for fasting blood glucose (mg/dL) reduction efficacy of antidiabetic treatments after 6 months. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in reverse order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea. [a]Results indicate statistical significance.

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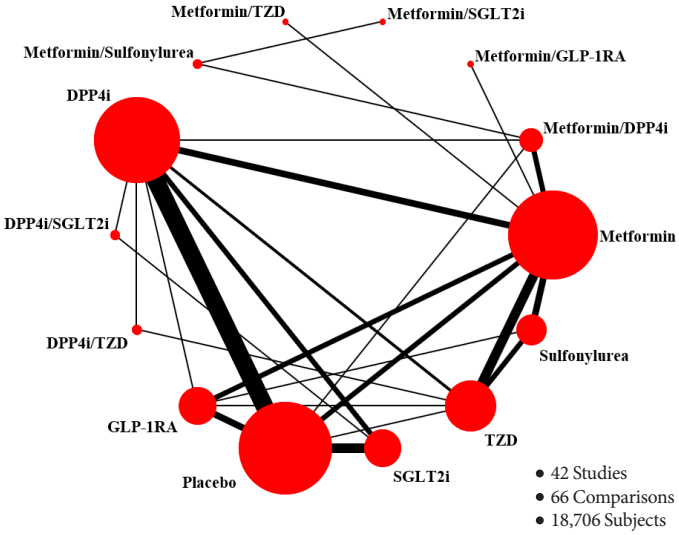
Supplementary Fig. 3. Continued

C

	Placebo	DPP4i	GLP-1RA	SU	Met+ TZD	TZD	Met+ SU	Met	SGLT2i	Met+ SGLT2i	Met+ GLP-1RA	DPP4i+ SGLT2i	DPP4i+ TZD	Met+ DPP4i
Placebo	Placebo	−19.5[a] (−33.5 to −5.5)	−37.5[a] (−54.1 to −21.1)	−25.4[a] (−45.2 to −5.7)	−27.6[a] (−45.0 to −10.2)	−30.6[a] (−48.5 to −12.6)	−31.6 (−64.7 to 1.5)	−13.0[a] (−25.4 to −0.7)	−36.9[a] (−54.8 to −19.1)	−40.6[a] (−67.1 to −14.1)	−41.6[a] (−58.5 to −24.6)	−42.5[a] (−60.4 to −24.7)	−45.2[a] (−63.8 to −26.7)	−48.0[a] (−71.7 to −24.4)
DPP4i	10.7[a] (9.8 to 11.6) I^2=68.6% 16 sutides	DPP4i	−18.1[a] (−33.4 to −2.7)	−5.9 (−24.7 to 12.8)	−8.1 (−24.4 to 8.2)	−11.0 (−27.9 to 5.8)	−12.1 (−44.7 to 20.5)	−4.9 (−15.6 to 5.7)	−17.4[a] (−28.5 to −6.4)	−21.1 (−46.9 to 4.7)	−22.0[a] (−37.9 to −6.2)	−23.0[a] (−34.1 to −12.0)	−25.7[a] (−38.0 to −13.5)	−28.5[a] (−51.3 to −5.7)
GLP-1RA	23.9[a] (20.7 to 27.1) I^2=71.9% 4 studies		GLP-1RA	12.1 (−4.7 to 29.0)	10.0 (−4.1 to 24.0)	7.0 (−7.7 to 21.7)	6.0 (−25.6 to 37.5)	8.4 (−10.4 to 27.2)	0.6 (−18.3 to 19.5)	−3.0 (−27.5 to 21.4)	−4.0 (−17.6 to 9.6)	−5.0 (−23.9 to 13.9)	−7.7 (−27.3 to 11.9)	−10.5 (−31.8 to 10.9)
SU	6.4 (−2.6 to 15.4) I^2=89.6% 2 studies	−2.5 (−15.6 to 10.6) I^2=0.0% 1 study	−10.7[a] (−15.2 to −6.3) I^2=0.0% 1 study	SU	−2.2 (−19.9 to 15.5)	−5.1 (−23.3 to 13.1)	−6.2 (−39.5 to 27.1)	−14.2 (−31.7 to 3.4)	−11.5 (−33.3 to 10.3)	−15.2 (−41.9 to 11.5)	−16.1 (−33.4 to 1.2)	−17.1 (−38.9 to 4.7)	−19.8 (−42.2 to 2.6)	−22.6 (−46.5 to 1.3)
Met+ TZD					Met+ TZD	−2.9 (−18.6 to 12.8)	−4.0 (−36.0 to 28.0)	8.1 (−14.6 to 30.7)	−9.3 (−29.0 to 10.4)	−13.0 (−38.0 to 12.0)	−13.9 (−28.5 to 0.7)	−14.9 (−34.6 to 4.8)	−17.6 (−38.0 to 2.8)	−20.4 (−42.4 to 1.6)
TZD	12.6[a] (3.9 to 21.4) I^2=48.5% 2 studies	21.9[a] (14.0 to 29.8) I^2=0.0% 1 study		−0.2 (−1.7 to 1.3) I^2=0.0% 4 studies	−9.0[a] (−15.6 to −2.5) I^2=0.0% 1 study	TZD	−1.0 (−33.3 to 31.2)	12.7 (−4.7 to 30.0)	−6.4 (−26.5 to 13.8)	−10.0 (−35.4 to 15.4)	−11.0 (−26.2 to 4.2)	−12.0 (−32.1 to 8.2)	−14.7 (−35.5 to 6.1)	−17.5 (−40.0 to 5.0)
Met+ SU							Met+ SU	11.9 (−3.7 to 27.6)	−5.3 (−39.7 to 29.1)	−9.0 (−29.0 to 10.9)	−10.0 (−41.7 to 21.8)	−10.9 (−45.3 to 23.5)	−13.6 (−48.4 to 21.2)	−16.4 (−39.7 to 6.9)
Met	14.1[a] (9.7 to 18.4) I^2=81.4% 5 sutides	8.6[a] (5.9 to 11.3) I^2=0.0% 5 studies	4.0 (−0.6 to 8.6) I^2=0.0% 2 studies	−1.1 (−2.6 to 0.4) I^2=0.0% 5 studies	−1.9 (−7.0 to 3.1) I^2=60.8% 3 studies	−0.9 (−2.4 to 0.5) I^2=35.2% 7 studies		Met	−10.0 (−26.5 to 6.6)	−9.0 (−19.0 to 1.0)	−15.5 (−34.7 to 3.8)	1.0 (−29.2 to 31.1)	−4.4 (−18.7 to 9.9)	−2.6 (−25.5 to 20.4)
SGLT2i	32.2[a] (28.8 to 35.5) I^2=46.1% 6 studies	16.2[a] (12.2 to 20.2) I^2=0.0% 2 studies							SGLT2i	−3.7 (−31.7 to 24.4)	−4.6 (−23.9 to 14.7)	−5.6 (−16.1 to 4.9)	−8.3 (−24.8 to 8.2)	−11.1 (−36.5 to 14.3)
Met+ SGLT2i							9.0 (−8.7 to 26.7) I^2=0.0% 1 study			Met+ SGLT2i	−1.0 (−25.7 to 23.8)	−1.9 (−30.0 to 26.1)	−4.6 (−33.2 to 23.9)	−7.4 (−19.5 to 4.7)
Met+ GLP-1RA								9.0[a] (5.4 to 12.6) I^2=0.0% 1 study			Met+ GLP-1RA	−1.0 (−20.3 to 18.3)	−3.7 (−23.7 to 16.3)	−6.5 (−28.1 to 15.2)
DPP4i+ SGLT2i		23.0[a] (17.0 to 29.0) I^2=0.0% 1 study							5.6[a] (0.7 to 10.5) I^2=0.0% 1 study			DPP4i+ SGLT2i	−2.7 (−19.2 to 13.8)	−5.5 (−30.9 to 19.9)
DPP4i+ TZD		25.7[a] (17.8 to 33.7) I^2=0.0% 1 study				3.8 (−1.9 to 9.5) I^2=0.0% 1 study							DPP4i+ TZD	−2.8 (−28.7 to 23.1)
Met+ DPP4i	51.3[a] (40.7 to 61.9) I^2=0.0% 1 study	31.5[a] (22.9 to 40.1) I^2=0.0% 1 study						16.8[a] (9.2 to 24.5) I^2=0.0% 2 studies		7.4 (−0.4 to 15.1) I^2=0.0% 1 study				Met+ DPP4i

