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Effects of different hypoglycaemic drugs on beta-cell function in type 2 diabetes mellitus: a systematic review and network meta-analysis

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Abstract

Aim This study compared the effects of hypoglycaemic drugs on beta-cell function among type 2 diabetes mellitus (T2DM) patients through a network meta-analysis of randomized controlled trials (RCTs).

Methods We searched the PubMed, EMBASE, and Cochrane Library databases for RCTs of different hypoglycaemic drugs as T2DM treatment from database inception to December 1, 2024. The primary outcome was homeostasis model assessment-β (HOMA-β), and the secondary outcome was glycated haemoglobin (HbA1c). Direct and indirect evidence types were combined to calculate weighted mean difference (WMD) and 95% confidence interval (CI) values for the change in (Δ) HOMA-β and ΔHbA1c, and to determine surface under the cumulative ranking curve (SUCRA) values.

Results A total of 58 RCTs involving 16,345 T2DM patients were incorporated into this network meta-analysis. The mean patient age was 66.70 years, and 54.14% were male. For improving HOMA-β, the top treatments were glimepiride + rosiglitazone (WMD = 81.83, 95% CI 45.85–117.82) and glibenclamide + rosiglitazone (WMD = 79.51, 95% CI 40.66–118.36). Acarbose (WMD = 60.90, 95% CI 27.56–94.25) ranked third as monotherapy. For reducing HbA1c, glibenclamide + rosiglitazone was the most efficacious treatment (WMD = − 2.48, 95% CI − 3.67 to − 1.29), followed by metformin + exenatide (WMD = − 1.77, 95% CI − 2.25 to − 1.29) and liraglutide (WMD = − 1.77, 95% CI − 2.33 to − 1.21). The treatment with the highest SUCRA value for HOMA-β improvement was glimepiride + rosiglitazone (95.1%), followed by glibenclamide + rosiglitazone (94.9%). For HbA1c improvement, glibenclamide + rosiglitazone had the highest SUCRA value (97.6%).

Conclusions The combination of glimepiride/glibenclamide and rosiglitazone was the most effective hypoglycaemic regimen for protecting beta-cell function and improving glycaemic control in T2DM treatment, possibly due to control of HbA1c and glycotoxicity.

Keywords Type 2 diabetes mellitus, Hypoglycaemic drugs, Insulin-secreting cells, Network meta-analysis

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Introduction

Type 2 diabetes mellitus (T2DM) is a complex, chronic metabolic disease that seriously threatens human health worldwide [1, 2]. T2DM is a risk factor for serious conditions, such as cardiovascular and cerebrovascular diseases and diabetic nephropathy [3], leading to life-threatening, disabling and costly complications and shortened life expectancy [4]. A dramatic increase in the global incidence of diabetes has occurred in recent decades, and the number of people with diabetes worldwide is predicted to reach 783.2 million by 2045 according to the International Diabetes Federation (IDF) [5], with approximately 95% of these patients having T2DM [6].

T2DM is characterized by deterioration of the function of pancreatic beta-cells, leading to insulin secretion dysfunction and insulin resistance, which may be associated with beta-cell failure [7]. Multiple studies have shown that beta-cell failure may be associated with glucotoxicity [8], lipid toxicity [9, 10], and inflammation-mediated stress pathways [11], including endoplasmic reticulum stress [12, 13], oxidative stress [14, 15], mitochondrial dysfunction, and autophagy [16, 17]. Thus, the goal of T2DM management has shifted from merely preserving normal blood glucose levels to maintaining or regenerating beta-cell quality and function [18]. Treatments that can improve the function of pancreatic beta-cells and prevent their progressive failure could fundamentally cure the disease.

The drugs commonly used to control blood glucose currently, such as metformin, sulfonylureas, thiazolidinediones, α-glycosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter-2 (SGLT-2) inhibitors, insulin, and glucagon-like peptide-1 (GLP-1) receptor agonists [19], or herbal medicines, such as cinnamon [20, 21], etc., have achieved significant clinical success. For cases in which a single drug offers poor efficacy, multiple drug combination therapy can be chosen. Different treatment regimens have different protective effects on beta-cells, and such differences exist not only between different drug analogues but also between drugs within the same class.

Previous randomized controlled trials (RCTs) have evaluated the protective effects of different treatments on beta-cells; however, most previous trials compared treatments with a placebo or two individual drugs, making determination of the most effective drugs among many treatment options difficult. When direct data are not available, a network meta-analysis is the preferred method to evaluate the relative effectiveness of multiple treatments. In our analysis, direct evidence pertains to comparisons made directly between two interventions within a single study, typically originating from head-to-head RCTs. Indirect evidence, on the other hand, involves comparisons between two interventions through a shared comparator. For instance, if RCTs compare intervention A with intervention B, and other RCTs compare intervention B with intervention C, an indirect comparison between interventions A and C can be inferred via intervention B. This methodology is particularly pertinent in the context of T2DM due to the extensive array of pharmacological options available, many of which lack direct head-to-head trial comparisons. An RCT-based network meta-analysis can indirectly compare and rank the effectiveness of beta-cell protection between drugs. Until now, there have been few network meta-analyses on the protective effects of different hypoglycaemic drugs on beta cell function in T2DM patients, and the comparisons of drug types were limited. A network meta-analysis that included 132 studies and evaluated the protective effect of incretin-based therapies on beta-cell function in T2DM patients showed that these therapies could improve the homeostasis model assessment-β (HOMA-β) index, potentially making them a suitable option for long-term therapy to preserve beta-cell function in T2DM patients [22]. Another network meta-analysis evaluated the effect of exenatide monotherapy on beta-cell function in T2DM patients, and the results showed that exenatide monotherapy had a better therapeutic effect on the HOMA-β index than did insulin, achieving good glycaemic control and protecting beta-cell function [23]. The HOMA-β index is an important indicator of beta-cell function in vivo, and thus, was selected as the main outcome in the present study. For this study, we collected all RCTs comparing treatments with placebo or other hypoglycaemic drugs for at least 12 weeks among T2DM patients and evaluated the comparative effectiveness of hypoglycaemic drugs on improving the HOMA-β index in T2DM patients through a network meta-analysis.

Methods

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Network Meta-analyses (PRISMA–NMA) [24], and the protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, No. CRD 42022381644).

Data sources and searches

We searched the PubMed, EMBASE, and Cochrane Library databases from inception to December 1, 2024. The default search keywords were "diabetes mellitus, type 2", "hypoglycaemic drugs", "insulin-secreting cells", and "randomized controlled trial".

Study selection

We included only RCTs, including crossover and parallel-group trials, published in English in which adult patients with T2DM were treated for at least 12 weeks using the following hypoglycaemic drugs as monotherapy or in combination therapy: metformin, sulfonylureas, thiazolidinediones, α-glycosidase inhibitors, DPP-4 inhibitors, SGLT-2 inhibitors, insulin and GLP-1 receptor agonists or placebo, with HOMA-β index assessed in the outcome. Due to the small number of RCTs evaluating HOMA-β, we also included open-label studies. Because this review is on chronic treatment, we only included the studies that provided long-term data (≥ 12 weeks). All eligible single or combination drug regimens were considered as one treatment type, and comparisons between different doses of the same drug or different treatment periods were excluded. Background treatment was defined as the therapeutic use of hypoglycaemic drugs or diet and exercise before or after randomization, and because it could change based on the actual situation, it was not defined as one of the combination treatment options. All the articles retrieved from the database were imported into Endnote. First, the duplicate studies were removed using the duplicate function of Endnote, and other duplicate studies were removed by reading. Second, endnote filtered out other types of articles, such as reviews, meta, cases and so on, and other types of articles also were removed upon reading. Finally, the studies that did not meet the inclusion criteria were eliminated through detailed reading. All data were screened by two independent reviewers (ZhiFeng Guo and LingHong Huang) based on the titles and abstracts of the retrieved records, and the full text of records that might qualify were examined. Disagreements were resolved by discussion with other reviewers (HuiBin Huang).

Outcome

The primary efficacy outcome in this study was a change in HOMA-β score from baseline to study endpoint, and a secondary efficacy outcome was a change in glycated haemoglobin (HbA1c) from baseline to study endpoint.

Study selection and data extraction

For all eligible trials, a pair of independent reviewers (ZhiFeng Guo and LingHong Huang) extracted study data and assessed the risk of bias. In case of any disagreement, a consensus was reached through consultation with other reviewers (HuiBin Huang). We collected information on participant clinical features, interventions, outcome indicators and dates of trial. For each treatment, we pooled the outcome data for all flexible doses into a single intervention group as these allowed the investigators to titrate the dose to that adequate for the individual patient. If a study reported results for different doses or different durations of intervention, we extracted data for the highest dose or longest duration of intervention. During the data extraction process, if relevant information was missing from the published report included in the trial, we contacted the corresponding author by email at least three times to request the original data. When the relevant data were not explicitly provided in a trial report and presented only in a graph, we used appropriate software to extract the data. If the outcome data were presented in a format other than mean ± standard error (mean ± SE) in a trial report, we used a formula to convert the data uniformly to mean ± SE. The kappa coefficient was used to assess agreement among assessors for quality of randomized controlled trial.

Assessment of study quality and assessment of the meta-evidence

The Cochrane Bias Risk Tool—Review Manager (RevMan, version 5.3) (https://www.thecochranelibrary.com) was used to assess the risk of bias in included studies. The following six domains were evaluated based on low, moderate, and high risks of bias: random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessors, incomplete data, and selective reporting. Because the outcome measures in this study (HOMA-β score and HbA1c) are determined by objective laboratory measurement, all outcomes had the same level of detection bias, and thus, only one bias risk assessment was conducted.

The credibility of RCT was assessed using the GRADE (Grading of Recommendations, Assessment, and Evaluation), which consisted of risk of bias, consistency of results, directness, precision, and potential for publication bias. Evidence was divided into four categories: high, moderate, low, and very low.

Data synthesis and analysis

Initially, we performed pairwise meta-analyses to explore the transitivity hypothesis and prove that the network meta-analysis method was appropriate. Then we used the I^2 statistic to assess the global inconsistency of the entire network mate analysis ($I^2 > 50\%$ taken to indicate substantial heterogeneity). Funnel plots were used to assess publication bias, and Egger's regression asymmetry test was employed to explore the impacts of small studies. Subsequently, we conducted a network meta-analysis using a frequentist approach based on a consistency effect model to calculate the weighted mean difference (WMD) and 95% confidence interval (CI) for the continuous variables. For the persistence variable HOMA-β index, a larger mean increase in treatment from baseline is

desirable, with positive values indicating improvement in beta-cell function after treatment, while negative values indicated worsening beta-cell function. Greater positive values indicated better protection of beta-cell function. For HbA1c, on the other hand, treatment with a greater mean reduction from baseline was desirable, with a positive negative indicating a reduction after treatment, and a negative indicating an increase after treatment. A smaller negative was more beneficial. Finally, we reported the features included in the study and summarized the data in a table. For all results, we summarized the evidence using a network working graph. We also generated a forest map to provide results compared to a common comparator (placebo). The ability of the treatments to affect each outcome was ranked using the surface under the cumulative ranking curve (SUCRA) and average ranking values. All statistical analyses were done in Stata 16.0 using the network package (https://www.stata.com/).

Results

Study characteristics

This study searched three databases (PubMed, EMBASE, and Cochrane Library) from the establishment of the database to December 1, 2024. The detailed search strategies are described in Supplement 1. A total of 8811 articles were initially identified. After removing duplicates (n = 1408), a total of 7403 records remained. Following title and abstract screening, 3863 irrelevant studies were excluded. Full-text reviews led to further exclusions based on predefined criteria, such as non-RCTs, inappropriate populations, interventions, or outcomes, resulting in 58 RCTs (Supplement 2) that met the inclusion criteria for this study and were included in the systematic review and network meta-analysis. A flow chart of trial selection is shown in Fig. 1. The included trials reported data for 16,345 patients in total, of whom 54.14% were male, and the overall mean age was 66.70 years. Other characteristics of the RCTs, such as study details, treatment and outcome-specific data are reported in Table 1. The present study included 39 interventions consisting of 9 hypoglycaemic drugs and placebo, including single and combination therapies. Network maps are shown in Fig. 2. Each node indicates a treatment, and the size of each node is proportional to the number of participants. Lines between two nodes represent direct comparisons between two treatments. The thickness of each line is proportional to the number of trials directly comparing the two connected treatments. All trials included in the network meta-analysis formed a linking network, with 58 studies (100.0%) providing data for assessment of the primary efficacy outcome (△HOMA-β) and 53 studies (91.4%) providing data for assessment of the secondary efficacy outcome (△HbA1c).

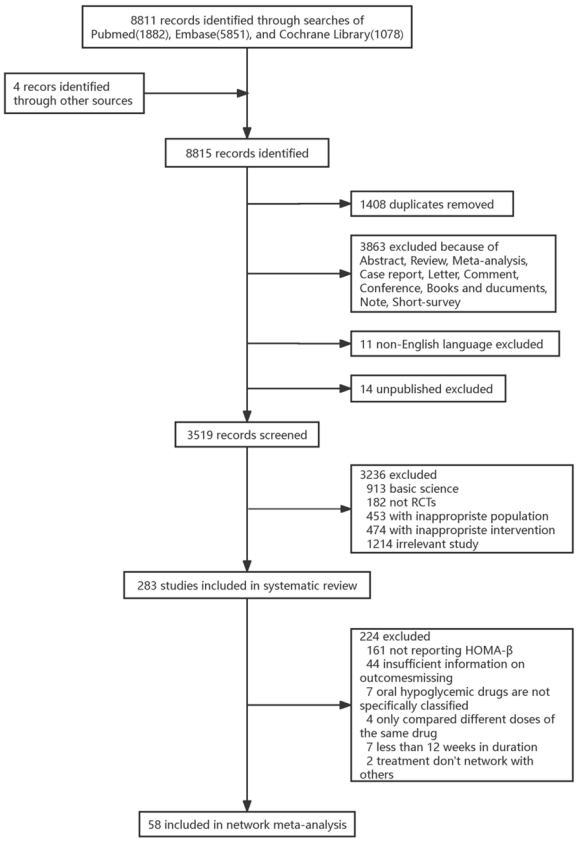

Fig. 1 Study selection process

Risk of bias assessment and quality of evidence

Of the 58 included trials, 34 were double-blind, 2 were single-blind, and 11 were open-label. The blinding strategy for the remaining trials was unclear. There was no high migration risk study in the other six fields. The proportions of appropriate descriptions by domain were 39.66% (23/58) for random sequence generation, 8.62% (5/58) for allocation concealment, 60.34% (35/58) for blinding of participants and personnel, 6.90% (4/58) for blinding of outcome assessors, 43.10% (25/58) for incomplete data, and 37.93% (22/58) for selective reporting. A graph and summary of the results regarding the risk of bias are presented in Supplement 3. HOMA-β and HbA1c had moderate-quality based on the GRADE approach (Table 2). Agreement between reviewers regarding the studies' risk of bias assessment was considered perfect (kappa coefficient = 0.75).