A



B

Treatment	SUCRA	PrBest	Mean rank
GLP-1RA	89.0	18.9	2.4
Met+GLP-1RA	88.5	38.9	2.5
Met+SGLT2i	71.1	37.6	4.8
DPP4i+SGLT2i	68.8	1.7	5.1
Met+DPP4i	64.6	0.2	5.6
SGLT2i	62.7	0.9	5.9
Met+TZD	57.9	1.5	6.5
Met	55.6	0.0	6.8
Placebo	50.4	0.0	7.4
Met+SU	30.5	0.3	10.0
DPP4i	29.0	0.0	10.2
SU	18.6	0.0	11.6
DPP4i+TZD	10.1	0.0	12.7
TZD	3.0	0.0	13.6

Supplementary Fig. 4. Network geometry (A), rank test (B), the results of network and pairwise meta-analysis (C) for effect on body weight of antidiabetic treatments after 6 months. (A) Each circle represents an antidiabetic treatment that was included in the analysis, with the size of the circle proportional to the number of trials involving the treatment. The width of each connecting line is proportional to the number of subjects who participated in each pair of trials. The global test for inconsistency yielded a *P* value of 0.1806, indicating no evidence of inconsistency in the network. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for effect on body weight (kg) of antidiabetic treatments after 6 months. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in reverse order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea. [a]Results indicate statistical significance.

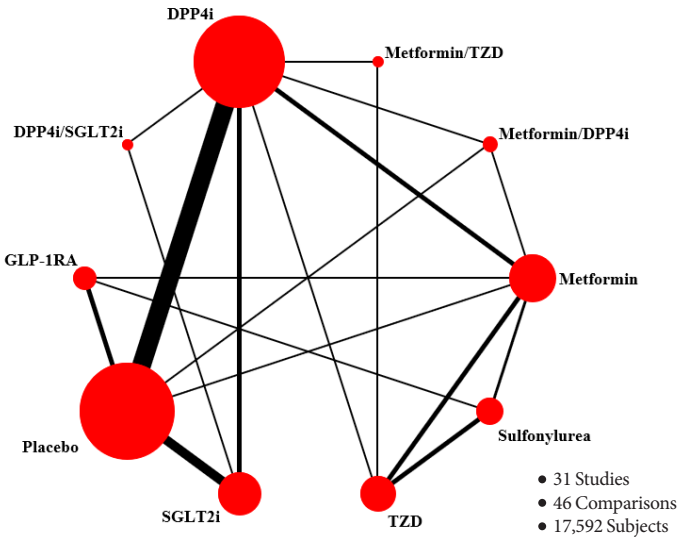
(*Continued to the next page*)

Supplementary Fig. 4. Continued

C

	TZD	DPP4i+ TZD	SU	DPP4i	Met+SU	Placebo	Met	Met+ TZD	SGLT2i	Met+ DPP4i	DPP4i+ SGLT2i	Met+ SGLT2i	Met+ GLP-1RA	GLP-1RA
TZD	TZD	−0.75 (−3.17 to 1.67)	−1.59 (−3.24 to 0.06)	−2.37[a] (−3.87 to −0.87)	−2.30 (−4.96 to 0.35)	−3.34[a] (−4.89 to −1.79)	−0.23 (−1.66 to 1.21)	−3.57[a] (−5.67 to −1.47)	−3.77[a] (−5.68 to −1.86)	−3.80[a] (−5.20 to −2.41)	−3.97[a] (−5.88 to −2.06)	−4.80 (−10.44 to 0.84)	−5.50[a] (−8.13 to −2.87)	−3.50[a] (−4.60 to −2.40)
DPP4i+ TZD	1.22[a] (0.02 to 2.42) I^2=0.0% 1 study	DPP4i+ TZD	−0.84 (−3.31 to 1.63)	−1.62 (−3.51 to 0.27)	−1.55 (−4.79 to 1.68)	−2.59[a] (−4.78 to −0.40)	−0.07 (−1.57 to 1.43)	−2.82[a] (−5.62 to −0.02)	−3.02[a] (−5.26 to −0.78)	−3.05[a] (−5.37 to −0.74)	−3.22[a] (−5.46 to −0.98)	−4.05 (−9.98 to 1.88)	−4.75[a] (−7.96 to −1.54)	−2.75[a] (−5.13 to −0.37)
SU	0.32 (−0.78 to 1.41) I^2=0.0% 3 studies		SU	−0.78 (−2.37 to 0.81)	−0.71 (−3.42 to 2.00)	−1.75[a] (−3.39 to −0.11)	1.62 (0.02 to 3.21)	−1.98 (−4.15 to 0.19)	−2.18[a] (−4.17 to −0.19)	−2.21[a] (−3.71 to −0.72)	−2.38[a] (−4.36 to −0.39)	−3.21 (−8.87 to 2.45)	−3.91[a] (−6.59 to −1.23)	−1.91[a] (−3.50 to −0.32)
DPP4i	2.40[a] (1.66 to 3.15) I^2=0.0% 2 studies	1.62 (−0.08 to 3.32) I^2=0.0% 1 study		DPP4i	0.07 (−2.55 to 2.69)	−0.97 (−2.06 to 0.12)	−1.20 (−3.62 to 1.22)	−1.20 (−3.26 to 0.86)	−1.40[a] (−2.59 to −0.21)	−1.43[a] (−2.76 to −0.10)	−1.60[a] (−2.79 to −0.41)	−2.43 (−8.05 to 3.19)	−3.13[a] (−5.72 to −0.54)	−1.13 (−2.56 to 0.30)
Met+SU					Met+SU	−1.04 (−3.69 to 1.61)	0.07 (−1.72 to 1.86)	−1.27 (−4.28 to 1.74)	−1.47 (−4.35 to 1.41)	−1.50 (−3.76 to 0.76)	−1.67 (−4.55 to 1.21)	−2.50 (−7.47 to 2.47)	−3.20 (−6.59 to 0.20)	−1.20 (−3.82 to 1.42)
Placebo	0.50 (−4.64 to 5.64) I^2=0.0% 1 study			0.34[a] (0.09 to 0.60) I^2=52.5% 11 studies		Placebo	0.47 (−1.09 to 2.03)	−0.23 (−2.32 to 1.86)	−0.43 (−2.05 to 1.19)	−0.46 (−1.85 to 0.92)	−0.63 (−2.25 to 0.99)	−1.46 (−7.10 to 4.17)	−2.16 (−4.78 to 0.46)	−0.16 (−1.65 to 1.33)
Met	1.82[a] (1.60 to 2.05) I^2=81.0% 6 studies		2.13[a] (1.42 to 2.84) I^2=0.0% 4 studies	1.13[a] (0.86 to 1.39) I^2=0.0% 4 studies		0.22 (−0.46 to 0.90) I^2=30.8% 3 studies	Met	−1.30 (−6.83 to 4.23)	2.75 (0.60 to 4.90)	0.43 (−0.89 to 1.75)	−0.06 (−1.29 to 1.16)	−2.00 (−4.38 to 0.38)	−0.30 (−1.16 to 0.55)	1.13[a] (0.11 to 2.15)
Met+TZD							−0.07 (−1.65 to 1.51) I^2=0.0% 1 study	Met+TZD	−0.20 (−2.58 to 2.18)	−0.23 (−2.22 to 1.75)	−0.40 (−2.78 to 1.98)	−1.23 (−7.04 to 4.58)	−1.93 (−4.91 to 1.05)	0.07 (−1.99 to 2.13)
SGLT2i				2.37[a] (1.96 to 2.79) I^2=71.5% 3 studies		2.08[a] (1.81 to 2.34) I^2=21.2% 6 studies			SGLT2i	−0.03 (−1.82 to 1.75)	−0.20 (−1.28 to 0.88)	−1.03 (−6.78 to 4.72)	−1.73 (−4.58 to 1.12)	0.27 (−1.59 to 2.13)
Met+ DPP4i				1.00[a] (0.45 to 1.56) I^2=0.0% 1 study	1.50 (−0.60 to 3.60) I^2=0.0% 1 study	0.03 (−0.65 to 0.71) I^2=0.0% 1 study	0.19 (−0.16 to 0.55) I^2=40.7% 3 studies			Met+DPP4i	−0.17 (−1.95 to 1.62)	−1.00 (−6.46 to 4.46)	−1.70 (−4.23 to 0.83)	0.30 (−1.02 to 1.63)
DPP4i+ SGLT2i				1.60[a] (0.76 to 2.44) I^2=0.0% 1 study					0.20 (−0.48 to 0.88) I^2=0.0% 1 study		DPP4i+ SGLT2i	−0.83 (−6.58 to 4.91)	−1.53 (−4.38 to 1.32)	0.47 (−1.39 to 2.33)
Met+ SGLT2i					2.50 (−2.40 to 7.40) I^2=0.0% 1 study							Met+ SGLT2i	−0.70 (−6.72 to 5.32)	1.30 (−4.32 to 6.92)
Met+ GLP-1RA							2.00 (−0.23 to 4.23) I^2=0.0% 1 study						Met+ GLP-1RA	2.00 (−0.59 to 4.59)
GLP-1RA	3.50[a] (2.79 to 4.21) I^2=0.0% 1 study		1.99[a] (1.53 to 2.45) I^2=0.0% 1 study	1.20[a] (0.50 to 1.90) I^2=0.0% 1 study		1.71[a] (1.33 to 2.08) I^2=68.2% 4 studies	0.16 (−0.56 to 0.24) I^2=50.3% 3 studies							GLP-1RA

A



B

Treatment	SUCRA	PrBest	Mean rank
Placebo	91.1	75.9	1.8
GLP-1RA	77.9	4.3	3.0
DPP4i	51.1	2.1	5.4
TZD	49.7	8.2	5.5
Met+DPP4i	47.8	4.1	5.7
Met	43.0	0.4	6.1
DPP4i+SGLT2i	39.2	1.7	6.5
Met+TZD	37.8	1.7	6.6
SGLT2i	34.2	1.3	6.9
SU	28.3	0.3	7.5

Supplementary Fig. 5. Network geometry (A), rank test (B), the results of network and pairwise meta-analysis (C) for odds ratios of any adverse events of antidiabetic treatments. (A) The global test for inconsistency yielded a *P* value of 0.8471, indicating no evidence of inconsistency in the network. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for odds ratios of any adverse events of antidiabetic treatments. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea.

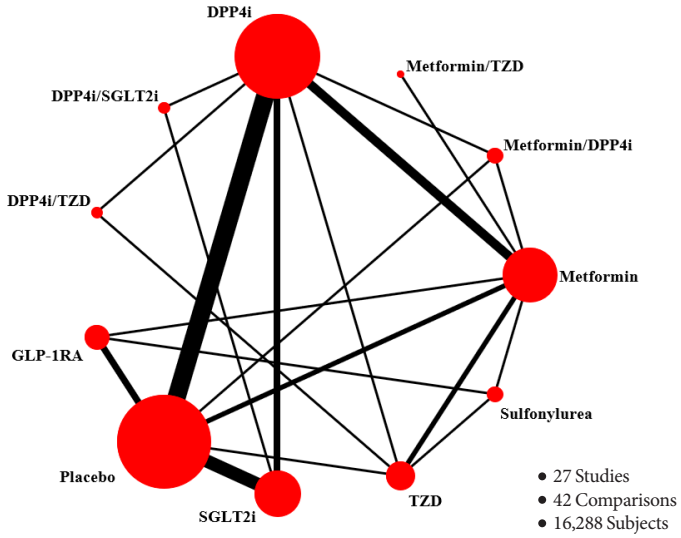
(*Continued to the next page*)