Inconsistency and heterogeneity

No significant difference was found in the test of global inconsistency between the consistency and inconsistency models for both outcomes ($p = 0.6712$ for HOMA-β

Table 1 Characteristics of the included studies

StudyID	First author	Year	N	Age (years)	Male (%)	Background treatment	Interventions	Treatment period	△HOMA-B(%)		△HbA1c(%)	
									N1	Mean ± SE	N2	Mean ± SE
1	Kerenyi,Z	2004	335	59.95	58.51	Diet	Glibenclamide 15 mg	26 weeks	170	6.162 ± 0.111	170	− 0.14 ± 0.076
							Glibenclamide 8 mg, Rosiglitazone 7.5 mg		165	33.000 ± 0.360	165	− 0.91 ± 0.081
2	Wallace,T.M	2004	30	61.84	73.33	Diet	Pioglitazone 45 mg	12 weeks	19	11.500 ± 1.101	19	− 0.30 ± 0.100
							Placebo		11	− 1.900 ± 1.447	11	0.30 ± 0.100
3	Bailey,C.J	2004	416	57.85	57.57	–	Metformin 3000 mg	24 weeks	203	2.500 ± 2.521	203	− 0.13 ± 0.047
							Metformin 2000 mg, Rosiglitazone 8 mg		213	15.900 ± 4.202	213	− 0.33 ± 0.053
4	Ristic,S	2005	78	55.43	56.20	–	Vildagliptin 100 mg	12 weeks	41	22.540 ± 7.000	41	− 0.53 ± 0.100
							Placebo		37	− 4.300 ± 7.200	37	− 0.13 ± 0.100
5	Tan,M.H	2005	241	56.48	62.26	–	Gliclazide 320 mg	2 years	116	31.717 ± 0.386	128	− 0.95 ± 0.053
							Pioglitazone 45 mg		125	20.356 ± 0.408	147	− 1.3 ± 0.007
6	Aschner,P	2006	463	NA	NA	–	Sitagliptin 200 mg	24 weeks	228	13.100 ± 3.240	238	− 0.77 ± 0.096
							Placebo		235	0.300 ± 3.189	244	0.17 ± 0.102
7	Charbonnel,B	2006	614	NA	NA	Metformin	Sitagliptin 100 mg		418	19.500 ± 3.418	453	− 0.7 ± 0.059
							Placebo		196	3.500 ± 4.260	224	− 0.08 ± 0.087
8	Raz,I	2006	251	NA	NA	–	Sitagliptin 200 mg	18 weeks	171	13.000 ± 3.138	199	− 0.33 ± 0.113
							Placebo		80	1.000 ± 4.592	103	0.16 ± 0.160
9	Li,J	2007	223	55.97	NA	Metformin	Repaglinide 3 mg	12 weeks	110	17.220 ± 5.988	110	− 1.57 ± 0.197
							Nateglinide 270 mg		113	7.920 ± 5.690	113	− 0.68 ± 0.185
10	Chou,H.S	2008	583	53.82	59.10	Diet and exercise	Glimepiride 4 mg	28 weeks	197	58.700 ± 3.087	221	− 1.72 ± 0.105
							Rosiglitazone 8 mg		196	46.100 ± 2.985	227	− 1.75 ± 0.110
							Glimepiride 4 mg,Rosiglitazone 8 mg		190	105.800 ± 4.923	214	− 2.52 ± 0.112
11	Dorkhan,M	2008	36	61.38	72.22	Metformin and sulfonylurea/meglitinide	Pioglitazone 45 mg	26 weeks	17	10.000 ± 6.408	17	− 1.30 ± 0.432
							Insulin glargine		19	37.000 ± 19.229	19	− 2.20 ± 0.339
12	Pratley,R.E	2008	1506	53.11	54.90	–	Vildagliptin 100 mg	24 weeks	1340	10.300 ± 1.500	227	− 1.30 ± 0.100
							Placebo		166	− 1.200 ± 4.100	29	− 0.30 ± 0.200
13	Raz,I	2008	139	54.84	45.26	Metformin	Sitagliptin 100 mg	18 weeks	74	17.000 ± 2.883	95	− 1.00 ± 0.152
							Placebo		65	2.500 ± 3.010	92	0.00 ± 0.128
14	Seino,Y	2008	90	56.52	66.67	Diet with or without oral antidiabetic drug	Liraglutide 0.9 mg	14 weeks	44	21.050 ± 5.639	44	− 1.67 ± 0.188
							Placebo		46	0.890 ± 3.877	46	0.10 ± 0.236
15	Charpentier,G	2009	289	59.71	65.40	–	Pioglitazone 30 mg	7 months	142	7.700 ± 11.796	–	–
							Placebo		147	− 17.200 ± 10.445	–	–

Table 1 (continued)

StudyID	First author	Year	N	Age (years)	Male (%)	Background treatment	Interventions	Treatment period	△HOMA-B(%)		△HbA1c(%)	
									N1	Mean ± SE	N2	Mean ± SE
16	Hollander,P	2009	278	53.60	47.03	Thiazolidinedione	Saxagliptin 5 mg	24 weeks	140	11.000 ± 2.610	140	− 0.90 ± 0.065
							Placebo		138	2.900 ± 2.660	138	− 0.30 ± 0.071
17	Williams-Herman,D	2009	357	53.78	45.50	–	Sitagliptin 100 mg	54 weeks	88	18.100 ± 5.510	88	− 0.80 ± 0.102
							Metformin 2000 mg		126	17.500 ± 4.592	126	− 1.30 ± 0.076
							Sitagliptin 100 mg, Metformin 2000 mg		143	41.900 ± 4.311	143	− 1.80 ± 0.076
18	Aschner,P	2010	762	56.01	48.77	–	Sitagliptin 100 mg	24 weeks	379	8.200 ± 3.673	455	− 0.40 ± 0.046
							Metformin 2000 mg		383	12.700 ± 3.648	439	− 0.50 ± 0.044
19	Derosa,G	2010	116	56.49	49.22	Metformin	Exenatide 20 ug	12 months	59	11.700 ± 9.627	59	− 1.50 ± 0.099
							Glibenclamide 15 mg		57	− 1.500 ± 9.073	57	− 1.80 ± 0.109
20	Derosa,G	2010	137	57.50	50.33	Diet and exercise	Sitagliptin 100 mg, Pioglitazone 30 mg		69	15.200 ± 9.143	69	− 1.40 ± 0.114
							Metformin 1700 mg, Pioglitazone 30 mg		68	14.800 ± 8.789	68	− 1.40 ± 0.100
21	Seck,T	2010	466	57.30	60.12	Metformin	Sitagliptin 100 mg	2 years	232	12.900 ± 6.939	248	− 0.53 ± 0.055
							Glipizide 20 mg		234	19.200 ± 6.888	256	− 0.51 ± 0.059
22	Bosi,E	2011	758	55.10	51.18	Metformin and Pioglitazone	Alogliptin 25 mg	52 weeks	381	15.020 ± 2.740	381	− 0.25 ± 0.049
							Placebo		377	2.060 ± 2.754	377	− 0.71 ± 0.052
23	Del Prato,S	2011	214	55.74	48.31	–	Linagliptin 5 mg	24 weeks	157	5.000 ± 5.900	333	− 0.44 ± 0.050
							Placebo		57	− 17.200 ± 9.700	163	0.25 ± 0.070
24	Gomis, R	2011	270	57.50	60.93	–	Linagliptin 5 mg, Pioglitazone 30 mg		191	− 2.170 ± 2.580	252	− 1.25 ± 0.070
							Pioglitazone 30 mg		79	− 1.440 ± 3.890	128	− 0.75 ± 0.110
25	Wang,J.S	2011	51	53.66	49.01	Metformin	Glibenclamide 7.5 mg	16 weeks	23	9.200 ± 12.776	23	− 1.20 ± 0.417
							Acarbose 150 mg		28	10.200 ± 9.525	28	− 0.70 ± 0.214
26	Yoon,K.H	2011	425	50.95	54.23	Diet and exercise	Pioglitazone 30 mg	24 weeks	208	19.300 ± 5.383	246	− 1.50 ± 0.179
							Pioglitazone 30 mg, Sitagliptin 100 mg		217	31.000 ± 5.281	251	− 2.40 ± 0.102
27	Chou,H.S	2012	1446	55.08	51.71	–	Rivoglitazone 2.5 mg	26 weeks	676	19.700 ± 5.132	733	− 0.70 ± 0.030
							Pioglitazone 45 mg		668	14.200 ± 3.501	728	− 0.60 ± 0.030
							Placebo		102	7.100 ± 9.807	134	0.20 ± 0.060
28	De Fronzo,R.A	2012	260	54.50	46.92	Metformin	Pioglitazone 15 mg		130	5.056 ± 3.049	–	–
							Pioglitazone 15 mg, Alogliptin 25 mg		130	22.231 ± 3.049	–	–

Table 1 (continued)

StudyID	First author	Year	N	Age (years)	Male (%)	Background treatment	Interventions	Treatment period	△HOMA-B(%)		△HbA1c(%)	
									N1	Mean ± SE	N2	Mean ± SE
29	Derosa,G	2012	169	55.36	48.31	Diet and exercise	Metformin 2500 ± 500 mg	12 months	83	22.500 ± 12.102	83	− 0.70 ± 0.080
							Metformin 2500 ± 500 mg, Sitagliptin 100 mg		86	42.700 ± 12.496	86	− 1.40 ± 0.087
30	Derosa,G	2012	163	57.05	51.59	Diet and exercise	Metformin 2500 ± 500 mg		82	5.800 ± 13.072	82	− 0.40 ± 0.074
							Metformin 2500 ± 500 mg, Exenatide 20 ug		81	31.600 ± 14.687	81	− 1.20 ± 0.091
31	Derosa,G	2012	160	53.45	50.00	Diet and exercise	Metformin 2500 ± 500 mg		79	24.800 ± 11.816	79	− 0.80 ± 0.082
							Metformin 2500 ± 500 mg, Vildagliptin 100 mg		81	42.700 ± 12.882	81	− 1.20 ± 0.068
32	Henry,R.R	2012	207	54.06	51.69	Metformin and Pioglitazone	Taspoglutide 20 mg	24 weeks	113	33.520 ± 5.260	113	− 1.40 ± 0.083
							Placebo		94	2.030 ± 5.830	94	− 0.45 ± 0.100
33	Wainstein,J	2012	389	52.30	53.58	Diet	Pioglitazone 45 mg	32 weeks	197	21.500 ± 6.556	197	− 1.40 ± 0.051
							Metformin 2000 mg, Sitagliptin 100 mg		192	43.700 ± 6.623	192	− 1.90 ± 0.077
34	Williams-Herman,D	2012	219	53.37	48.75	–	Metformin 2000 mg	104 weeks	78	23.764 ± 6.974	–	–
							Sitagliptin 100 mg		43	27.638 ± 9.041	–	–
							Metformin 2000 mg, Sitagliptin 100 mg		98	50.886 ± 6.458	–	–
35	Yuan,G.H	2012	59	57.75	49.15	Diet and exercise	Metformin 1500 mg	26 weeks	26	4.150 ± 7.053	26	− 1.66 ± 1.380
							Exenatide 20 ug		33	5.050 ± 8.939	33	− 2.10 ± 1.790
36	Bi,Y	2013	138	55.04	NA	–	Metformin 1500 mg	24 weeks	68	18.500 ± 3.100	68	− 1.70 ± 0.200
							Glipizide 15 mg		70	18.400 ± 2.600	70	− 2.00 ± 0.200
37	Derosa,G	2013	436	NA	49.77	Metformin and Pioglitazone	Glibenclamide 15 mg	36 months	214	63.300 ± 5.567	–	–
							Sitagliptin 100 mg		222	3.500 ± 7.750	–	–
38	Nauck, M	2013	262		NA	–	Metformin 2000 mg	2 years	31	− 7.900 ± 34.500	31	− 0.30 ± 0.100
							Metformin 2000 mg, Glimepiride 4 mg		113	11.300 ± 25.300	113	− 0.50 ± 0.100
							Metformin 2000 mg, Liraglutide 1.8 mg		118	17.800 ± 25.000	118	− 0.60 ± 0.100
39	Pistrosch,F	2013	75	60.97	58.67	–	Metformin 2000 mg	36 weeks	36	4.400 ± 3.250	36	− 0.60 ± 0.068
							Insulin glargine		39	77.200 ± 15.661	39	− 0.80 ± 0.110
40	Rhee,E.J	2013	268	NA	NA	Metformin	Sitagliptin 100 mg	24 weeks	133	15.870 ± 3.359	133	− 0.80 ± 0.069
							Gemigliptin 50 mg		135	31.700 ± 12.263	135	− 0.77 ± 0.069

Table 1 (continued)

StudyID	First author	Year	N	Age (years)	Male (%)	Background treatment	Interventions	Treatment period	△HOMA-B(%)		△HbA1c(%)	
									N1	Mean ± SE	N2	Mean ± SE
41	Stenlöf, K	2013	246	55.50	45.50	Diet and exercise	Canagliflozin 300 mg	26 weeks	130	20.300 ± 2.000	130	− 1.03 ± 0.056
							Placebo		116	− 2.500 ± 2.100	116	0.14 ± 0.069
42	Wilding,J.P	2013	76	56.45	52.24	Metformin and sulphonylurea	Canagliflozin 300 mg		38	25.900 ± 4.800	38	− 0.95 ± 0.077
							Placebo		38	− 1.000 ± 4.800	38	0.02 ± 0.077
43	Chen,P.H	2014	51	53.66	49.02	–	Glibenclamide 15 mg	24 weeks	23	− 6.700 ± 20.330	23	− 1.20 ± 0.417
							Acarbose 300 mg		28	9.100 ± 9.479	28	− 0.7 ± 0.169
44	Fang,F.S	2014	59	47.50	61.67	Diet and exercise	Metformin 1500 mg	15 weeks	20	17.100 ± 5.232	20	− 1.60 ± 0.335
							Repaglinide 2 mg		39	20.500 ± 3.667	39	− 1.80 ± 0.240
45	Ma,J	2014	76	57.09	57.01	Diet and lifestyle	Metformin 750–1500 mg	3 months	54	1.420 ± 1.049	54	− 0.61 ± 0.020
							Repaglinide 0.75–1.5 mg		22	27.370 ± 1.394	22	− 1.14 ± 0.034
46	Moon,J.S	2014	72	53.00	38.89	Metformin	Glimepiride 8 mg	52 weeks	34	5.700 ± 2.392	34	− 1.18 ± 0.206
							Insulin glargine		38	1.730 ± 1.418	38	− 1.80 ± 0.211
47	Nauck,M	2014	614	54.60	47.98	Metformin	Sitagliptin 100 mg		310	6.700 ± 0.141	310	− 0.39 ± 0.053
							Dulaglutide 1.5 mg		304	33.600 ± 0.143	304	− 1.10 ± 0.054
48	Cheng,Q	2015	44	56.49	65.96	Diet and exercise	Metformin 2500 mg	6 months	24	0.570 ± 0.194	24	− 5.55 ± 0.399
							Insulin glargine		20	1.120 ± 0.222	20	− 5.33 ± 0.418
49	Wang,D	2015	219	48.00	49.32	Diet and exercise	Metformin 1500 mg	12 weeks	55	1.050 ± 0.074	–	–
							Gliclazide 160 mg		52	0.920 ± 0.059	–	–
							Pioglitazone 30 mg		57	0.840 ± 0.060	–	–
							Insulin Novolin R		55	2.260 ± 0.074	–	–
50	Wu,W	2015	55	51.98	60.00	–	Linagliptin 5 mg	24 weeks	33	11.080 ± 3.648	33	− 1.2 ± 0.165
							Placebo		22	3.990 ± 7.200	22	− 0.41 ± 0.184
51	Zografou,I	2015	64	54.40	59.38	–	Metformin 1700 mg	6 months	32	8.100 ± 9.864	32	− 1.20 ± 0.212
							Metformin 1700 mg, Vildagliptin 100 mg		32	22.000 ± 5.975	32	− 1.70 ± 0.124
52	Wang,Y	2016	28	60.20	46.43	–	Dapagliflozin	24 weeks	18	− 7.180 ± 6.111	18	− 1.54 ± 0.186
							Placebo		10	− 2.820 ± 8.154	10	− 0.55 ± 0.240
53	Kim,G	2017	34	55.95	58.82	–	Glimepiride 2 mg	12 weeks	17	18.140 ± 13.026	17	− 0.90 ± 0.141
							Vildagliptin 100 mg		17	− 1.600 ± 9.334	17	− 0.80 ± 0.224
54	Kashiwagi,A	2018	993	58.82	68.37	–	Ipragliflozin 50 mg	24 weeks	626	3.600 ± 0.554	626	− 0.72 ± 0.026
							Placebo		367	− 2.400 ± 0.747	367	0.33 ± 0.047
55	Tsurutani,Y	2018	101	NA	NA	–	Sitagliptin 50 mg	12 weeks	49	17.500 ± 6.122	49	− 0.81 ± 0.105
							Ipragliflozin 50 mg		52	− 0.990 ± 6.071	52	− 1.10 ± 0.117

Table 1 (continued)

StudyID	First author	Year	N	Age (years)	Male (%)	Background treatment	Interventions	Treatment period	△HOMA-B(%)		△HbA1c(%)	
									N1	Mean ± SE	N2	Mean ± SE
56	Yin,T.T	2018	37	47.94	64.86	Metformin	Insulin glargine	16 weeks	18	32.900 ± 7.634	18	− 1.10 ± 0.067
							Exenatide 20 ug		19	74.000 ± 11.289	19	− 1.20 ± 0.083
57	Kim,J M	2020	116	59.62	47.41	Metformin and alogliptin	Glimepiride 2–4 mg	26 weeks	58	5.210 ± 7.846	66	− 1.05 ± 0.107
							Pioglitazone 15–30 mg		58	6.150 ± 3.171	69	− 0.81 ± 0.132
58	Wang,X	2020	81	58.17	56.84	–	Insulin Lispro	24 weeks	41	− 0.670 ± 4.089	41	− 0.99 ± 0.192
							Exenatide 20 ug		40	3.110 ± 5.260	40	− 1.38 ± 0.235

Data are presented as mean or mean ± standard error

HOMA-β homeostasis model assessment of beta-cell function, *HbA1c* glycated haemoglobin, *N* the total number of patient, *N1*, *N2* the number of patients included in the study, *NA* not available

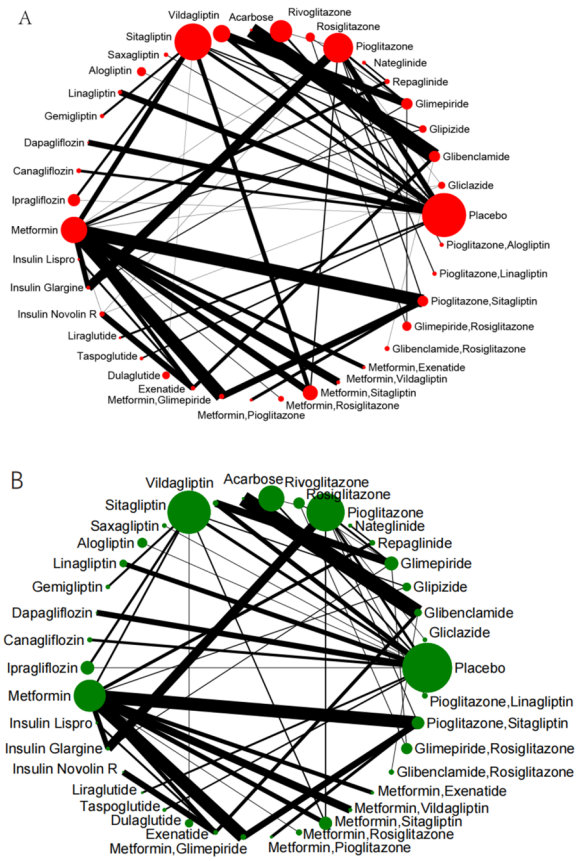

Fig. 2 Network meta-analysis of eligible comparisons for HOMA-β index (**A**) and HbA1c (**B**). *HOMA-β* homeostasis model assessment for beta-cell function, *HbA1c* glycated haemoglobin. Each node indicates a treatment, and its size is proportional to the number of participants; lines connecting two nodes representing direct comparisons between two treatments; and the thickness of the lines is proportional to the number of trials directly comparing the two connected treatments

index, $p=0.2164$ for HbA1c). The global I^2 values were 11.19% and 13.13% for HOMA-β index and HbA1c, respectively. The test for local inconsistency showed that most loops were consistent for HOMA-β index (42/53 loops, Supplements 4–5). A small-study effect was shown by Egger's analyses ($p=0.870$). Moreover, there was no publication bias observed by visual inspection of the funnel plot (Fig. 3).

HOMA-β index

A total of 58 studies (16,345 patients) were included in the main analysis for change in HOMA-β index. The results of the pairwise meta-analysis are presented in Supplement 6. Compared with placebo, treatment regimens glimepiride + rosiglitazone, glibenclamide + rosiglitazone, acarbose, glibenclamide, insulin glargine, metformin + exenatide, dulaglutide, metformin + sitagliptin, exenatide, pioglitazone + alogliptin, pioglitazone + sitagliptin, glimepiride, taspoglutide, metformin + vildagliptin, repaglinide, canagliflozin, and pioglitazone were associated with a significant increase in HOMA-β score. Among them, the top treatments were glimepiride + rosiglitazone (WMD = 81.83, 95% CI 45.85–117.82), glibenclamide + rosiglitazone (WMD = 79.51, 95% CI 40.66–118.36), and acarbose (WMD = 60.90, 95% CI 27.56–94.25). As shown in Fig. 4A, the top two treatments were combination treatments, and both included a sulfonylurea with rosiglitazone. Acarbose was the most efficacious agent as monotherapy, followed by glibenclamide (WMD = 52.73, 95% CI 27.12–78.34), exenatide (WMD = 46.28, 95% CI 22.55–70.02), insulin glargine (WMD = 45.49, 95% CI 25.92–65.06), insulin lispro (WMD = 42.46, 95% CI 4.76–80.15), and dulaglutide (WMD = 39.71, 95% CI 8.08–71.34). No increase in HOMA-β score was found after treatment with metformin alone, but combination treatment with metformin and exenatide (WMD = 42.59, 95% CI 9.44–75.73), sitagliptin (WMD = 39.21, 95% CI 21.34–57.07) did result in HOMA-β score improvement. Glibenclamide showed a better effect than glimepiride (WMD = 34.77, 95% CI 13.78–55.76), and its combination with rosiglitazone ranked higher than the glimepiride + rosiglitazone combination treatment. Among insulins, only insulin glargine (WMD = 45.49, 95% CI 25.92–65.06) could increase HOMA-β score. Moderate efficacy was found for some additional treatment types, such as taspoglutide, repaglinide, canagliflozin, and pioglitazone. No significant difference was detected between the other treatments and placebo.

Table 2 Summary of findings and quality of evidence assessment using the GRADE approach

Index	Summary of findings		Quality of evidence assessment(GRADE)					
	No of patients (trials)	WMD (95% CI)	Risk of bias*	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
ΔHOMA-β(%)	16,345(58)	14.491(11.341,17.640)	Serious	Not Serious	Not Serious	Not Serious	Not Serious	Moderate
ΔHbA1c(%)	14,768(53)	− 0.961(− 1.111,− 0.811)	Serious	Not Serious	Not Serious	Not Serious	Not Serious	Moderate

HOMA-β homeostasis model assessment-β, *HbA1c* glycated haemoglobin

* Some included studies did not use randomization and blinding, which may lead to performance bias and detection bias

The curves for determining SUCRA values are presented in Fig. 5A. Because the top 12 treatments showed a statistical difference compared with placebo, we selected the top 12 treatments based on SUCRA value for analysis in this study. The SUCRA results for the other treatments are shown in Supplement 7. The treatment with the highest SUCRA value for HOMA-β improvement was glimepiride + rosiglitazone (95.1%), followed by glibenclamide + rosiglitazone (94.9%) and acarbose (85.7%).

HbA1c

Nearly all of the examined treatments significantly reduced HbA1c in T2DM patients compared with placebo. Glibenclamide + rosiglitazone (WMD = − 2.48, 95% CI − 3.67 to − 1.29) was the most efficacious treatment, which significantly reduced HbA1c with a mean decrease of 2.48%. This treatment was followed by metformin + exenatide (WMD = − 1.77, 95% CI − 2.25 to − 1.29) and liraglutide (WMD = − 1.77, 95% CI − 2.33 to − 1.21), which ranked first among monotherapies for reducing HbA1c. Glimepiride + rosiglitazone and glibenclamide + rosiglitazone ranked first and second for improving the HOMA-β index and ranked fourth and first for reducing HbA1c, respectively. Regarding other treatments, metformin in combination with exenatide, sitagliptin, vigliptin, pioglitazone, glimepiride and rosiglitazone also reduced HbA1c significantly, and the efficacy of each of these combined treatments was greater than that of monotherapy. The efficacy of liraglutide was better than that of dulaglutide and exenatide. Among insulin-based treatments, insulin novolin R showed better efficacy than insulin glargine. Acarbose produced a significant benefit but with a modest effect. Insulin lispro, nateglinide, gliclazide, and alogliptin alone resulted in no significant decrease in HbA1c compared with placebo (Fig. 4B).

As mentioned above, we evaluated the top 12 treatments according to SUCRA values (Fig. 5B). The treatment with the highest SUCRA value for HbA1c improvement was glibenclamide + rosiglitazone (97.6%), followed by metformin + exenatide (88.7%) and then liraglutide (88.1%). Alogliptin (0.2%) had the lowest SUCRA value in this analysis.

Summary

The overall results of the present network meta-analysis of treatments that improved the HOMA-β score and HbA1c among T2DM patients are presented in Fig. 6. Figure 7 shows the two-dimensional plots for HOMA-β and HbA1c in all studies and head-to-head studies. Based on efficacy estimates, combination therapies including a sulfonamide with rosiglitazone provided the most two efficacious treatments compared with placebo. For all treatments, efficacy was estimated in comparison with the placebo control, and the findings regarding the secondary outcome were consistent with those for the primary outcome.

Discussion

With continued breakthroughs in understanding the pathogenic characteristics of T2DM, the therapeutic goal has shifted from glycaemic control to preserving or regenerating beta-cell viability and function. In this study, a network meta-analysis of 58 RCTs including a total of 16,345 patients showed that, compared with placebo, most treatments had beneficial effects on beta-cell function. Combining direct and indirect evidence, combination therapies including a sulfonamide with rosiglitazone ranked first and second not only among combination treatments but among all treatments. Acarbose was the most beneficial monotherapy and ranked third among all treatments, followed by glibenclamide and insulin glargine. Comparing monotherapy agents and combination treatments, the two most effective treatments were combination treatments that had a better protective effect on beta-cell function than acarbose, and most of the combinations had better efficacy for protecting beta-cell function than any monotherapy agent. Almost all of the included treatments led to significant reductions in HbA1c compared with placebo, and the treatments with the greatest effect were combination treatments including a sulfonamide and rosiglitazone, consistent with the results for HOMA-β index.

We searched for other pertinent network meta-analyses related to T2DM to identify correlation analyses of the efficacy and safety of different hypoglycaemic drugs for T2DM. Previous network meta-analyses on the efficacy of different hypoglycaemic drugs for T2DM mainly focused on evaluating the ranges of changes in HbA1c and fasting glucose [25–27], partly evaluated the effects of weight reduction [28], or examined the protection of microvascular [29] and endothelial cells [30], including comparisons of different types of drugs [31] or single- and double-drugs [32], and different drug types or different doses of the same drug [23]. Safety analyses mainly covered adverse reactions, such as hypoglycaemia [33], gastrointestinal reactions [34], cardiovascular effects [35–37], urinary tract infections [38] and fracture [39, 40]. As mentioned in the introduction, there have been few network meta-analyses on the protective effects of different hypoglycaemic drugs on beta cell function in T2DM patients, and the comparisons of drug types were limited. Compared with previous studies, the RCTs included in the present study covered different hypoglycaemic regimens, consisting of 38 types of monotherapy

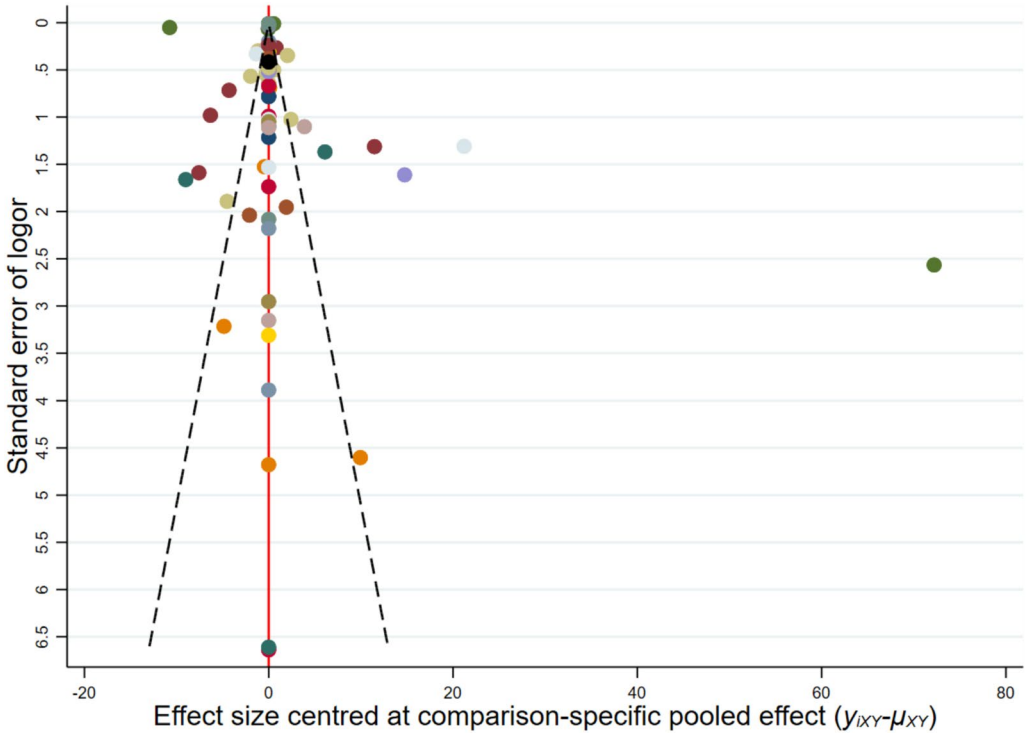

Fig. 3 Funnel plot displaying publication bias in the reporting studies

or combined drug therapies, including 7 oral hypoglycaemic drugs, insulin, and incretin. In contrast, we conducted a broader and more comprehensive analysis of the direct and indirect evidence for the different efficacies of hypoglycaemic drugs.

Various types of drugs are used to treat T2DM. In the course of treatment, monotherapy drugs often have specific side effects, whereas treatment with combinations of drugs can not only improve the therapeutic effect but also reduce the occurrence of adverse reactions. Previous network meta-analyses mainly evaluated the efficacy of monotherapy drugs; however, in the present study, a comparative analysis was conducted between monotherapy drugs and combination therapies. The network meta-analyses showed that most combination therapies were more effective than monotherapy agents for beta-cell protection, such as glimepiride combined with rosiglitazone versus glimepiride or rosiglitazone alone, glibenclamide combined with rosiglitazone versus glibenclamide or rosiglitazone alone, and metformin combined with exenatide versus metformin or exenatide. The above conclusions also held true upon evaluation of efficacy for HbA1c reduction. Yang et al. performed a comparison between single- and double-drugs [32] and found that the combined drug therapies were more effective than individual drug regimens, which was consistent with our findings.