Supplementary Fig. 5. Continued

C

	Placebo	GLP-1RA	DPP4i	TZD	Met+DPP4i	Met	DPP4i+SGLT2i	Met+TZD	SGLT2i	SU
Placebo	Placebo	4.83 (0.57–41.19)	3.91 (0.47–32.38)	3.93 (0.38–40.89)	3.95 (0.48–32.69)	3.83 (0.44–33.31)	4.43 (0.50–39.35)	4.59 (0.52–40.39)	4.65 (0.52–41.34)	5.29 (0.63–44.51)
GLP-1RA	0.80 (0.60–1.05) I^2=33.2% 3 studies	GLP-1RA	0.81 (0.27–2.45)	0.81 (0.26–2.50)	0.82 (0.27–2.47)	1.01 (0.32–3.22)	0.92 (0.27–3.16)	0.95 (0.28–3.22)	0.96 (0.28–3.32)	1.09 (0.63–1.91)
DPP4i	0.92 (0.76–1.12) I^2=34.9% 12 studies		DPP4i	1.00 (0.23–4.30)	1.01 (0.35–2.87)	1.06 (0.36–3.07)	1.13 (0.65–1.97)	1.17 (0.70–1.97)	1.19 (0.68–2.08)	1.35 (0.46–3.98)
TZD			0.79 (0.52–1.20) I^2=0.0% 1 study	TZD	1.01 (0.23–4.30)	0.29 (0.03–2.42)	1.13 (0.24–5.34)	1.17 (0.25–5.46)	1.18 (0.25–5.61)	1.35 (0.45–4.03)
Met+DPP4i	0.25 (0.03–2.05) I^2=0.0% 1 study		0.99 (0.37–2.69) I^2=0.0% 1 study		Met+DPP4i	1.13 (0.41–3.13)	1.12 (0.34–3.66)	1.16 (0.36–3.73)	1.18 (0.36–3.85)	1.34 (0.45–3.94)
Met	0.22 (0.03–1.79) I^2=0.0% 1 study	1.08 (0.81–1.45) I^2=0.0% 1 study	0.84 (0.68–1.04) I^2=0.0% 3 studies	0.99 (0.79–1.26) I^2=0.0% 3 studies	0.89 (0.34–2.34) I^2=0.0% 1 study	Met	0.88 (0.32–2.43)	1.03 (0.33–3.22)	1.08 (0.71–1.66)	5.38 (0.62–47.04)
DPP4i+SGLT2i			0.88 (0.56–1.41) I^2=0.0% 1 study				DPP4i+SGLT2i	1.04 (0.48–2.22)	1.05 (0.64–1.72)	1.19 (0.35–4.03)
Met+TZD			0.85 (0.56–1.29) I^2=0.0% 1 study	1.08 (0.79–1.46) I^2=0.0% 1 study				Met+TZD	1.01 (0.47–2.17)	1.15 (0.35–3.82)
SGLT2i	0.96 (0.81–1.14) I^2=0.0% 6 studies		0.83 (0.65–1.07) I^2=0.0% 3 studies				0.95 (0.65–1.40) I^2=0.0% 1 study		SGLT2i	1.14 (0.34–3.84)
SU		1.25 (0.92–1.71) I^2=0.0% 1 study		0.85 (0.58–1.23) I^2=41.6% 3 studies		0.74 (0.343–1.64) I^2=85.4% 2 studies				SU

A



B

Treatment	SUCRA	PrBest	Mean rank
DPP4i	63.6	11.1	4.6
SU	60.7	6.5	4.9
Met+DPP4i	58.3	16.7	5.2
TZD	58.2	25.0	5.2
Met	57.0	2.4	5.3
Met+TZD	55.4	21.4	5.5
DPP4i+TZD	53.6	4.7	5.6
GLP-1RA	44.1	5.7	6.6
Placebo	43.7	4.8	6.6
DPP4i+SGLT2i	33.8	1.6	7.6
SGLT2i	21.4	0.1	8.9

Supplementary Fig. 6. Network geometry (A), rank test (B), the results of network and pairwise meta-analysis (C) for odds ratios of serious adverse events of antidiabetic treatments. (A) The global test for inconsistency yielded a *P* value of 0.9773, indicating no evidence of inconsistency in the network. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for odds ratios of serious adverse events of antidiabetic treatments. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea. [a]Results indicate statistical significance.

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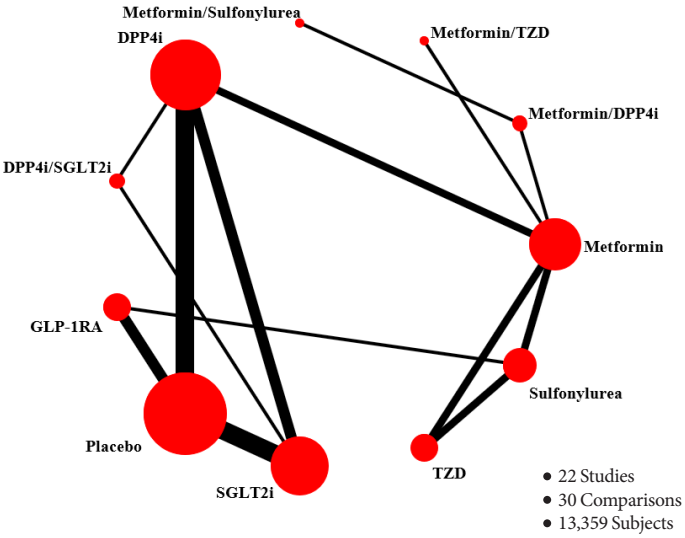
Supplementary Fig. 6. Continued

C

	DPP4i	SU	Met+DPP4i	TZD	Met	Met+TZD	DPP4i+TZD	GLP-1RA	Placebo	DPP4i+SGLT2i	SGLT2i
DPP4i	DPP4i	0.93 (0.02–50.23)	1.01 (0.02–52.8)	0.85 (0.00–237.5)	0.83 (0.01–46.5)	1.04 (0.00–280.9)	1.33 (0.53–3.35)	1.11 (0.02–62.4)	2.09 (0.04–109.2)	3.34 (0.68–16.4)	5.03[a] (1.06–24.0)
SU		SU	1.08 (0.02–58.7)	0.92 (0.02–52.5)	2.34 (0.04–127.4)	1.12 (0.02–61.4)	1.43 (0.02–85.5)	1.19 (0.45–3.15)	2.24 (0.04–121.2)	3.58 (0.05–262.2)	5.40 (0.07–391.2)
Met+DPP4i	0.99 (0.02–50.1) I^2=0.0% 1 study		Met+DPP4i	0.85 (0.00–236.4)	1.00 (0.02–52.3)	1.03 (0.00–279.6)	1.32 (0.02–76.6)	1.10 (0.02–62.2)	2.07 (0.04–108.4)	3.31 (0.05–235.4)	4.99 (0.07–351.1)
TZD	1.20 (0.54–2.66) I^2=0.0% 1 study	0.87 (0.73–1.04) I^2=0.0% 1 study		TZD	1.94 (0.01–542.9)	1.22 (0.00–342.7)	1.56 (0.01–465.9)	1.30 (0.02–77.4)	2.44 (0.01–679.9)	3.90 (0.01–1352.7)	5.89 (0.02–2023.9)
Met	1.18 (0.58–2.39) I^2=0.0% 4 studies	0.92 (0.77–1.10) I^2=0.0% 1 study	1.00 (0.02–50.6) I^2=0.0% 1 study	1.06 (0.89–1.26) I^2=0.0% 2 studies	Met	1.03 (0.02–54.5)	3.30 (0.05–233.4)	1.32 (0.02–76.0)	1.92 (0.03–115.6)	0.99 (0.02–51.4)	1.10 (0.49–2.45)
Met+TZD					0.97 (0.02–50.0) I^2=0.0% 1 study	Met+TZD	1.28 (0.00–372.4)	1.07 (0.02–61.2)	2.01 (0.01–543.2)	3.21 (0.01–1081.8)	4.84 (0.01–1618.5)
DPP4i+TZD	0.75 (0.35–1.61) I^2=0.0% 1 study			0.63 (0.36–1.09) I^2=0.0% 1 study			DPP4i+TZD	0.83 (0.01–52.1)	1.57 (0.03–91.3)	2.51 (0.40–15.8)	3.79 (0.62–23.2)
GLP-1RA		0.60 (0.16–2.21) I^2=0.0% 1 study			0.91 (0.49–1.68) I^2=0.0% 1 study			GLP-1RA	1.88 (0.03–106.2)	3.01 (0.04–229.1)	4.54 (0.06–341.9)
Placebo	1.10 (0.69–1.75) I^2=0.0% 8 studies		0.48 (0.01–24.4) I^2=0.0% 1 study	0.80 (0.02–42.4) I^2=0.0% 1 study	0.67 (0.04–11.0) I^2=0.0% 2 studies			1.18 (0.35–3.94) I^2=71.9 3 studies	Placebo	1.60 (0.02–113.9)	2.41 (0.03–169.9)
DPP4i+SGLT2i	0.30 (0.07–1.35) I^2=0.0% 1 study									DPP4i+SGLT2i	1.51 (0.62–3.69)
SGLT2i	0.51 (0.18–1.41) I^2=34.3% 3 studies								0.90 (0.49–1.68) I^2=0.0% 6 studies	0.66 (0.32–1.37) I^2=0.0% 1 study	SGLT2i