According to the results of the present study, treatment with a sulfonamide combined with rosiglitazone ranked first in terms of both protective effect on beta-cell function and HbA1c reduction, and treatment with another sulfonamide combined with rosiglitazone ranked second in terms of protective effect on beta-cell function. Thus, the beneficial effect of a sulfonamide combined with rosiglitazone for preservation of beta-cell function are biologically reasonable. Sulfonamides, including glimepiride and glibenclamide, are universally recognized as effective hypoglycaemic drugs and have often been used as the next treatment after metformin monotherapy fails as the first-line drug. These drugs promote insulin secretion and then reduce plasma glucose rapidly, showing a powerful effect on glycaemic control; however, hypoglycaemia is a common side effect of sulfonamide treatment [41–43]. Thiazolidinediones, which are insulin sensitizers, and sulfonamides have complementary effects. Rosiglitazone, a member of the thiazolidinediones, has beneficial effects on beta-cell function by improving insulin sensitivity [41, 42]. Combined with the effect on beta-cells and HbA1c, the protective effect of sulfonamides combined with rosiglitazone on beta-cell function may be mainly derived from the resulting control of HbA1c. Sulfonamides promote insulin secretion and rapidly reduce plasma glucose to improve the damage to beta-cells caused by glucotoxicity. At the same time, their

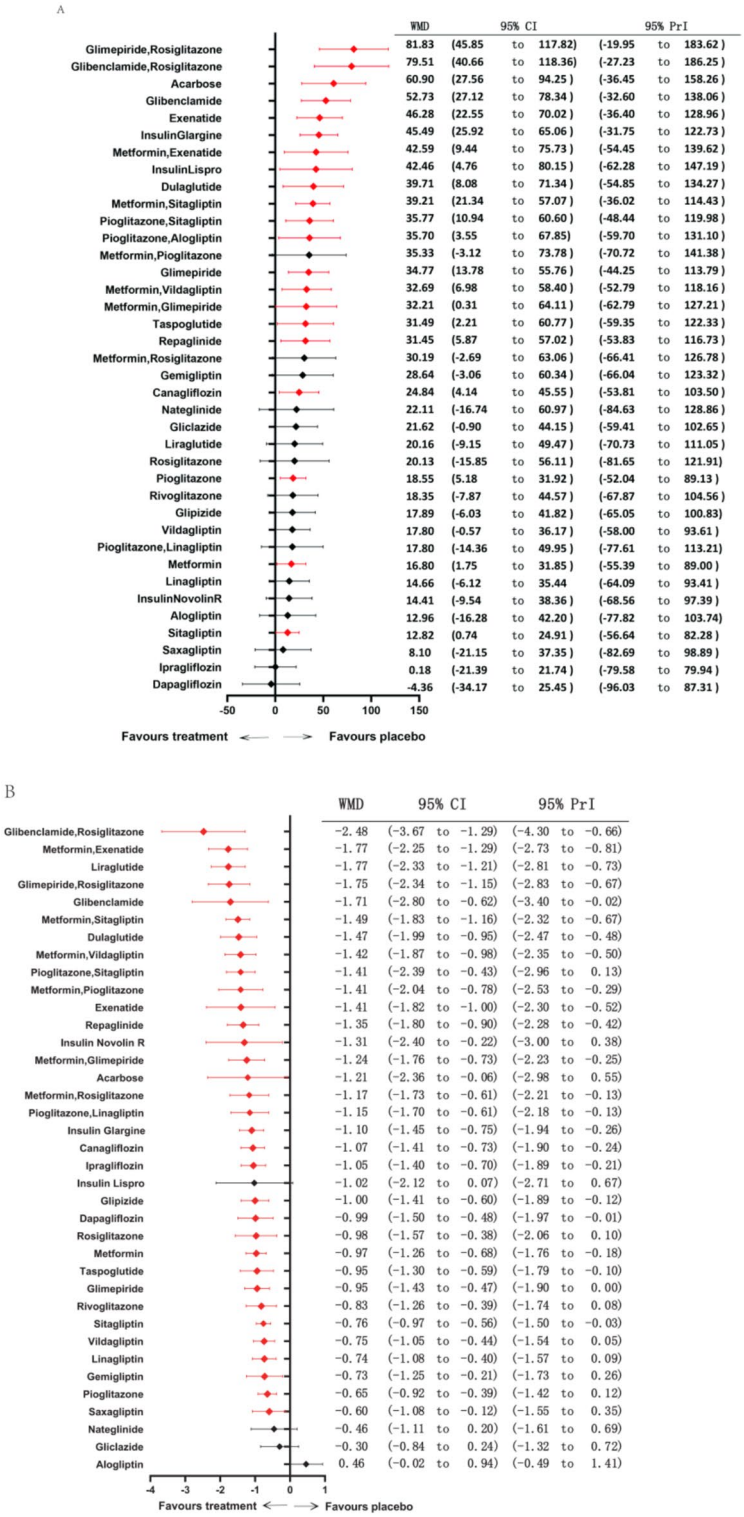

Fig. 4 Forest plots from network meta-analysis of all trials for HOMA-β index (**A**) and HbA1c (**B**). *HOMA-β* homeostasis model assessment for beta-cell function, *HbA1c* glycated haemoglobin, *WMD* weighted mean difference, *CI* confidence interval, *PrI* predictive interval

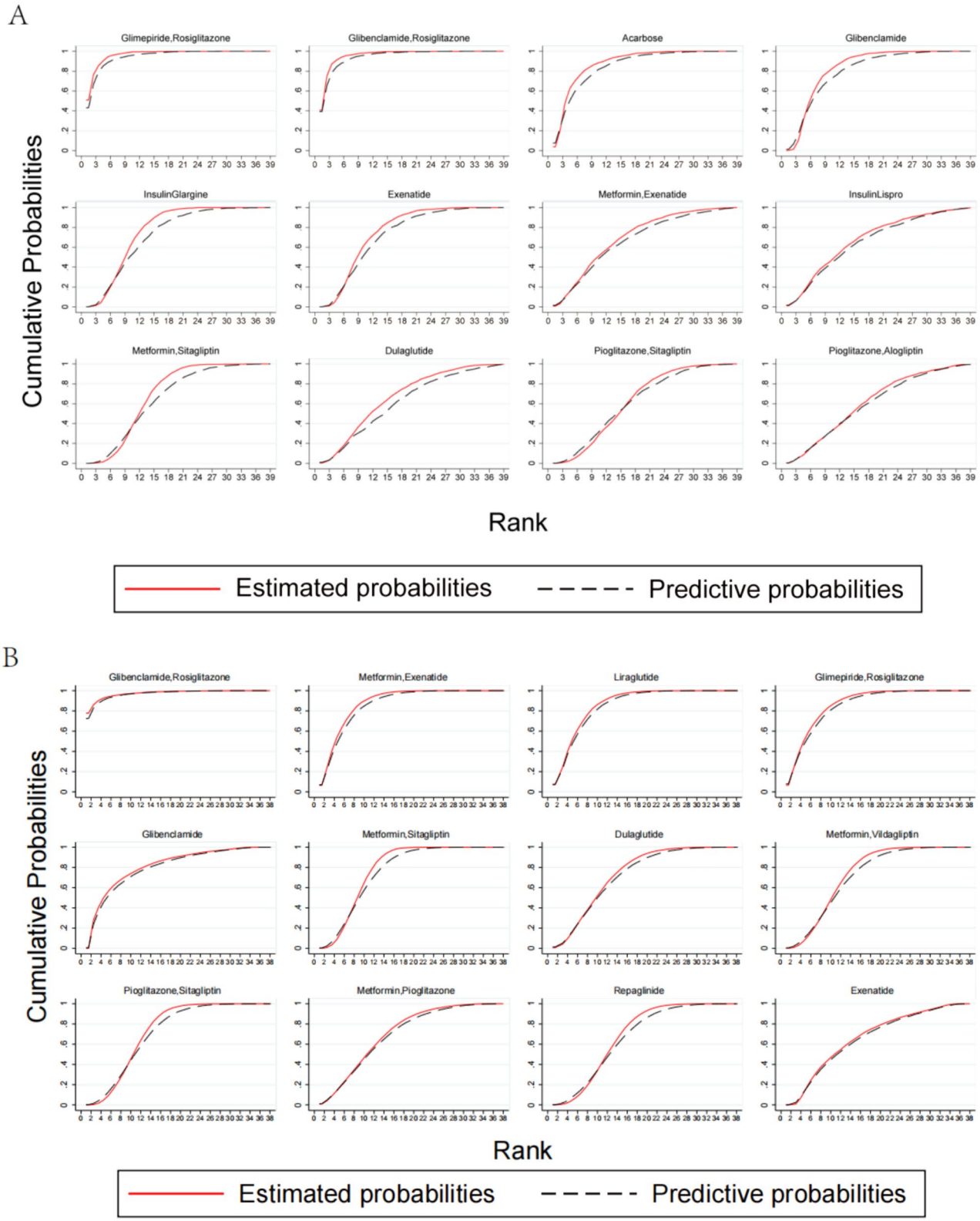

Fig. 5 SUCRA values for the top 12 hypoglycaemic treatments in terms of HOMA-β (**A**) and HbA1c (**B**) improvement. *SUCRA* surface under the cumulative ranking curve, *HOMA-β* homeostasis model assessment for beta-cell function; *HbA1c* glycated haemoglobin, ranking: probability of being the best treatment, second best, third best and so on, among the comparisons. Hypoglycaemic treatments were compared with placebo, which served as the reference compound

combination with rosiglitazone could increase insulin sensitivity, thus increasing the effect of glycaemic control, and also reducing the dosage of sulfonamides and, therefore, the risk of hypoglycaemia. The improvement in insulin sensitivity and insulin secretion enabled residual beta-cell function to continue to contribute to the regulation of the glycaemic response and ameliorate the negative effects of hyperglycaemia on beta-cells. Notably, the side effects of this regimen, such as weight gain, are less than those of other hypoglycaemic regimens, such as insulin. While eliminating the toxicity to beta-cells, such therapies can also relieve insulin resistance and reduce the burden on beta-cells. Acarbose, one of the α-glycosidase inhibitors, ranked first among monotherapy agents in terms of effective protection of beta-cell function, and this drug inhibits disaccharide hydrolase enzymes in the small intestine to reduce glucose absorption and control postprandial hyperglycaemia [43]. In addition, it has been shown to indirectly improve insulin resistance and secretion in obese T2DM patients, which is possibly a result of improved glucotoxicity [44].

The findings of this study suggested that sulfanilamide + rosiglitazone was the most effective hypoglycaemic regimen for protecting beta-cell function and improving glycaemic control in T2DM treatment, thereby holding substantial clinical significance. Primarily, sulfanilamide + rosiglitazone optimizes glycemic regulation, which is crucial for preventing or delaying the onset and progression of diabetic complications. This therapeutic combination mitigates the risk of both hyperglycemia and hypoglycemia, thereby improving the quality of life for individuals withT2DM. Second, sulfanilamide + rosiglitazone has been shown to mitigate glycotoxicity, decelerate the progressive deterioration of beta-cell, and facilitate the regeneration or differentiation of these cells, thereby aiding in the maintenance or potential restoration of their function. This dual therapy not only enhances short-term glycemic control but also lays a more robust foundation for long-term diabetes management. Furthermore, the cardiovascular risk associated with rosiglitazone is mitigated when used in conjunction with agents, such as sulfanilamide. By achieving effective glycemic regulation, this combination therapy demonstrates significant therapeutic potential. Through effective glycemic control, sulfanilamide + rosiglitazone has the potential to substantially decrease the incidence of cardiovascular diseases, nephropathy, retinopathy, and other complications, thereby enhancing the prognosis of T2DM. Finally, in patients with newly diagnosed T2DM, particularly those with compromised beta-cell function or those at elevated risk, the early intervention with sulfanilamide + rosiglitazone may prove to be an optimal therapeutic strategy. Early protection of beta-cell function could decelerate disease progression and mitigate the complexity and financial burden of future treatments. In individuals with obesity and T2DM, the sulfanilamide + rosiglitazone not only regulates blood glucose levels but also enhances insulin sensitivity and facilitates weight reduction.

HOMA-β score serves as a crucial metric for assessing the functionality of pancreatic islet beta cells. Even minor enhancements in beta cell function can decelerate the progression of diabetes and improve glycemic control. The combination therapies of glimepiride + rosiglitazone and glibenuride + rosiglitazone have been shown to significantly enhance HOMA-β scores, indicating that these treatments may exert a substantial protective effect on beta cell function in patients with T2DM and contribute to sustained glucose management. Acarbose also demonstrated a significant increase in HOMA-β scores; although its effect size was somewhat lower than that of the aforementioned combinations, it still exhibited a positive impact on beta cell function, particularly in the regulation of postprandial blood glucose levels. Acarbose achieves this by inhibiting carbohydrate absorption, thereby alleviating the burden on islet beta cells. Glibenclamide + rosiglitazone resulted in an average reduction of HbA1c by 2.48%, a change deemed clinically significant. Numerous studies have demonstrated that a 1% reduction in HbA1c is associated with approximately a 37% decrease in the risk of microvascular complications, such as retinopathy and kidney disease, and about a 14% reduction in the risk of macrovascular events, including myocardial infarction and stroke. Consequently, this therapeutic regimen holds substantial promise for mitigating diabetes-related complications and enhancing long-term patient outcomes. In addition, the treatment regimens of metformin combined with exenatide and liraglutide also exhibited significant HbA1c-lowering effects. Although their effect sizes were slightly less pronounced than that of the glibenclamide and rosiglitazone combination, they remain effective hypoglycemic treatment options, particularly for patients who are unsuitable for or intolerant of sulfonylureas. While these effect sizes are statistically significant, larger randomized controlled trials and extended follow-up data are necessary to substantiate their long-term clinical efficacy and safety across a broader patient population. Furthermore, it is essential to investigate optimal treatment strategies for various patient subgroups. Given that individual patients may exhibit differential responses to specific drug combinations, selecting the most appropriate treatment should be informed by individual patient characteristics, such as age, disease progression, and comorbidities. By

Gliclazide	31.11 (0.52,61.70)	-3.73 (-33.21,25.75)	13.15 (-13.85,40.15)	9.83 (-19.84,39.49)	0.49 (-41.17,42.16)	-3.08 (-22.52,16.37)	-1.49 (-41.28,38.30)
-31.11 (-61.70,-0.52)	Glibenclamide	-34.84 (-65.89,-3.78)	-17.96 (-48.89,12.98)	-21.28 (-53.41,10.85)	-30.62 (-74.07,12.84)	-34.18 (-60.24,-8.12)	-32.60 (-75.15,9.96)
3.73 (-25.75,33.21)	34.84 (3.78,65.89)	Glipizide	16.88 (-12.47,46.23)	13.56 (-16.41,43.52)	4.22 (-37.65,46.10)	0.65 (-23.71,25.02)	2.24 (-39.18,43.66)
-13.15 (-40.15,13.85)	17.96 (-12.98,48.89)	-16.88 (-46.23,12.47)	Glimepiride	-3.32 (-33.16,26.52)	-12.66 (-54.45,29.13)	-16.23 (-35.98,3.53)	-14.64 (-43.88,14.60)
-9.83 (-39.49,19.84)	21.28 (-10.85,53.41)	-13.56 (-43.52,16.41)	3.32 (-26.52,33.16)	Repaglinide	-9.33 (-38.61,19.94)	-12.90 (-37.88,12.08)	-11.32 (-53.08,30.45)
-0.49 (-42.16,41.17)	30.62 (-12.84,74.07)	-4.22 (-46.10,37.65)	12.66 (-29.13,54.45)	9.33 (-19.94,38.61)	Nateglinide	-3.57 (-42.03,34.90)	-1.98 (-52.97,49.01)
3.08 (-16.37,22.52)	34.18 (8.12,60.24)	-0.65 (-25.02,23.71)	16.23 (-3.53,35.98)	12.90 (-12.08,37.88)	3.57 (-34.90,42.03)	Pioglitazone	1.59 (-33.69,36.86)
1.49 (-38.30,41.28)	32.60 (-9.96,75.15)	-2.24 (-43.66,39.18)	14.64 (-14.60,43.88)	11.32 (-30.45,53.08)	1.98 (-49.01,52.97)	-1.59 (-36.86,33.69)	Rosiglitazone
3.28 (-28.98,35.53)	34.38 (-1.19,69.95)	-0.45 (-34.81,33.91)	16.43 (-15.40,48.25)	13.10 (-22.06,48.27)	3.77 (-41.97,49.51)	0.20 (-26.00,26.40)	1.79 (-41.42,45.00)
-39.28 (-76.59,-1.97)	-8.17 (-29.56,13.21)	-43.01 (-80.70,-5.32)	-26.13 (-63.72,11.46)	-29.45 (-68.04,9.13)	-38.79 (-87.21,9.63)	-42.36 (-76.05,-8.67)	-40.77 (-88.38,6.84)
3.82 (-24.01,31.65)	34.93 (4.13,65.73)	0.09 (-29.26,29.44)	16.97 (-5.30,39.24)	13.65 (-16.79,44.08)	4.31 (-37.90,46.52)	0.74 (-20.30,21.79)	2.33 (-34.42,39.08)
8.80 (-13.87,31.46)	39.91 (16.42,63.40)	5.07 (-16.60,26.74)	21.95 (-0.14,44.04)	18.63 (-5.75,43.00)	9.29 (-28.79,47.37)	5.72 (-9.06,20.51)	7.31 (-29.32,43.94)
13.52 (-23.39,50.44)	44.63 (5.76,83.51)	9.79 (-27.99,47.58)	26.67 (-9.33,62.67)	23.35 (-15.50,62.20)	14.01 (-34.62,62.65)	10.45 (-21.71,42.61)	12.03 (-34.33,58.40)
8.66 (-28.25,45.58)	39.77 (0.90,78.64)	4.93 (-32.85,42.72)	21.81 (-14.18,57.81)	18.49 (-20.36,57.34)	9.15 (-39.47,57.78)	5.59 (-26.57,37.74)	7.17 (-39.19,53.54)
6.96 (-23.69,37.61)	38.07 (5.09,71.05)	3.23 (-28.46,34.92)	20.11 (-9.43,49.65)	16.79 (-16.17,49.74)	7.45 (-36.61,51.52)	3.89 (-20.83,28.60)	5.47 (-36.08,47.03)
-7.02 (-44.07,30.03)	24.09 (-13.47,61.65)	-10.75 (-47.19,25.70)	6.13 (-30.56,42.83)	2.81 (-35.31,40.93)	-6.52 (-54.58,41.53)	-10.09 (-42.92,22.73)	-8.51 (-55.42,38.41)
25.98 (-11.38,63.34)	57.09 (17.79,96.39)	22.25 (-15.97,60.47)	39.13 (2.68,75.59)	35.81 (-3.47,75.09)	26.47 (-22.50,75.44)	22.91 (-9.76,55.58)	24.49 (-22.23,71.22)
-3.22 (-33.82,27.37)	27.89 (-5.05,60.82)	-6.95 (-38.59,24.69)	9.93 (-19.56,39.41)	6.60 (-26.30,39.51)	-2.73 (-46.76,41.30)	-6.30 (-30.95,18.35)	-4.71 (-46.22,36.80)
21.45 (-8.60,51.49)	52.55 (20.99,84.12)	17.72 (-12.51,47.94)	34.60 (5.33,63.86)	31.27 (-0.61,63.16)	21.94 (-21.33,65.21)	18.37 (-5.94,42.68)	19.96 (-21.40,61.31)
4.82 (-16.44,26.08)	35.93 (11.34,60.51)	1.09 (-20.58,22.76)	17.97 (-3.54,39.47)	14.65 (-6.06,35.35)	5.31 (-30.53,41.15)	1.74 (-12.26,15.74)	3.33 (-32.96,39.62)
-20.83 (-60.97,19.30)	10.28 (-27.34,47.89)	-24.56 (-65.94,16.82)	-7.68 (-48.67,33.30)	-11.01 (-52.52,30.51)	-20.34 (-71.13,30.44)	-23.91 (-61.23,13.42)	-22.32 (-72.66,28.02)
-23.87 (-48.74,1.01)	7.24 (-21.49,35.97)	-27.60 (-54.28,-0.91)	-10.72 (-31.68,10.24)	-14.04 (-40.61,12.53)	-23.37 (-62.90,16.15)	-26.94 (-44.63,-9.26)	-25.36 (-61.32,10.61)
7.21 (-17.91,32.33)	38.32 (9.39,67.25)	3.48 (-26.43,33.39)	20.36 (-8.11,48.83)	17.04 (-12.94,47.02)	7.70 (-34.19,49.59)	4.14 (-18.09,26.36)	5.72 (-35.08,46.52)
1.46 (-35.50,38.43)	32.57 (-6.35,71.49)	-2.27 (-40.10,35.57)	14.61 (-21.44,50.66)	11.29 (-27.61,50.19)	1.95 (-46.71,50.62)	-1.61 (-33.83,30.60)	-0.03 (-46.43,46.38)
-9.87 (-46.81,27.07)	21.24 (-17.66,60.14)	-13.60 (-51.41,24.21)	3.28 (-32.74,39.31)	-0.04 (-38.92,38.84)	-9.38 (-58.03,39.28)	-12.94 (-45.13,19.25)	-11.36 (-57.74,35.03)
-18.09 (-55.07,18.90)	13.02 (-24.48,50.52)	-21.82 (-58.20,14.57)	-4.94 (-41.57,31.70)	-8.26 (-46.32,29.80)	-17.59 (-65.60,30.41)	-21.16 (-53.92,11.59)	-19.58 (-66.44,27.29)
-24.66 (-52.10,2.78)	6.45 (-17.14,30.03)	-28.39 (-57.62,0.84)	-11.51 (-40.18,17.16)	-14.83 (-44.25,14.58)	-24.17 (-65.66,17.32)	-27.74 (-50.87,-4.60)	-26.15 (-67.09,14.79)
-10.59 (-45.74,24.56)	20.52 (-17.34,58.38)	-14.32 (-50.56,21.93)	2.56 (-32.74,37.87)	-0.76 (-36.75,35.22)	-10.10 (-56.47,36.28)	-13.66 (-44.36,17.03)	-12.08 (-57.91,33.76)
-13.71 (-54.83,27.42)	17.40 (-26.46,61.27)	-17.44 (-60.05,25.18)	-0.56 (-41.81,40.70)	-3.88 (-46.47,38.71)	-13.21 (-64.89,38.46)	-16.78 (-53.77,20.21)	-15.19 (-65.75,35.36)
-8.56 (-44.71,27.59)	22.55 (-15.65,60.74)	-12.29 (-48.68,24.10)	4.59 (-31.71,40.88)	1.26 (-34.56,37.09)	-8.07 (-54.33,38.18)	-11.64 (-44.05,20.78)	-10.05 (-56.65,36.55)
-17.58 (-41.66,6.50)	13.52 (-13.52,40.57)	-21.31 (-46.26,3.63)	-4.43 (-28.52,19.65)	-7.76 (-33.13,17.62)	-17.09 (-55.82,21.64)	-20.66 (-37.58,-3.74)	-19.07 (-56.94,18.80)
-11.06 (-40.84,18.71)	20.04 (-12.19,52.28)	-14.79 (-44.86,15.28)	2.09 (-27.87,32.04)	-1.24 (-30.62,28.15)	-10.57 (-52.04,30.89)	-14.14 (-39.25,10.97)	-12.55 (-54.40,29.30)
-20.96 (-57.36,15.43)	10.15 (-28.29,48.58)	-24.69 (-61.33,11.94)	-7.81 (-44.35,28.73)	-11.14 (-47.21,24.94)	-20.47 (-66.92,25.98)	-24.04 (-56.73,8.65)	-22.45 (-69.24,24.34)
-57.89 (-100.19,-15.59)	-26.78 (-56.01,2.45)	-61.62 (-104.25,-18.98)	-44.74 (-87.28,-2.19)	-48.06 (-91.49,-4.63)	-57.40 (-109.76,-5.04)	-60.96 (-100.11,-21.82)	-59.38 (-110.99,-7.76)
-60.21 (-100.00,-20.42)	-29.10 (-71.66,13.46)	-63.94 (-105.36,-22.52)	-47.06 (-76.31,-17.82)	-50.38 (-92.16,-8.61)	-59.72 (-110.72,-8.72)	-63.29 (-98.57,-28.01)	-61.70 (-90.95,-32.45)
-14.15 (-42.93,14.64)	16.96 (-15.62,49.54)	-17.88 (-48.75,13.00)	-1.00 (-29.97,27.98)	-4.32 (-35.17,26.53)	-13.65 (-56.17,28.86)	-17.22 (-39.71,5.27)	-15.63 (-56.79,25.52)
3.83 (-31.30,38.95)	34.93 (-4.24,74.10)	0.10 (-37.97,38.16)	16.98 (-18.31,52.27)	13.65 (-24.81,52.11)	4.32 (-44.00,52.64)	0.75 (-28.50,30.00)	2.34 (-43.48,48.16)
-14.08 (-49.20,21.04)	17.03 (-22.14,56.20)	-17.81 (-55.87,20.25)	-0.93 (-36.22,34.36)	-4.25 (-42.71,34.20)	-13.59 (-61.91,34.73)	-17.15 (-46.40,12.09)	-15.57 (-61.39,30.25)
21.62 (-0.90,44.15)	52.73 (27.12,78.34)	17.89 (-6.03,41.82)	34.77 (13.78,55.76)	31.45 (5.87,57.02)	22.11 (-16.74,60.97)	18.55 (5.18,31.92)	20.13 (-15.85,56.11)

Fig. 6 WMD with 95% CI from network meta-analysis for HOMA-β index and HbA1c. *HOMA-β* homeostasis model assessment for beta-cell function, *HbA1c* glycated haemoglobin. Results of network meta-analysis for HOMA-β and HbA1c are listed in the lower and upper triangles, and the estimation was calculated as the column-defining treatment compared with the row-defining treatment. *NA* not available