A



B

Treatment	SUCRA	PrBest	Mean rank
DPP4i+SGLT2i	92.4	75.1	1.8
Placebo	77.8	8.0	3.2
DPP4i	70.9	1.8	3.9
TZD	55.9	1.6	5.4
SGLT2i	52.8	0.3	5.7
Met+TZD	46.5	10.6	6.4
GLP-1RA	45.1	0.8	6.5
Met	44.4	0.0	6.6
Met+DPP4i	35.2	0.2	7.5
Met+SU	19.0	1.6	9.1
SU	10.1	0.0	10

Supplementary Fig. 7. Network geometry (A), rank test (B), the results of network and pairwise meta-analysis (C) for odds ratios of hypoglycemia risk of antidiabetic treatments. (A) The global test for inconsistency yielded a *P* value of 0.9385, indicating no evidence of inconsistency in the network. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for odds ratios of odds ratios of hypoglycemia risk of antidiabetic treatments. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea. [a]Results indicate statistical significance.

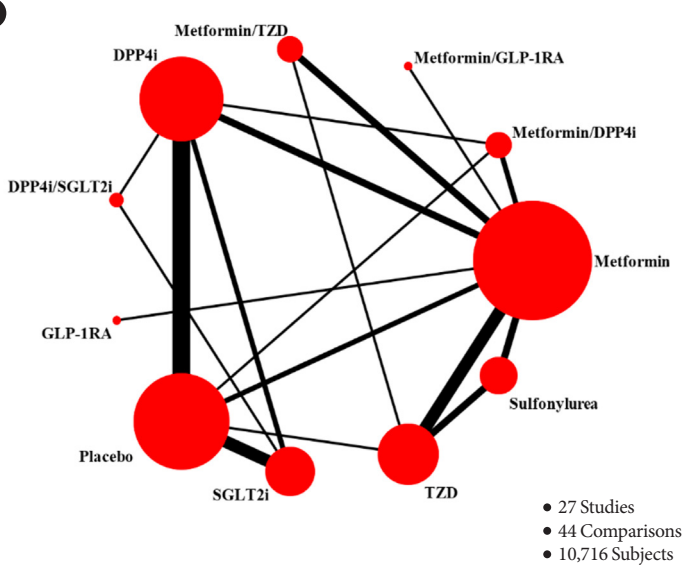
(*Continued to the next page*)

Supplementary Fig. 7. Continued

C

	DPP4i+SGLT2i	Placebo	DPP4i	TZD	SGLT2i	Met+TZD	GLP-1RA	Met	Met+DPP4i	Met+SU	SU
DPP4i+SGLT2i	DPP4i+SGLT2i	4.97 (0.18–136.0)	6.08 (0.25–150.2)	15.10 (0.27–840.6)	11.29 (0.62–205.2)	18.12 (0.07–4997.0)	16.85 (0.48–596.6)	17.60 (0.32–973.2)	25.60 (0.42–1548.9)	103.12 (0.55–19460.3)	85.4[a] (1.54–4741.2)
Placebo		Placebo	1.22 (0.54–2.75)	3.04 (0.24–39.1)	2.27 (0.31–16.6)	3.64 (0.03–394.9)	3.39 (0.89–12.9)	1.04 (0.06–18.5)	5.15 (0.35–75.4)	20.73 (0.30–1415.1)	17.2[a] (1.34–220.3)
DPP4i	0.17 (0.01–4.07) I^2=0.0% 1 study	0.83 (0.38–1.81) I^2=0.0% 5 studies	DPP4i	2.48 (0.22–28.0)	1.86 (0.30–11.4)	2.98 (0.03–301.1)	2.77 (0.58–13.2)	2.90 (0.26–32.3)	4.21 (0.33–54.5)	16.97 (0.27–1070.5)	14.0[a] (1.25–157.9)
TZD				TZD	0.75 (0.04–15.5)	1.20 (0.02–61.8)	1.12 (0.06–19.9)	0.41 (0.04–3.8)	1.70 (0.70–4.11)	6.83 (0.23–200.2)	5.65[a] (4.64–6.89)
SGLT2i	0.09 (0.01–1.61) I^2=0.0% 1 study	1.05 (0.42–2.66) I^2=0.0% 5 studies	0.60 (0.16–2.24) I^2=0.0% 3 studies		SGLT2i	1.60 (0.01–228.7)	1.49 (0.14–16.4)	0.84 (0.05–15.2)	2.27 (0.10–52.3)	9.13 (0.10–842.9)	7.56 (0.37–155.8)
Met+TZD						Met+TZD	0.93 (0.01–121.4)	0.97 (0.02–49.7)	1.41 (0.03–79.2)	5.69 (0.03–1011.6)	4.71 (0.09–241.9)
GLP-1RA		0.30 (0.08–1.12) I^2=0.0% 3 studies					GLP-1RA	1.80 (0.10–33.2)	1.52 (0.08–30.4)	6.12 (0.07–512.7)	5.06 (0.28–90.1)
Met			0.35 (0.03–3.86) 2 studies	1.05 (0.48–2.25) I^2=48.8% 2 studies		1.03 (0.02–52.6) I^2=0.0% 1 study		Met	1.45 (0.62–3.42)	5.86 (0.20–170.4)	0.28 (0.02–3.60)
Met+DPP4i								0.69 (0.29.1.62) I^2=0.0% 1 study	Met+DPP4i	4.03 (0.15–104.9)	3.33[a] (1.39–8.00)
Met+SU									0.25 (0.01–6.45) I^2=0.0% 1 study	Met+SU	0.83 (0.03–24.20)
SU				0.20[a] (0.12–0.31) I^2=38.7% 2 studies			0.11[a] (0.07–0.18) I^2=0.0% 1 study	0.21[a] (0.17–0.25) I^2=0.0% 2 studies			SU