-3.28 (-35.53,28.98)	39.28 (1.97,76.59)	-3.82 (-31.65,24.01)	-8.80 (-31.46,13.87)	-13.52 (-50.44,23.39)	-8.66 (-45.58,28.25)	-6.96 (-37.61,23.69)	7.02 (-30.03,44.07)		
-34.38 (-69.95,1.19)	8.17 (-13.21,29.56)	-34.93 (-65.73,-4.13)	-39.91 (-63.40,-16.42)	-44.63 (-83.51,-5.76)	-39.77 (-78.64,-0.90)	-38.07 (-71.05,-5.09)	-24.09 (-61.65,13.47)		
0.45 (-33.91,34.81)	43.01 (5.32,80.70)	-0.09 (-29.44,29.26)	-5.07 (-26.74,16.60)	-9.79 (-47.58,27.99)	-4.93 (-42.72,32.85)	-3.23 (-34.92,28.46)	10.75 (-25.70,47.19)		
-16.43 (-48.25,15.40)	26.13 (-11.46,63.72)	-16.97 (-39.24,5.30)	-21.95 (-44.04,0.14)	-26.67 (-62.67,9.33)	-21.81 (-57.81,14.18)	-20.11 (-49.65,9.43)	-6.13 (-42.83,30.56)		
-13.10 (-48.27,22.06)	29.45 (-9.13,68.04)	-13.65 (-44.08,16.79)	-18.63 (-43.00,5.75)	-23.35 (-62.20,15.50)	-18.49 (-57.34,20.36)	-16.79 (-49.74,16.17)	-2.81 (-40.93,35.31)		
-3.77 (-49.51,41.97)	38.79 (-9.63,87.21)	-4.31 (-46.52,37.90)	-9.29 (-47.37,28.79)	-14.01 (-62.65,34.62)	-9.15 (-57.78,39.47)	-7.45 (-51.52,36.61)	6.52 (-41.53,54.58)		
-0.20 (-26.40,26.00)	42.36 (8.67,76.05)	-0.74 (-21.79,20.30)	-5.72 (-20.51,9.06)	-10.45 (-42.61,21.71)	-5.59 (-37.74,26.57)	-3.89 (-28.60,20.83)	10.09 (-22.73,42.92)		
-1.79 (-45.00,41.42)	40.77 (-6.84,88.38)	-2.33 (-39.08,34.42)	-7.31 (-43.94,29.32)	-12.03 (-58.40,34.33)	-7.17 (-53.54,39.19)	-5.47 (-47.03,36.08)	8.51 (-38.41,55.42)		
Rivoglitazone	42.56 (1.07,84.04)	-0.54 (-31.98,30.89)	-5.52 (-33.45,22.41)	-10.25 (-49.53,29.03)	-5.39 (-44.66,33.89)	-3.69 (-37.14,29.77)	10.29 (-30.19,50.78)		
-42.56 (-84.04,-1.07)	Acarbose	-43.10 (-80.58,-5.62)	-48.08 (-79.83,-16.34)	-52.80 (-97.16,-8.45)	-47.94 (-92.29,-3.59)	-46.24 (-85.53,-6.95)	-32.27 (-75.47,10.94)		
0.54 (-30.89,31.98)	43.10 (5.62,80.58)	Vildagliptin	-4.98 (-26.24,16.28)	-9.70 (-44.24,24.83)	-4.84 (-39.38,29.69)	-3.14 (-30.88,24.59)	10.84 (-25.37,47.04)		
5.52 (-22.41,33.45)	48.08 (16.34,79.83)	4.98 (-16.28,26.24)	Sitagliptin	-4.72 (-36.37,26.92)	0.14 (-31.51,31.78)	1.84 (-22.21,25.88)	15.82 (-13.50,45.13)		
10.25 (-29.03,49.53)	52.80 (8.45,97.16)	9.70 (-24.83,44.24)	4.72 (-26.92,36.37)	Saxagliptin	4.86 (-36.50,46.22)	6.56 (-29.32,42.44)	20.54 (-22.59,63.67)		
5.39 (-33.89,44.66)	47.94 (3.59,92.29)	4.84 (-29.69,39.38)	-0.14 (-31.78,31.51)	-4.86 (-46.22,36.50)	Alogliptin	1.70 (-34.18,37.58)	15.68 (-27.45,58.81)		
3.69 (-29.77,37.14)	46.24 (6.95,85.53)	3.14 (-24.59,30.88)	-1.84 (-25.88,22.21)	-6.56 (-42.44,29.32)	-1.70 (-37.58,34.18)	Linagliptin	13.98 (-23.93,51.89)		
-10.29 (-50.78,30.19)	32.27 (-10.94,75.47)	-10.84 (-47.04,25.37)	-15.82 (-45.13,13.50)	-20.54 (-63.67,22.59)	-15.68 (-58.81,27.45)	-13.98 (-51.89,23.93)	Gemigliptin		
22.71 (-16.99,62.41)	65.26 (20.54,109.99)	22.16 (-12.85,57.18)	17.18 (-14.98,49.35)	12.46 (-29.30,54.22)	17.32 (-24.44,59.08)	19.02 (-17.32,55.36)	33.00 (-10.52,76.51)		
-6.50 (-39.91,26.91)	36.06 (-3.19,75.31)	-7.04 (-34.72,20.64)	-12.02 (-36.00,11.95)	-16.74 (-52.58,19.09)	-11.88 (-47.72,23.95)	-10.18 (-39.52,19.15)	3.79 (-34.07,41.66)		
18.17 (-15.38,51.72)	60.73 (22.62,98.84)	17.63 (-10.42,45.67)	12.65 (-8.93,34.22)	7.92 (-28.42,44.26)	12.78 (-23.55,49.12)	14.48 (-15.47,44.43)	28.46 (-7.93,64.86)		
1.54 (-26.90,29.98)	44.10 (11.53,76.67)	1.00 (-21.33,23.33)	-3.98 (-16.87,8.91)	-8.70 (-41.60,24.19)	-3.84 (-36.73,29.05)	-2.14 (-27.80,23.52)	11.83 (-20.18,43.85)		
-24.11 (-68.88,20.67)	18.45 (-24.81,61.71)	-24.65 (-65.89,16.58)	-29.63 (-66.47,7.21)	-34.36 (-82.07,13.36)	-29.50 (-77.21,18.21)	-27.80 (-70.84,15.25)	-13.82 (-60.89,33.26)		
-27.14 (-57.89,3.60)	15.42 (-20.38,51.21)	-27.69 (-52.13,-3.24)	-32.67 (-52.00,-13.33)	-37.39 (-72.58,-2.20)	-32.53 (-67.71,2.66)	-30.83 (-59.37,-2.28)	-16.85 (-51.96,18.26)		
3.94 (-29.70,37.57)	46.49 (10.53,82.45)	3.39 (-25.69,32.47)	-1.59 (-24.95,21.77)	-6.31 (-44.11,31.49)	-1.45 (-39.25,36.35)	0.25 (-31.46,31.96)	14.23 (-23.25,51.71)		
-1.81 (-41.14,37.51)	40.74 (-3.65,85.14)	-2.36 (-36.95,32.23)	-7.34 (-39.04,24.37)	-12.06 (-53.47,29.35)	-7.20 (-48.60,34.20)	-5.50 (-41.43,30.43)	8.48 (-34.69,51.65)		
-13.14 (-52.45,26.16)	29.41 (-14.96,73.79)	-13.69 (-48.25,20.88)	-18.67 (-50.34,13.01)	-23.39 (-64.78,18.00)	-18.53 (-59.91,22.85)	-16.83 (-52.74,19.08)	-2.85 (-46.01,40.30)		
-21.36 (-61.79,19.07)	21.20 (-21.96,64.35)	-21.91 (-58.05,14.24)	-26.89 (-56.12,2.35)	-31.61 (-74.69,11.47)	-26.75 (-69.82,16.33)	-25.05 (-62.89,12.80)	-11.07 (-52.47,30.33)		
-27.94 (-61.80,5.93)	14.62 (-17.21,46.45)	-28.48 (-57.51,0.55)	-33.46 (-55.81,-11.11)	-38.18 (-75.85,-0.51)	-33.32 (-70.99,4.34)	-31.62 (-63.17,-0.07)	-17.64 (-54.50,19.21)		
-13.86 (-53.58,25.85)	28.69 (-14.78,72.16)	-14.41 (-50.29,21.47)	-19.39 (-50.82,12.05)	-24.11 (-67.39,19.17)	-19.25 (-62.53,24.02)	-17.55 (-55.62,20.52)	-3.57 (-46.55,39.41)		
-16.98 (-61.94,27.97)	25.58 (-23.21,74.36)	-17.53 (-59.32,24.27)	-22.51 (-60.89,15.88)	-27.23 (-75.54,21.08)	-22.37 (-70.68,25.94)	-20.67 (-64.38,23.04)	-6.69 (-54.98,41.60)		
-11.84 (-52.62,28.95)	30.72 (-13.05,74.48)	-12.38 (-49.17,24.40)	-17.36 (-49.31,14.59)	-22.09 (-66.09,21.92)	-17.23 (-61.23,26.78)	-15.53 (-54.42,23.37)	-1.55 (-44.90,41.81)		
-20.86 (-50.86,9.15)	21.70 (-12.76,56.16)	-21.40 (-45.88,3.07)	-26.38 (-42.39,-10.38)	-31.11 (-65.38,3.17)	-26.25 (-60.52,8.02)	-24.55 (-51.95,2.86)	-10.57 (-43.96,22.83)		
-14.34 (-49.60,20.92)	28.22 (-10.45,66.89)	-14.88 (-45.43,15.66)	-19.86 (-44.38,4.65)	-24.59 (-63.53,14.35)	-19.73 (-58.66,19.21)	-18.03 (-51.09,15.03)	-4.05 (-42.26,34.16)		
-24.24 (-65.24,16.76)	18.32 (-25.65,62.29)	-24.78 (-61.81,12.24)	-29.76 (-61.99,2.47)	-34.49 (-78.69,9.72)	-29.63 (-73.83,14.58)	-27.93 (-67.05,11.20)	-13.95 (-57.51,29.62)		
-61.16 (-107.19,-15.14)	-18.61 (-54.83,17.61)	-61.71 (-104.16,-19.26)	-66.69 (-104.17,-29.20)	-71.41 (-120.04,-22.78)	-66.55 (-115.17,-17.93)	-64.85 (-108.91,-20.79)	-50.87 (-98.46,-3.29)		
-63.49 (-106.70,-20.27)	-20.93 (-68.55,26.69)	-64.03 (-100.78,-27.28)	-69.01 (-105.63,-32.38)	-73.73 (-120.10,-27.36)	-68.87 (-115.24,-22.51)	-67.17 (-108.73,-25.62)	-53.19 (-100.11,-6.28)		
-17.42 (-51.46,16.62)	25.14 (-13.82,64.09)	-17.97 (-47.70,11.77)	-22.95 (-47.66,1.77)	-27.67 (-66.03,10.70)	-22.81 (-61.17,15.55)	-21.11 (-53.49,11.27)	-7.13 (-45.47,31.21)		
0.55 (-38.72,39.82)	43.11 (-1.50,87.72)	0.01 (-36.02,36.03)	-4.97 (-37.74,27.79)	-9.70 (-53.16,33.77)	-4.84 (-48.30,38.63)	-3.14 (-41.42,35.15)	10.84 (-33.12,54.80)		
-17.35 (-56.62,21.91)	25.20 (-19.41,69.81)	-17.90 (-53.92,18.12)	-22.88 (-55.64,9.88)	-27.60 (-71.06,15.86)	-22.74 (-66.20,20.72)	-21.04 (-59.32,17.24)	-7.06 (-51.02,36.90)		
18.35 (-7.87,44.57)	60.90 (27.56,94.25)	17.80 (-0.57,36.17)	12.82 (0.74,24.91)	8.10 (-21.15,37.35)	12.96 (-16.28,42.20)	14.66 (-6.12,35.44)	28.64 (-3.06,60.34)		

Fig. 6 continued

-25.98 (-63.34,11.38)	3.22 (-27.37,33.82)	-21.45 (-51.49,8.60)	-4.82 (-26.08,16.44)	20.83 (-19.30,60.97)	23.87 (-1.01,48.74)	-7.21 (-32.33,17.91)	-1.46 (-38.43,35.50)		
-57.09 (-96.39,-17.79)	-27.89 (-60.82,5.05)	-52.55 (-84.12,-20.99)	-35.93 (-60.51,-11.34)	-10.28 (-47.89,27.34)	-7.24 (-35.97,21.49)	-38.32 (-67.25,-9.39)	-32.57 (-71.49,6.35)		
-22.25 (-60.47,15.97)	6.95 (-24.69,38.59)	-17.72 (-47.94,12.51)	-1.09 (-22.76,20.58)	24.56 (-16.82,65.94)	27.60 (0.91,54.28)	-3.48 (-33.39,26.43)	2.27 (-35.57,40.10)		
-39.13 (-75.59,-2.68)	-9.93 (-39.41,19.56)	-34.60 (-63.86,-5.33)	-17.97 (-39.47,3.54)	7.68 (-33.30,48.67)	10.72 (-10.24,31.68)	-20.36 (-48.83,8.11)	-14.61 (-50.66,21.44)		
-35.81 (-75.09,3.47)	-6.60 (-39.51,26.30)	-31.27 (-63.16,0.61)	-14.65 (-35.35,6.06)	11.01 (-30.51,52.52)	14.04 (-12.53,40.61)	-17.04 (-47.02,12.94)	-11.29 (-50.19,27.61)		
-26.47 (-75.44,22.50)	2.73 (-41.30,46.76)	-21.94 (-65.21,21.33)	-5.31 (-41.15,30.53)	20.34 (-30.44,71.13)	23.37 (-16.15,62.90)	-7.70 (-49.59,34.19)	-1.95 (-50.62,46.71)		
-22.91 (-55.58,9.76)	6.30 (-18.35,30.95)	-18.37 (-42.68,5.94)	-1.74 (-15.74,12.26)	23.91 (-13.42,61.23)	26.94 (9.26,44.63)	-4.14 (-26.36,18.09)	1.61 (-30.60,33.83)		
-24.49 (-71.22,22.23)	4.71 (-36.80,46.22)	-19.96 (-61.31,21.40)	-3.33 (-39.62,32.96)	22.32 (-28.02,72.66)	25.36 (-10.61,61.32)	-5.72 (-46.52,35.08)	0.03 (-46.38,46.43)		
-22.71 (-62.41,16.99)	6.50 (-26.91,39.91)	-18.17 (-51.72,15.38)	-1.54 (-29.98,26.90)	24.11 (-20.67,68.88)	27.14 (-3.60,57.89)	-3.94 (-37.57,29.70)	1.81 (-37.51,41.14)		
-65.26 (-109.99,-20.54)	-36.06 (-75.31,3.19)	-60.73 (-98.84,-22.62)	-44.10 (-76.67,-11.53)	-18.45 (-61.71,24.81)	-15.42 (-51.21,20.38)	-46.49 (-82.45,-10.53)	-40.74 (-85.14,3.65)		
-22.16 (-57.18,12.85)	7.04 (-20.64,34.72)	-17.63 (-45.67,10.42)	-1.00 (-23.33,21.33)	24.65 (-16.58,65.89)	27.69 (3.24,52.13)	-3.39 (-32.47,25.69)	2.36 (-32.23,36.95)		
-17.18 (-49.35,14.98)	12.02 (-11.95,36.00)	-12.65 (-34.22,8.93)	3.98 (-8.91,16.87)	29.63 (-7.21,66.47)	32.67 (13.33,52.00)	1.59 (-21.77,24.95)	7.34 (-24.37,39.04)		
-12.46 (-54.22,29.30)	16.74 (-19.09,52.58)	-7.92 (-44.26,28.42)	8.70 (-24.19,41.60)	34.36 (-13.36,82.07)	37.39 (2.20,72.58)	6.31 (-31.49,44.11)	12.06 (-29.35,53.47)		
-17.32 (-59.08,24.44)	11.88 (-23.95,47.72)	-12.78 (-49.12,23.55)	3.84 (-29.05,36.73)	29.50 (-18.21,77.21)	32.53 (-2.66,67.71)	1.45 (-36.35,39.25)	7.20 (-34.20,48.60)		
-19.02 (-55.36,17.32)	10.18 (-19.15,39.52)	-14.48 (-44.43,15.47)	2.14 (-23.52,27.80)	27.80 (-15.25,70.84)	30.83 (2.28,59.37)	-0.25 (-31.96,31.46)	5.50 (-30.43,41.43)		
-33.00 (-76.51,10.52)	-3.79 (-41.66,34.07)	-28.46 (-64.86,7.93)	-11.83 (-43.85,20.18)	13.82 (-33.26,60.89)	16.85 (-18.26,51.96)	-14.23 (-51.71,23.25)	-8.48 (-51.65,34.69)		
Dapagliflozin	29.20 (-7.09,65.50)	4.54 (-32.25,41.33)	21.16 (-12.23,54.56)	46.82 (-1.24,94.87)	49.85 (14.19,85.51)	18.77 (-19.47,57.01)	24.52 (-17.28,66.32)		
-29.20 (-65.50,7.09)	**Canagliflozin**	-24.67 (-54.56,5.23)	-8.04 (-33.64,17.56)	17.61 (-25.40,60.62)	20.64 (-7.84,49.13)	-10.43 (-42.09,21.23)	-4.68 (-40.57,31.20)		
-4.54 (-41.33,32.25)	24.67 (-5.23,54.56)	**Ipragliflozin**	16.63 (-7.64,40.89)	42.28 (0.07,84.49)	45.31 (17.55,73.07)	14.23 (-16.62,45.09)	19.98 (-16.41,56.37)		
-21.16 (-54.56,12.23)	8.04 (-17.56,33.64)	-16.63 (-40.89,7.64)	**Metformin**	25.65 (-10.33,61.64)	28.68 (12.01,45.36)	-2.39 (-24.09,19.30)	3.36 (-29.59,36.30)		
-46.82 (-94.87,1.24)	-17.61 (-60.62,25.40)	-42.28 (-84.49,-0.07)	-25.65 (-61.64,10.33)	**Insulin Lispro**	3.03 (-36.08,42.15)	-28.04 (-65.17,9.08)	-22.30 (-70.05,25.45)		
-49.85 (-85.51,-14.19)	-20.64 (-49.13,7.84)	-45.31 (-73.07,-17.55)	-28.68 (-45.36,-12.01)	-3.03 (-42.15,36.08)	**Insulin Glargine**	-31.08 (-57.09,-5.07)	-25.33 (-60.57,9.91)		
-18.77 (-57.01,19.47)	10.43 (-21.23,42.09)	-14.23 (-45.09,16.62)	2.39 (-19.30,24.09)	28.04 (-9.08,65.17)	31.08 (5.07,57.09)	**Insulin Novolin R**	5.75 (-32.10,43.60)		
-24.52 (-66.32,17.28)	4.68 (-31.20,40.57)	-19.98 (-56.37,16.41)	-3.36 (-36.30,29.59)	22.30 (-25.45,70.05)	25.33 (-9.91,60.57)	-5.75 (-43.60,32.10)	**Liraglutide**		
-35.85 (-77.63,5.93)	-6.65 (-42.51,29.22)	-31.31 (-67.68,5.05)	-14.69 (-47.61,18.24)	10.97 (-36.77,58.70)	14.00 (-21.22,49.22)	-17.08 (-54.91,20.75)	-11.33 (-52.76,30.10)		
-44.07 (-87.53,-0.61)	-14.86 (-52.67,22.94)	-39.53 (-75.86,-3.20)	-22.90 (-54.85,9.04)	2.75 (-44.28,49.77)	5.78 (-29.27,40.83)	-25.30 (-62.72,12.12)	-19.55 (-62.67,23.57)		
-50.64 (-88.75,-12.54)	-21.44 (-52.94,10.06)	-46.11 (-76.50,-15.71)	-29.48 (-50.39,-8.57)	-3.83 (-33.13,25.48)	-0.79 (-26.72,25.13)	-31.87 (-54.67,-9.07)	-26.12 (-63.84,11.59)		
-36.57 (-80.23,7.09)	-7.37 (-45.40,30.66)	-32.03 (-69.39,5.32)	-15.41 (-44.84,14.03)	10.24 (-35.92,56.41)	13.28 (-19.81,46.36)	-17.80 (-53.63,18.04)	-12.05 (-55.37,31.27)		
-39.69 (-88.34,8.96)	-10.48 (-54.16,33.19)	-35.15 (-78.38,8.07)	-18.52 (-55.75,18.70)	7.13 (-44.13,58.39)	10.16 (-29.54,49.86)	-20.92 (-62.90,21.06)	-15.17 (-63.32,33.18)		
-34.55 (-78.93,9.83)	-5.34 (-44.20,33.51)	-30.01 (-68.00,7.98)	-13.38 (-42.62,15.86)	12.27 (-34.10,58.64)	15.30 (-18.35,48.96)	-15.77 (-52.18,20.63)	-10.03 (-54.07,34.02)		
-43.57 (-78.32,-8.81)	-14.36 (-41.71,12.99)	-39.03 (-65.11,-12.95)	-22.40 (-37.09,-7.71)	3.25 (-34.96,41.46)	6.28 (-14.67,27.23)	-24.79 (-49.76,0.17)	-19.05 (-53.37,15.28)		
-37.05 (-76.41,2.32)	-7.84 (-40.85,25.17)	-32.51 (-64.50,-0.52)	-15.88 (-36.74,4.97)	9.77 (-31.82,51.36)	12.80 (-13.89,39.50)	-18.28 (-48.37,11.81)	-12.53 (-51.51,26.46)		
-46.95 (-91.53,-2.37)	-17.74 (-56.82,21.34)	-42.41 (-80.63,-4.18)	-25.78 (-55.32,3.76)	-0.13 (-46.69,46.43)	2.90 (-31.02,36.82)	-28.17 (-64.82,8.48)	-22.43 (-66.67,21.82)		
-83.87 (-132.84,-34.91)	-54.67 (-98.69,-10.65)	-79.33 (-122.34,-36.33)	-62.71 (-100.89,-24.53)	-37.06 (-84.68,10.57)	-34.02 (-74.99,6.95)	-65.10 (-106.21,-23.98)	-59.35 (-108.01,-10.69)		
-86.19 (-132.92,-39.47)	-56.99 (-98.51,-15.47)	-81.66 (-123.02,-40.30)	-65.03 (-101.32,-28.74)	-39.38 (-89.72,10.96)	-36.34 (-72.32,-0.37)	-67.42 (-108.23,-26.62)	-61.67 (-108.08,-15.26)		
-40.13 (-78.92,-1.34)	-10.92 (-43.25,21.40)	-35.59 (-67.31,-3.87)	-18.96 (-41.84,3.91)	6.69 (-35.33,48.70)	9.72 (-16.99,36.43)	-21.36 (-51.36,8.64)	-15.61 (-54.02,22.80)		
-22.16 (-66.00,21.69)	7.05 (-31.20,45.29)	-17.62 (-55.65,20.41)	-0.99 (-33.42,31.43)	24.66 (-22.76,72.08)	27.69 (-6.48,61.87)	-3.39 (-40.12,33.35)	2.36 (-41.14,45.87)		
-40.06 (-83.90,3.78)	-10.86 (-49.10,27.38)	-35.52 (-73.55,2.50)	-18.90 (-51.32,13.52)	6.75 (-40.66,54.17)	9.79 (-24.38,43.96)	-21.29 (-58.02,15.44)	-15.54 (-59.05,27.96)		
-4.36 (-34.17,25.45)	24.84 (4.14,45.55)	0.18 (-21.39,21.74)	16.80 (1.75,31.85)	42.46 (4.76,80.15)	45.49 (25.92,65.06)	14.41 (-9.54,38.36)	20.16 (-9.15,49.47)		

Fig. 6 continued

9.87 (-27.07,46.81)	18.09 (-18.90,55.07)	24.66 (-2.78,52.10)	10.59 (-24.56,45.74)	13.71 (-27.42,54.83)	8.56 (-27.59,44.71)	17.58 (-6.50,41.66)	11.06 (-18.71,40.84)		
-21.24 (-60.14,17.66)	-13.02 (-50.52,24.48)	-6.45 (-30.03,17.14)	-20.52 (-58.38,17.34)	-17.40 (-61.27,26.46)	-22.55 (-60.74,15.65)	-13.52 (-40.57,13.52)	-20.04 (-52.28,12.19)		
13.60 (-24.21,51.41)	21.82 (-14.57,58.20)	28.39 (-0.84,57.62)	14.32 (-21.93,50.56)	17.44 (-25.18,60.05)	12.29 (-24.10,48.68)	21.31 (-3.63,46.26)	14.79 (-15.28,44.86)		
-3.28 (-39.31,32.74)	4.94 (-31.70,41.57)	11.51 (-17.16,40.18)	-2.56 (-37.87,32.74)	0.56 (-40.70,41.81)	-4.59 (-40.88,31.71)	4.43 (-19.65,28.52)	-2.09 (-32.04,27.87)		
0.04 (-38.84,38.92)	8.26 (-29.80,46.32)	14.83 (-14.58,44.25)	0.76 (-35.22,36.75)	3.88 (-38.71,46.47)	-1.26 (-37.09,34.56)	7.76 (-17.62,33.13)	1.24 (-28.15,30.62)		
9.38 (-39.28,58.03)	17.59 (-30.41,65.60)	24.17 (-17.32,65.66)	10.10 (-36.28,56.47)	13.21 (-38.46,64.89)	8.07 (-38.18,54.33)	17.09 (-21.64,55.82)	10.57 (-30.89,52.04)		
12.94 (-19.25,45.13)	21.16 (-11.59,53.92)	27.74 (4.60,50.87)	13.66 (-17.03,44.36)	16.78 (-20.21,53.77)	11.64 (-20.78,44.05)	20.66 (3.74,37.58)	14.14 (-10.97,39.25)		
11.36 (-35.03,57.74)	19.58 (-27.29,66.44)	26.15 (-14.79,67.09)	12.08 (-33.76,57.91)	15.19 (-35.36,65.75)	10.05 (-36.55,56.65)	19.07 (-18.80,56.94)	12.55 (-29.30,54.40)		
13.14 (-26.16,52.45)	21.36 (-19.07,61.79)	27.94 (-5.93,61.80)	13.86 (-25.85,53.58)	16.98 (-27.97,61.94)	11.84 (-28.95,52.62)	20.86 (-9.15,50.86)	14.34 (-20.92,49.60)		
-29.41 (-73.79,14.96)	-21.20 (-64.35,21.96)	-14.62 (-46.45,17.21)	-28.69 (-72.16,14.78)	-25.58 (-74.36,23.21)	-30.72 (-74.48,13.05)	-21.70 (-56.16,12.76)	-28.22 (-66.89,10.45)		
13.69 (-20.88,48.25)	21.91 (-14.24,58.05)	28.48 (-0.55,57.51)	14.41 (-21.47,50.29)	17.53 (-24.27,59.32)	12.38 (-24.40,49.17)	21.40 (-3.07,45.88)	14.88 (-15.66,45.43)		
18.67 (-13.01,50.34)	26.89 (-2.35,56.12)	33.46 (11.11,55.81)	19.39 (-12.05,50.82)	22.51 (-15.88,60.89)	17.36 (-14.59,49.31)	26.38 (10.38,42.39)	19.86 (-4.65,44.38)		
23.39 (-18.00,64.78)	31.61 (-11.47,74.69)	38.18 (0.51,75.85)	24.11 (-19.17,67.39)	27.23 (-21.08,75.54)	22.09 (-21.92,66.09)	31.11 (-3.17,65.38)	24.59 (-14.35,63.53)		
18.53 (-22.85,59.91)	26.75 (-16.33,69.82)	33.32 (-4.34,70.99)	19.25 (-24.02,62.53)	22.37 (-25.94,70.68)	17.23 (-26.78,61.23)	26.25 (-8.02,60.52)	19.73 (-19.21,58.66)		
16.83 (-19.08,52.74)	25.05 (-12.80,62.89)	31.62 (0.07,63.17)	17.55 (-20.52,55.62)	20.67 (-23.04,64.38)	15.53 (-23.37,54.42)	24.55 (-2.86,51.95)	18.03 (-15.03,51.09)		
2.85 (-40.30,46.01)	11.07 (-30.33,52.47)	17.64 (-19.21,54.50)	3.57 (-39.41,46.55)	6.69 (-41.60,54.98)	1.55 (-41.81,44.90)	10.57 (-22.83,43.96)	4.05 (-34.16,42.26)		
35.85 (-5.93,77.63)	44.07 (0.61,87.53)	50.64 (12.54,88.75)	36.57 (-7.09,80.23)	39.69 (-8.96,88.34)	34.55 (-9.83,78.93)	43.57 (8.81,78.32)	37.05 (-2.32,76.41)		
6.65 (-29.22,42.51)	14.86 (-22.94,52.67)	21.44 (-10.06,52.94)	7.37 (-30.66,45.40)	10.48 (-33.19,54.16)	5.34 (-33.51,44.20)	14.36 (-12.99,41.71)	7.84 (-25.17,40.85)		
31.31 (-5.05,67.68)	39.53 (3.20,75.86)	46.11 (15.71,76.50)	32.03 (-5.32,69.39)	35.15 (-8.07,78.38)	30.01 (-7.98,68.00)	39.03 (12.95,65.11)	32.51 (0.52,64.50)		
14.69 (-18.24,47.61)	22.90 (-9.04,54.85)	29.48 (8.57,50.39)	15.41 (-14.03,44.84)	18.52 (-18.70,55.75)	13.38 (-15.86,42.62)	22.40 (7.71,37.09)	15.88 (-4.97,36.74)		
-10.97 (-58.70,36.77)	-2.75 (-49.77,44.28)	3.83 (-25.48,33.13)	-10.24 (-56.41,35.92)	-7.13 (-58.39,44.13)	-12.27 (-58.64,34.10)	-3.25 (-41.46,34.96)	-9.77 (-51.36,31.82)		
-14.00 (-49.22,21.22)	-5.78 (-40.83,29.27)	0.79 (-25.13,26.72)	-13.28 (-46.36,19.81)	-10.16 (-49.86,29.54)	-15.30 (-48.96,18.35)	-6.28 (-27.23,14.67)	-12.80 (-39.50,13.89)		
17.08 (-20.75,54.91)	25.30 (-12.12,62.72)	31.87 (9.07,54.67)	17.80 (-18.04,53.63)	20.92 (-21.06,62.90)	15.77 (-20.63,52.18)	24.79 (-0.17,49.76)	18.28 (-11.81,48.37)		
11.33 (-30.10,52.76)	19.55 (-23.57,62.67)	26.12 (-11.59,63.84)	12.05 (-31.27,55.37)	15.17 (-33.18,63.52)	10.03 (-34.02,54.07)	19.05 (-15.28,53.37)	12.53 (-26.46,51.51)		
Taspoglutide	8.22 (-34.88,51.32)	14.79 (-22.90,52.49)	0.72 (-42.58,44.02)	3.84 (-44.49,52.17)	-1.30 (-45.33,42.72)	7.72 (-26.58,42.02)	1.20 (-37.77,40.16)		
-8.22 (-51.32,34.88)	**Dulaglutide**	6.57 (-30.22,43.37)	-7.50 (-50.42,35.43)	-4.38 (-52.63,43.87)	-9.52 (-52.83,33.78)	-0.50 (-33.83,32.82)	-7.02 (-45.17,31.13)		
-14.79 (-52.49,22.90)	-6.57 (-43.37,30.22)	**Exenatide**	-14.07 (-49.76,21.61)	-10.95 (-53.02,31.11)	-16.10 (-52.04,19.85)	-7.08 (-31.61,17.46)	-13.60 (-43.12,15.93)		
-0.72 (-44.02,42.58)	7.50 (-35.43,50.42)	14.07 (-21.61,49.76)	**Metformin,Glimepiride**	3.12 (-37.68,43.92)	-2.03 (-43.51,39.46)	7.00 (-25.31,39.30)	0.48 (-35.60,36.55)		
-3.84 (-52.17,44.49)	4.38 (-43.87,52.63)	10.95 (-31.11,53.02)	-3.12 (-43.92,37.68)	**Metformin,Pioglitazone**	-5.14 (-52.48,42.19)	3.88 (-35.28,43.03)	-2.64 (-45.31,40.03)		
1.30 (-42.72,45.33)	9.52 (-33.78,52.83)	16.10 (-19.85,52.04)	2.03 (-39.46,43.51)	5.14 (-42.19,52.48)	**Metformin,Rosiglitazone**	9.02 (-23.70,41.74)	2.50 (-33.41,38.42)		
-7.72 (-42.02,26.58)	0.50 (-32.82,33.83)	7.08 (-17.46,31.61)	-7.00 (-39.30,25.31)	-3.88 (-43.03,35.28)	-9.02 (-41.74,23.70)	**Metformin,Sitagliptin**	-6.52 (-32.03,18.99)		
-1.20 (-40.16,37.77)	7.02 (-31.13,45.17)	13.60 (-15.93,43.12)	-0.48 (-36.55,35.60)	2.64 (-40.03,45.31)	-2.50 (-38.42,33.41)	6.52 (-18.99,32.03)	**Metformin,Vildagliptin**		
-11.10 (-55.32,33.13)	-2.88 (-46.39,40.63)	3.70 (-32.49,39.89)	-10.37 (-52.08,31.33)	-7.26 (-54.78,40.27)	-12.40 (-53.97,29.17)	-3.38 (-36.37,29.61)	-9.90 (-46.06,26.26)		
-48.02 (-96.67,0.63)	-39.80 (-87.34,7.73)	-33.23 (-70.78,4.32)	-47.30 (-95.12,0.52)	-44.18 (-96.88,8.52)	-49.33 (-97.41,-1.24)	-40.30 (-80.11,-0.49)	-46.82 (-90.33,-3.32)		
-50.34 (-96.74,-3.95)	-42.12 (-88.99,4.74)	-35.55 (-76.50,5.39)	-49.62 (-95.46,-3.79)	-46.51 (-97.07,4.06)	-51.65 (-98.25,-5.05)	-42.63 (-80.50,-4.75)	-49.15 (-91.00,-7.29)		
-4.28 (-42.67,34.11)	3.94 (-34.34,42.22)	10.51 (-19.61,40.64)	-3.56 (-31.87,24.75)	-0.44 (-29.83,28.95)	-5.58 (-42.71,31.54)	3.44 (-22.46,29.34)	-3.08 (-34.04,27.87)		
13.69 (-29.79,57.18)	21.91 (-22.00,65.82)	28.49 (-8.80,65.78)	14.41 (-27.98,56.81)	17.53 (-29.62,64.69)	12.39 (-31.27,56.05)	21.41 (-12.38,55.20)	14.89 (-23.66,53.44)		
-4.21 (-47.70,39.27)	4.01 (-39.90,47.91)	10.58 (-26.71,47.87)	-3.49 (-45.88,38.90)	-0.37 (-47.53,46.78)	-5.52 (-49.17,38.14)	3.50 (-30.28,37.29)	-3.01 (-41.56,35.53)		
31.49 (2.21,60.77)	39.71 (8.08,71.34)	46.28 (22.55,70.02)	32.21 (0.31,64.11)	35.33 (-3.12,73.78)	30.19 (-2.69,63.06)	39.21 (21.34,57.07)	32.69 (6.98,58.40)		