A



B

Treatment	SUCRA	PrBest	Mean rank
Placebo	82.2	38.1	2.8
Met	81.2	9.9	2.9
TZD	69.2	22.8	4.1
Met+GLP-1RA	66.6	1.5	4.3
DPP4i	51.3	0.9	5.9
GLP-1RA	51.2	17.2	5.9
SU	50.2	0.0	6.0
Met+DPP4i	34.5	8.1	7.5
SGLT2i	25.7	0.8	8.4
DPP4i+SGLT2i	24.9	0.5	8.5
Met+TZD	12.8	0.2	9.7

Supplementary Fig. 8. Network geometry (A) and the results of rank test (B) for effect on low-density lipoprotein (LDL) cholesterol of antidiabetic treatments after 6 months. (A) Each circle represents an antidiabetic treatment that was included in the analysis, with the size of the circle proportional to the number of trials involving the treatment. The width of each connecting line is proportional to the number of subjects who participated in each pair of trials. The global test for inconsistency yielded a *P* value of <0.0001, which suggests that there may be significant inconsistencies present in the network of treatments. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for effect on low-density lipoprotein cholesterol (mg/dL) of antidiabetic treatments after 6 months. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea. [a]Results indicate statistical significance.

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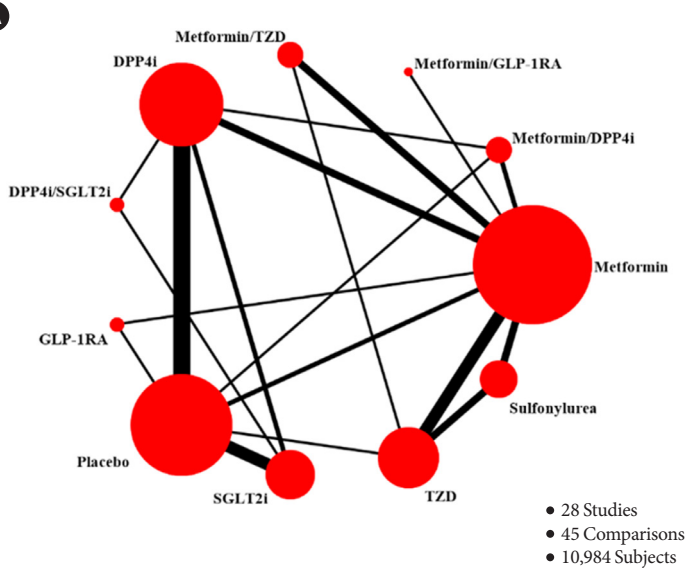
Supplementary Fig. 8. Continued

C

	Met+TZD	DPP4i+SGLT2i	SGLT2i	Met+DPP4i	SU	GLP-1RA	DPP4i	Met+GLP-1RA	TZD	Met	Placebo
Met+TZD	Met+TZD	−3.5 (−18.6 to 11.4)	−3.6 (−18.6 to 11.4)	−4.8 (−23.9 to 14.4)	−9.6 (−19.9 to 0.8)	−9.2 (−28.3 to 9.9)	−9.0 (−21.3 to 3.3)	−11.6 (−22.0 to −1.2)	−12.6 (−27.1 to 2.0)	−1.6 (−4.1 to 0.9)	−14.5[a] (−27.8 to −1.2)
DPP4i+SGLT2i		DPP4i+SGLT2i	0.0 (−7.0 to 7.0)	−1.2 (−20.9 to 18.5)	−6.0 (−17.3 to 5.3)	−5.6 (−25.2 to 14.0)	−5.4 (−14.0 to 3.2)	−8.0 (−19.4 to 3.4)	−9.0 (−24.2 to 6.2)	−13.2 (−23.3 to −3.1)	−10.9 (−23.1 to 1.3)
SGLT2i		0.0 (−7.0 to 7.0) I^2=0.0% 1 study	SGLT2i	−1.2 (−20.9 to 18.5)	−6.0 (−17.3 to 5.3)	−5.6 (−25.2 to 14.0)	−5.4 (−14.0 to 3.2)	−8.0 (−19.4 to 3.4)	−9.0 (−24.2 to 6.2)	−9.6 (−20.7 to 1.5)	−10.9 (−23.1 to 1.3)
Met+DPP4i				SGLT2i	−4.8 (−21.2 to 11.6)	−4.4 (−27.4 to 18.6)	−4.2 (−21.9 to 13.5)	−6.8 (−23.3 to 9.7)	−7.8 (−27.1 to 11.5)	15.3 (−2.4 to 33.0)	−9.7 (−28.2 to 8.8)
SU					SU	0.4 (−16.0 to 16.8)	0.6 (−6.8 to 8.0)	−2.0 (−5.4 to 1.4)	−3.0 (−13.7 to 7.7)	−5.2 (−24.2 to 13.8)	−4.9 (−13.9 to 4.1)
GLP-1RA						GLP-1RA	0.2 (−17.5 to 17.9)	−2.4 (−18.8 to 14.0)	−3.4 (−22.7 to 15.9)	−4.5 (−12.4 to 3.5)	−5.3 (−23.7 to 13.1)
DPP4i		5.4 (−3.2 to 14.0) I^2=0.0% 1 study	1.4 (−1.9 to 4.3) I^2=0.0% 2 studies	−11.1[a] (−18.0 to −4.2) I^2=0.0% 1 study			DPP4i	−2.6 (−10.1 to 4.9)	−3.6 (−16.2 to 9.0)	14.6 (−0.1 to 29.3)	−5.5 (−14.2 to 3.2)
Met+GLP-1RA								Met+GLP-1RA	−1.0 (−11.8 to 9.8)	−8.4 (−24.7 to 7.9)	−2.9 (−12.0 to 6.2)
TZD	−2.0 (−12.7 to 8.7) I^2=0.0% 1 study				−3.2[a] (−5.4 to −0.9) I^2=13.0% 3 studies				TZD	−4.0 (−20.2 to 12.2)	−1.9 (−15.5 to 11.7)
Met	6.3 (−1.0 to 13.7) I^2=55.7% 3 studies			−4.6 (−10.9 to 1.8) I^2=65.3% 2 studies	4.0[a] (1.7 to 6.2) I^2=40.1% 3 studies	4.0 (−12.2 to 20.2) I^2=0.0% 1 study	7.7[a] (4.4 to 11.0) I^2=0.0% 3 studies	1.6 (−0.9 to 4.1) I^2=0.0% 1 study	1.1 (−0.6 to 2.9) I^2=89.2% 5 studies	Met	4.2 (−2.8 to 11.2)
Placebo			4.5[a] (1.9 to 7.0) I^2=0.0% 5 studies	−5.6 (−14.2 to 3.0) I^2=0.0% 1 study			0.8 (−1.9 to 3.6) I^2=34.4% 7 studies		−0.1 (−17.8 to 17.6) I^2=0.0% 1 study	−0.2 (−8.0 to 7.6) I^2=0.0% 2 studies	Placebo

A



B

Treatment	SUCRA	PrBest	Mean rank
Met+TZD	87.6	47.2	2.2
TZD	65.7	15.3	4.4
Met	60.0	0.4	5
SGLT2i	54.8	11.3	5.5
DPP4i	51.6	2	5.8
SU	48.8	1.7	6.1
Met+GLP-1RA	47.3	2.9	6.3
Met+DPP4i	37.8	4.3	7.2
Placebo	38.5	1.2	7.2
GLP-1RA	34.6	13.3	7.5
DPP4i+SGLT2i	23.4	0.4	8.7

Supplementary Fig. 9. Network geometry (A) and the results of rank test (B) for effect on high-density lipoprotein (HDL) cholesterol of antidiabetic treatments after 6 months. (A) Each circle represents an antidiabetic treatment that was included in the analysis, with the size of the circle proportional to the number of trials involving the treatment. The width of each connecting line is proportional to the number of subjects who participated in each pair of trials. The global test for inconsistency yielded a *P* value of <0.0001, which suggests that there may be significant inconsistencies present in the network of treatments. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side) and pairwise (lower left side) meta-analytic results are depicted for effect on high-density lipoprotein cholesterol (mg/dL) of antidiabetic treatments after 6 months. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top-row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in reverse order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea. [a]It results indicate statistical significance.

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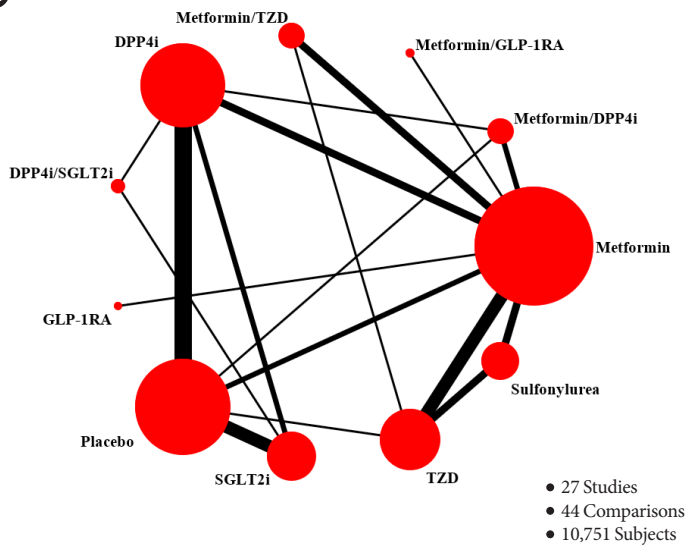
Supplementary Fig. 9. Continued

C

	DPP4i+SGLT2i	GLP-1RA	Placebo	Met+DPP4i	Met+GLP-1RA	SU	DPP4i	SGLT2i	Met	TZD	Met+TZD
DPP4i+SGLT2i	DPP4i+SGLT2i	0.2 (−13.8 to 14.2)	1.7 (−4.6 to 8.0)	1.4 (−6.9 to 9.7)	2.3 (−5.2 to 9.8)	2.4 (−4.6 to 9.5)	2.6 (−2.1 to 7.3)	2.7 (−1.7 to 7.1)	−2.8 (−6.90 to 1.2)	3.9 (−4.0 to 11.8)	6.0 (−1.4 to 13.4)
GLP-1RA		GLP-1RA	1.5 (−11.8 to 14.8)	1.2 (−12.5 to 14.9)	2.1 (−11.1 to 15.3)	2.2 (−10.8 to 15.3)	2.4 (−10.8 to 15.6)	2.5 (−11.5 to 16.5)	−0.3 (−5.6 to 5.1)	3.7 (−9.8 to 17.2)	5.8 (−7.4 to 19.1)
Placebo		0.4 (−0.6 to 1.4) I^2=0.0% 1 study	Placebo	−0.3 (−7.2 to 6.5)	0.6 (−5.3 to 6.4)	0.7 (−4.6 to 6.1)	0.9 (−3.3 to 5.1)	1.0 (−5.3 to 7.3)	0.6 (−3.5 to 4.6)	2.2 (−4.2 to 8.6)	4.3 (−1.5 to 10.1)
Met+DPP4i			−1.2 (−2.9 to 0.5) I^2=0.0% 1 study	Met+DPP4i	0.9 (−5.9 to 7.7)	1.1 (−5.3 to 7.4)	1.2 (−5.6 to 8.0)	1.3 (−7.0 to 9.6)	−1.5 (−8.3 to 5.3)	2.5 (−4.8 to 9.8)	4.6 (−2.1 to 11.4)
Met+GLP-1RA					Met+GLP-1RA	0.2 (−5.2 to 5.4)	0.3 (−5.5 to 6.1)	0.4 (−7.1 to 7.9)	1.8 (−3.6 to 7.2)	1.6 (−4.8 to 8.0)	3.7 (−2.0 to 9.5)
SU						SU	0.2 (−5.1 to 5.4)	0.3 (−6.8 to 7.3)	3.0 (−9.6 to 15.6)	1.5 (−4.4 to 7.3)	3.6 (−1.6 to 8.8)
DPP4i	−2.6 (−5.4 to 0.2) I^2=0.0% 1 study		0.0 (−0.7 to 0.7) I^2=29.0% 7 studies	0.3 (−1.1 to 1.7) I^2=0.0% 1 study			DPP4i	0.1 (−4.6 to 4.8)	5.7 (−0.5 to 12.0)	1.3 (−5.0 to 7.6)	3.4 (−2.3 to 9.1)
SGLT2i	−2.7[a] (−5.0 to −0.4) I^2=0.0% 1 study		−2.7[a] (−3.4 to −1.9) I^2=60.4% 5 studies				−2.9[a] (−3.8 to −2.1) I^2=76.6% 2 studies	SGLT2i	3.2 (−3.0 to 9.4)	1.2 (−6.7 to 9.1)	3.3 (−4.1 to 10.8)
Met		−3.0 (−15.0 to 9.0) I^2=0.0% 1 study	−0.7 (−2.3 to 0.8) I^2=82.3% 2 studies	−0.5 (−1.8 to 0.8) I^2=0.0% 2 studies	−0.9 (−2.5 to 0.7) I^2=0.0% 1 study	−0.3 (−1.0 to 0.5) I^2=99.6% 3 studies	−0.5 (−1.4 to 0.4) I^2=0.0% 3 studies		Met	1.9 (−11.9 to 15.7)	−0.9 (−5.0 to 3.2)
TZD			3.9 (−1.3 to 9.1) I^2=0.0% 1 study			−3.4[a] (−4.2 to −2.6) I^2=0.0% 3 studies			−1.7[a] (−2.4 to −1.1) I^2=82.1% 5 studies	TZD	2.1 (−4.2 to 8.4)
Met+TZD									0.0 (−1.9 to 2.0) I^2=74.7% 3 studies	3.6[a] (0.8 to 6.4) I^2=0.0% 1 study	Met+TZD