Fig. 6 continued

20.96 (-15.43,57.36)	57.89 (15.59,100.19)	60.21 (20.42,100.00)	14.15 (-14.64,42.93)	-3.83 (-38.95,31.30)	14.08 (-21.04,49.20)	-21.62 (-44.15,0.90)			
-10.15 (-48.58,28.29)	26.78 (-2.45,56.01)	29.10 (-13.46,71.66)	-16.96 (-49.54,15.62)	-34.93 (-74.10,4.24)	-17.03 (-56.20,22.14)	-52.73 (-78.34,-27.12)			
24.69 (-11.94,61.33)	61.62 (18.98,104.25)	63.94 (22.52,105.36)	17.88 (-13.00,48.75)	-0.10 (-38.16,37.97)	17.81 (-20.25,55.87)	-17.89 (-41.82,6.03)			
7.81 (-28.73,44.35)	44.74 (2.19,87.28)	47.06 (17.82,76.31)	1.00 (-27.98,29.97)	-16.98 (-52.27,18.31)	0.93 (-34.36,36.22)	-34.77 (-55.76,-13.78)			
11.14 (-24.94,47.21)	48.06 (4.63,91.49)	50.38 (8.61,92.16)	4.32 (-26.53,35.17)	-13.65 (-52.11,24.81)	4.25 (-34.20,42.71)	-31.45 (-57.02,-5.87)			
20.47 (-25.98,66.92)	57.40 (5.04,109.76)	59.72 (8.72,110.72)	13.65 (-28.86,56.17)	-4.32 (-52.64,44.00)	13.59 (-34.73,61.91)	-22.11 (-60.97,16.74)			
24.04 (-8.65,56.73)	60.96 (21.82,100.11)	63.29 (28.01,98.57)	17.22 (-5.27,39.71)	-0.75 (-30.00,28.50)	17.15 (-12.09,46.40)	-18.55 (-31.92,-5.18)			
22.45 (-24.34,69.24)	59.38 (7.76,110.99)	61.70 (32.45,90.95)	15.63 (-25.52,56.79)	-2.34 (-48.16,43.48)	15.57 (-30.25,61.39)	-20.13 (-56.11,15.85)			
24.24 (-16.76,65.24)	61.16 (15.14,107.19)	63.49 (20.27,106.70)	17.42 (-16.62,51.46)	-0.55 (-39.82,38.72)	17.35 (-21.91,56.62)	-18.35 (-44.57,7.87)			
-18.32 (-62.29,25.65)	18.61 (-17.61,54.83)	20.93 (-26.69,68.55)	-25.14 (-64.09,13.82)	-43.11 (-87.72,1.50)	-25.20 (-69.81,19.41)	-60.90 (-94.25,-27.56)			
24.78 (-12.24,61.81)	61.71 (19.26,104.16)	64.03 (27.28,100.78)	17.97 (-11.77,47.70)	-0.01 (-36.03,36.02)	17.90 (-18.12,53.92)	-17.80 (-36.17,0.57)			
29.76 (-2.47,61.99)	66.69 (29.20,104.17)	69.01 (32.38,105.65)	22.95 (-1.77,47.66)	4.97 (-27.79,37.74)	22.88 (-9.88,55.64)	-12.82 (-24.91,-0.74)			
34.49 (-9.72,78.69)	71.41 (22.78,120.04)	73.73 (27.36,120.10)	27.67 (-10.70,66.03)	9.70 (-33.77,53.16)	27.60 (-15.86,71.06)	-8.10 (-37.35,21.15)			
29.63 (-14.58,73.83)	66.55 (17.93,115.17)	68.87 (22.51,115.24)	22.81 (-15.55,61.17)	4.84 (-38.63,48.30)	22.74 (-20.72,66.20)	-12.96 (-42.20,16.28)			
27.93 (-11.20,67.05)	64.85 (20.79,108.91)	67.17 (25.62,108.73)	21.11 (-11.27,53.49)	3.14 (-35.15,41.42)	21.04 (-17.24,59.32)	-14.66 (-35.44,6.12)			
13.95 (-29.62,57.51)	50.87 (3.29,98.46)	53.19 (6.28,100.11)	7.13 (-31.21,45.47)	-10.84 (-54.80,33.12)	7.06 (-36.90,51.02)	-28.64 (-60.34,3.06)			
46.95 (2.37,91.53)	83.87 (34.91,132.84)	86.19 (39.47,132.92)	40.13 (1.34,78.92)	22.16 (-21.69,66.00)	40.06 (-3.78,83.90)	4.36 (-25.45,34.17)			
17.74 (-21.34,56.82)	54.67 (10.65,98.69)	56.99 (15.47,98.51)	10.92 (-21.40,43.25)	-7.05 (-45.29,31.20)	10.86 (-27.38,49.10)	-24.84 (-45.55,-4.14)			
42.41 (4.18,80.63)	79.33 (36.33,122.34)	81.66 (40.30,123.02)	35.59 (3.87,67.31)	17.62 (-20.41,55.65)	35.52 (-2.50,73.55)	-0.18 (-21.74,21.39)			
25.78 (-3.76,55.32)	62.71 (24.53,100.89)	65.03 (28.74,101.32)	18.96 (-3.91,41.84)	0.99 (-31.43,33.42)	18.90 (-13.52,51.32)	-16.80 (-31.85,-1.75)			
0.13 (-46.43,46.69)	37.06 (-10.57,84.68)	39.38 (-10.96,89.72)	-6.69 (-48.70,35.33)	-24.66 (-72.08,22.76)	-6.75 (-54.17,40.66)	-42.46 (-80.15,-4.76)			
-2.90 (-36.82,31.02)	34.02 (-6.95,74.99)	36.34 (0.37,72.32)	-9.72 (-36.43,16.99)	-27.69 (-61.87,6.48)	-9.79 (-43.96,24.38)	-45.49 (-65.06,-25.92)			
28.17 (-8.48,64.82)	65.10 (23.98,106.21)	67.42 (26.62,108.23)	21.36 (-8.64,51.36)	3.39 (-33.35,40.12)	21.29 (-15.44,58.02)	-14.41 (-38.36,9.54)			
22.43 (-21.82,66.67)	59.35 (10.69,108.01)	61.67 (15.26,108.08)	15.61 (-22.80,54.02)	-2.36 (-45.87,41.14)	15.54 (-27.96,59.05)	-20.16 (-49.47,9.15)			
11.10 (-33.13,55.32)	48.02 (-0.63,96.67)	50.34 (3.95,96.74)	4.28 (-34.11,42.67)	-13.69 (-57.18,29.79)	4.21 (-39.27,47.70)	-31.49 (-60.77,-2.21)			
2.88 (-40.63,46.39)	39.80 (-7.73,87.34)	42.12 (-4.74,88.99)	-3.94 (-42.22,34.34)	-21.91 (-65.82,22.00)	-4.01 (-47.91,39.90)	-39.71 (-71.34,-8.08)			
-3.70 (-39.89,32.49)	33.23 (-4.32,70.78)	35.55 (-5.39,76.50)	-10.51 (-40.64,19.61)	-28.49 (-65.78,8.80)	-10.58 (-47.87,26.71)	-46.28 (-70.02,-22.55)			
10.37 (-31.33,52.08)	47.30 (-0.52,95.12)	49.62 (3.79,95.46)	3.56 (-24.75,31.87)	-14.41 (-56.81,27.98)	3.49 (-38.90,45.88)	-32.21 (-64.11,-0.31)			
7.26 (-40.27,54.78)	44.18 (-8.52,96.88)	46.51 (-4.06,97.07)	0.44 (-28.95,29.83)	-17.53 (-64.69,29.62)	0.37 (-46.78,47.53)	-35.33 (-73.78,3.12)			
12.40 (-29.17,53.97)	49.33 (1.24,97.41)	51.65 (5.05,98.25)	5.58 (-31.54,42.71)	-12.39 (-56.05,31.27)	5.52 (-38.14,49.17)	-30.19 (-63.06,2.69)			
3.38 (-29.61,36.37)	40.30 (0.49,80.11)	42.63 (4.75,80.50)	-3.44 (-29.34,22.46)	-21.41 (-55.20,12.38)	-3.50 (-37.29,30.28)	-39.21 (-57.07,-21.34)			
9.90 (-26.26,46.06)	46.82 (3.32,90.33)	49.15 (7.29,91.00)	3.08 (-27.87,34.04)	-14.89 (-53.44,23.66)	3.01 (-35.53,41.56)	-32.69 (-58.40,-6.98)			
Metformin Exenatide	fibenclamide Rosiglitazon	Glimepiride Rosiglitazone	Pioglitazone Sitagliptin	Pioglitazone Linagliptin	Pioglitazone Alogliptin	Placebo			
-36.93 (-85.20,11.35)	36.93 (-11.35,85.20)	2.32 (-49.30,53.94)	-43.74 (-87.50,0.02)	-61.71 (-110.58,-12.85)	-43.81 (-92.67,5.05)	-79.51 (-118.36,-40.66			
-39.25 (-86.04,7.54)	-2.32 (-53.94,49.30)	-46.07 (-87.22,-4.91)	-64.04 (-109.86,-18.21)	-46.13 (-91.95,-0.31)	-81.83 (-117.82,-45.85				
6.82 (-30.55,44.18)	43.74 (-0.02,87.50)	46.07 (4.91,87.22)	17.97 (-18.92,54.87)	-17.97 (-54.87,18.92)	-0.07 (-36.96,36.82)	-35.77 (-60.60,-10.94)			
24.79 (-19.07,68.65)	61.71 (12.85,110.58)	64.04 (18.21,109.86)	17.91 (-23.45,59.26)	-17.80 (-49.95,14.36)					
6.88 (-36.97,50.74)	43.81 (-5.05,92.67)	46.13 (0.31,91.95)	0.07 (-36.82,36.96)	-17.91 (-59.26,23.45)	-35.70 (-67.85,-3.55)				
42.59 (9.44,75.73)	79.51 (40.66,118.36)	81.83 (45.85,117.82)	35.77 (10.94,60.60)	17.80 (-14.36,49.95)	35.70 (3.55,67.85)				

Fig. 6 continued

thoroughly examining the clinical implications of these effect sizes, we aim to enhance readers' comprehension and guide future research endeavors. We will persist in monitoring the implementation of these treatment options in clinical practice and will refine our conclusions as new evidence emerges.

Strengths and limitations

The major strength of this study was the comprehensive strategy for the literature search and subsequent analysis of beta-cell function after treatment with different hypoglycaemic drugs, which included a high-quality network-wide comparison. Furthermore, network meta-analysis was used to map all possible treatment comparisons, which used both direct and indirect evidence to increase the total sample size. The evaluation showed

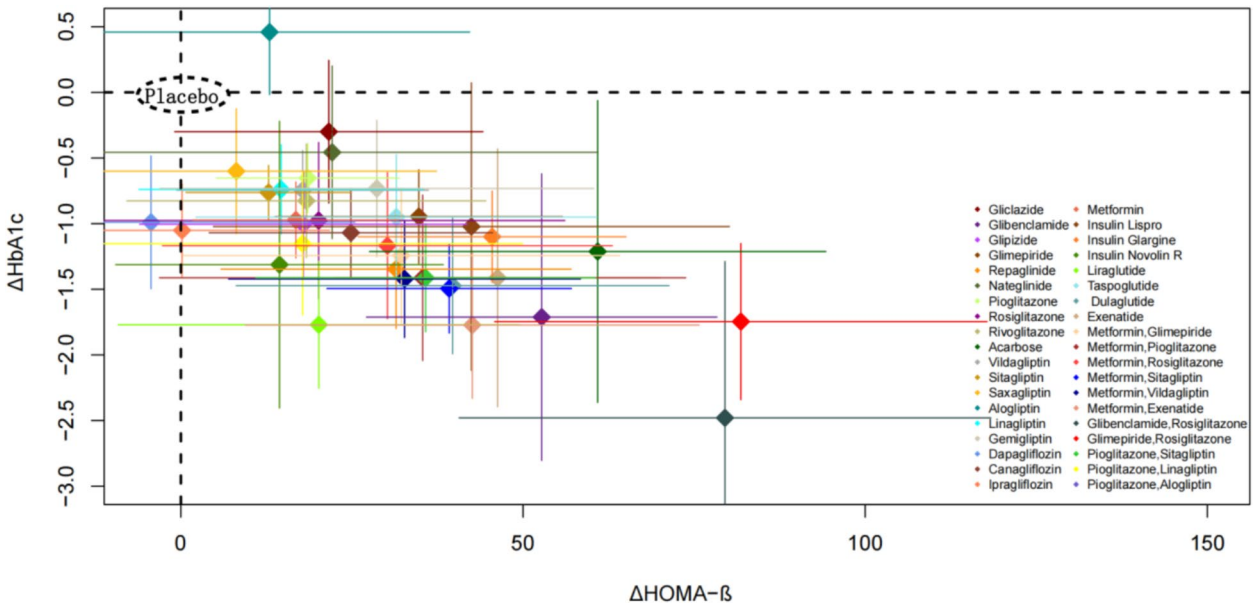

Fig. 7 Two-dimensional graphs showing the efficacy estimates from the network meta-analysis. All efficacy estimates are compared with the placebo control. Horizontal lines represent the efficacy estimates and their 95% credible intervals for HOMA-β, and vertical lines show the efficacy estimates and their 95% credible intervals for HbA1c. An intersection point between these two lines indicates the mean difference estimates for both HOMA-β and HbA1c

little heterogeneity among the included studies, and thus, a fixed-effects model was used for analysis. In addition, cumulative ranking probability plots were constructed for the purpose of statistically ranking the treatment options, which allowed the efficacy advantages of different hypoglycaemic drugs to be observed more directly.

Several limitations of this study also should be considered. First, this study included only RCTs published in the English literature due to our limited ability to translate studies published in other languages, which may result in language bias. Second, even though only RCTs were included, some studies were assessed as unclear regarding allocation concealment and outcome assessment by the Cochrane Bias Risk Tool, which might restrict the interpretation of the results. Moreover, due to constraints in time and human resources, and to ensure the consistency and reproducibility of our research methods, we conducted a systematic hazard search exclusively within standardized databases, excluding grey literature. We acknowledge that the omission of grey literature may limit the comprehensiveness of this study. Therefore, we intend to incorporate grey literature in future research endeavours to enhance the evidence base supporting our findings. Finally, we only evaluated the protective effect of different hypoglycaemic drugs on beta-cells in T2DM patients. We did not evaluate safety of the treatments in the present study, because many previous studies have already evaluated the safety of some hypoglycaemic drugs from various aspects. In addition, the drugs tested in 16 of the 58 studies included have not been evaluated for safety yet, and thus, the safety of different hypoglycaemic drugs could not be thoroughly analysed.

Conclusions

The results of the presented network meta-analysis indicate that a combination treatment pairing a glimepiride/glibenclamide with rosiglitazone is the most effective hypoglycaemic regimen for protecting beta-cell function and improving glycaemic control in T2DM patients. The resulting improvement in beta-cell function may be due to better control of HbA1c and glycotoxicity. These findings can be considered in future guidelines and the clinical treatment of T2DM patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02368-y.

Supplementary material 1.

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Author contributions
LingHong Huang and HuiBin Huang conceived the project; designed, performed, and analyzed experiments; and wrote the manuscript. ZhiFeng Guo contributed to analysis and ZhengRong Jiang and XueFeng Bai contributed

to prepared figures and table. HuiBin Huang is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Since this meta-analysis is based on previously published studies, no new data were collected from human or animal subjects by the authors of this study. Therefore, ethics approval and informed consent were not required for this particular meta-analysis according to the institutional and national guidelines followed by the authors.

Consent for publication
No individual person's data are contained in this meta-analysis, as it is based solely on previously published studies. Therefore, specific consent for publication was not required.

Competing interests
The authors declare no competing interests.

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