A



B

Treatment	SUCRA	PrBest	Mean rank
GLP-1RA	74.9	30.1	3.5
DPP4i	74.7	12.5	3.5
TZD	73.8	27.5	3.6
Met	71.6	3.0	3.8
Placebo	63.6	8.9	4.6
Met+DPP4i	52.9	14.4	5.7
DPP4i+SGLT2i	41.7	3.4	6.8
Met+GLP-1RA	37.9	0.0	7.2
SU	31.6	0.0	7.8
SGLT2i	13.9	0.2	9.6
Met+TZD	13.6	0.0	9.6

Supplementary Fig. 10. Network geometry (A) and the results of rank test (B) for effect on triglyceride of antidiabetic treatments after 6 months. (A) Each circle represents an antidiabetic treatment that was included in the analysis, with the size of the circle proportional to the number of trials involving the treatment. The width of each connecting line is proportional to the number of subjects who participated in each pair of trials. The global test for inconsistency yielded a *P* value of 0.0038, which suggests that there may be significant inconsistencies present in the network of treatments. (B) The table presents the results of the network rank test (surface under the cumulative ranking curve [SUCRA], probability of being the best [PrBest], mean rank) for different antidiabetic treatments, ordered by mean rank. (C) Network (upper right side, gray zone) and pairwise (lower left side, white zone) meta-analytic results are depicted for effect on triglyceride (mg/dL) of antidiabetic treatments after 6 months. The outcome of meta-analysis is expressed as effect size with 95% credible intervals in the case of network meta-analysis and 95% confidence intervals in the case of pairwise meta-analysis. Each value and interval refer to the efficacy of the top row treatment compared to the left column. The order of antidiabetic treatments in this league table is presented in order of the mean rank results. TZD, thiazolidinedione; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulfonylurea. [a]Results indicate statistical significance.

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Supplementary Fig. 10. Continued

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	Met+TZD	SGLT2i	SU	Met+GLP-1RA	DPP4i+SGLT2i	Met+DPP4i	Placebo	Met	TZD	DPP4i	GLP-1RA
Met+TZD	Met+TZD	2.3 (−29.1 to 33.7)	−8.9 (−25.3 to 7.6)	−10.9 (−27.5 to 5.6)	−11.0 (−42.4 to 20.4)	−17.0 (−54.1 to 20.0)	−20.5 (−45.9 to 4.9)	−11.9[a] (−18.9 to −4.9)	−26.4 (−55.7 to 3.0)	−24.3[a] (−47.0 to −1.6)	−27.8 (−59.4 to 3.8)
SGLT2i		SGLT2i	−11.2 (−39.7 to 17.4)	−13.3 (−41.7 to 15.2)	−13.3 (−31.2 to 4.6)	−19.4 (−63.0 to 24.3)	−22.8 (−53.3 to 7.7)	−11.9 (−39.4 to 15.7)	−28.7 (−66.1 to 8.7)	−26.6 (−48.3 to −4.9)	−30.2 (−69.3 to 9.0)
SU			SU	−2.1 (−12.3 to 8.1)	−2.1 (−30.7 to 26.4)	−8.2 (−42.9 to 26.5)	−11.7 (−33.5 to 10.2)	20.0 (−23.8 to 63.9)	−17.5 (−43.8 to 8.8)	−15.4 (−34.1 to 3.2)	−19.0 (−47.8 to 9.8)
Met+GLP-1RA				Met+GLP-1RA	−0.1 (−28.5 to 28.4)	−6.1 (−40.7 to 28.5)	−9.6 (−31.3 to 12.1)	−5.8 (−39.7 to 28.1)	−15.4 (−41.6 to 10.8)	−13.4 (−31.8 to 5.1)	−16.9 (−45.6 to 11.8)
DPP4i+SGLT2i		13.3 (−4.1 to 30.7) I^2=0.0% 1 study			DPP4i+SGLT2i	−6.1 (−49.7 to 37.6)	−9.5 (−40.0 to 21.0)	−22.8 (−37.8 to −7.9)	−15.4 (−52.8 to 22.0)	−13.3 (−35.0 to 8.4)	−16.9 (−56.0 to 22.3)
Met+DPP4i						Met+DPP4i	−3.5 (−43.1 to 36.2)	12.9 (−24.9 to 50.7)	−9.3 (−51.6 to 32.9)	−7.3 (−45.2 to 30.7)	−10.8 (−54.6 to 33.0)
Placebo		−11.7[a] (−18.7 to −4.8) I^2=0.0% 5 studies				−9.5 (−30.3 to 11.3) I^2=0.0% 1 study	Placebo	1.5 (−15.6 to 18.5)	−5.9 (−38.4 to 26.7)	−3.8 (−25.3 to 17.7)	−7.3 (−41.9 to 27.2)
Met	14.1 (1.7 to 26.5) I^2=74.9% 3 studies		13.3[a] (7.6 to 19.0) I^2=0.0% 3 studies	11.9[a] (6.3 to 17.5) I^2=0.0% 1 study		−4.6 (−19.3 to 10.0) I^2=0.0% 2 studies	−2.1 (−20.3 to 16.1) I^2=0.0% 2 studies	Met	−5.0 (−32.8 to 22.8)	−37.0[a] (−66.8 to −7.2)	−6.7 (−27.4 to 14.0)
TZD	−10.6 (−36.4 to 15.2) I^2=0.0% 1 study		15.7[a] (10.1 to 21.4) I^2=58.1% 3 studies				−8.9 (−45.7 to 27.9) I^2=0.0% 1 study	11.5[a] (7.8 to 15.3) I^2=81.7% 5 studies	TZD	2.1 (−28.4 to 32.6)	−1.5 (−39.0 to 36.1)
DPP4i		14.1 (−1.6 to 29.9) I^2=65.7% 2 studies			13.3 (−8.0 to 34.6) I^2=0.0% 1 study	−5.6 (−22.9 to 11.7) I^2=0.0% 1 study	9.9 (−0.3 to 20.2) I^2=20.8% 7 studies	6.2 (−3.0 to 15.5) I^2=0.0% 3 studies		DPP4i	−3.6 (−36.2 to 29.1)
GLP-1RA								5.0 (−22.5 to 32.5) I^2=0.0% 1 study			GLP-1RA