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Evaluation and comparison of efficacy and safety of tirzepatide, liraglutide and SGLT2i in patients with type 2 diabetes mellitus: a network meta-analysis

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Abstract

Objective The objective is to assess the effectiveness and safety of tirzepatide, liraglutide, and SGLT2i in individuals diagnosed with type 2 diabetes.

Methods An inquiry was undertaken within the electronic database spanning from its inception to February 11th, 2024, aimed at identifying randomized controlled trials that assess the efficacy and safety of tirzepatide, liraglutide, canagliflozin, ertugliflozin, empagliflozin, dapagliflozin, and henagliflozin. Perform a network meta-analysis to examine the distinctions among them (PROSPERO registration number: CRD42024537006).

Results Twenty-eight RCTs were included, involving 8499 participants. Compared with placebo, all treatments improved HbA1c levels: tirzepatide 15 mg reduced HbA1c the most (MD [95% CI], -2.24% [-2.52, -1.96]%), followed by tirzepatide 10 mg (MD [95% CI], -1.99% [-2.29, -1.69]%), tirzepatide 5 mg (MD [95% CI], -1.82% [-2.11, -1.53]%), and liraglutide 1.2 mg (MD [95% CI], -1.23% [-1.41, -1.05]%). Canagliflozin 300 mg also showed a significant reduction in HbA1c (MD [95% CI], -1.00% [-1.18, -0.82]). Tirzepatide was also the most effective in promoting weight loss, with the following results compared with placebo: tirzepatide 15 mg (MD [95% CI], -8.74 kg [-9.83, -7.66] kg), tirzepatide 10 mg (MD [95% CI], -7.13 kg [-8.40, -5.88] kg), tirzepatide 5 mg (MD [95% CI], -5.38 kg [-6.65, -4.11] kg), canagliflozin 300 mg (MD [95% CI], -2.31 kg [-2.79, -1.83] kg), and empagliflozin 10 mg (MD [95% CI], -2.00 kg [-2.44, -1.55] kg). In reducing systolic blood pressure (SBP), canagliflozin 300 mg showed the greatest effect (MD [95% CI], -5.96% [-7.96, -3.96] %). For diastolic blood pressure (DBP), henagliflozin 5 mg demonstrated the most significant reduction compared to placebo (MD [95% CI], -2.46% [-3.82, -1.10] %). Liraglutide 1.8 mg was most likely to cause adverse events (AE) (OR [95% CI], 2.57 [1.78, 3.70]), but there was no significant difference in serious adverse events (SAEs) between the interventions (including placebo).

Conclusion Out of the seven medications examined in this study, tirzepatide demonstrates the most effective antidiabetic and weight-reducing effects. Furthermore, the dosage of Liraglutide at 1.2 mg and above demonstrates a more pronounced hypoglycemic effect in comparison to SGLT2 inhibitors. SGLT2 inhibitors exhibit a distinct hypotensive effect and are suitable for diabetic individuals experiencing hypertension.

Keywords Tirzepatide, Liraglutide, SGLT2i, Type 2 diabetes mellitus, Meta-analysis

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Introduction

Diabetes affects approximately 537 million individuals worldwide, leading to chronic hyperglycemia that progressively damages multiple organs, including the retina, kidneys, nerves, blood vessels, and heart, with the potential to result in organ failure [1]. Moreover, a growing body of evidence indicates a close association between diabetes and an increased risk of various cancers [2]. The 10th IDF Diabetes Map illustrates that diabetes represents one of the most rapidly escalating global health crises of the twenty-first century. Projections indicate that the population of individuals with diabetes is expected to rise to 643 million by the year 2030 and further escalate to 783 million by 2045 [3]. Due to the high prevalence of diabetes and its detrimental effects on several bodily systems, treating diabetic patients has consistently posed a challenging issue for physicians across various fields. In recent 30 years, a series of new hypoglycemic drugs have emerged, such as GIP/GLP-1 double receptor agonists [4, 5], SGLT-2 inhibitors [6, 7] and GLP1 receptor agonists [8]. In contrast to certain conventional hypoglycemic medications, these alternatives show enhanced safety, greater efficacy, and increased simplicity, while also considering the protective benefits for cardiac and renal health. SGLT-2 inhibitors [6, 7] and GLP1 receptor agonists have been widely used in clinics. In May 2022, the first dual agonist of glucose-dependent insulinotropic peptide (GIP) and GLP-1 receptor, tizepatide, was approved for marketing by FDA. The half-life is about 5 days, allowing for administration weekly, which enhances its practicality of use. Current research indicates that teixeptide has the potential to significantly enhance blood sugar regulation and facilitate weight loss in individuals diagnosed with type 2 diabetes [4, 5].

The SGLT-2 inhibitor is a novel oral hypoglycemic medication that has garnered significant interest in recent times. It can inhibit the reabsorption of glucose by the kidney, lower the renal glucose threshold, thus promoting the excretion of urine glucose, and can significantly reduce the occurrence of cardiovascular adverse events and end-stage renal diseases [9, 10]. Liraglutide is a prominent medication belonging to the class of GLP1 receptor agonists. The mechanism operates by enhancing insulin secretion to reduce blood glucose levels while concurrently inhibiting glucagon secretion to increase blood sugar levels, all of which is contingent upon insulin's role. This medication proficiently lowers blood sugar levels by suppressing the appetite center, prolonging gastric emptying, and diminishing food consumption. Additionally, it has a minimal risk of causing hypoglycemia. At the same time, it also has a protective effect on the heart and kidney [8, 11].

While prior studies, including those by Ding et al. [5], Guan et al. [12], and Thomas et al. [13], have analyzed specific hypoglycemic agents or focused on single drug classes, our study offers a comprehensive network meta-analysis that compares three major classes of antidiabetic medications—GLP-1 receptor agonists, GIP/GLP-1 dual receptor agonists, and SGLT-2 inhibitors—within a unified analytical framework. This approach enables both direct and indirect comparisons of efficacy and safety outcomes, including HbA1c reduction, weight loss, blood pressure control, and adverse events, across a broad spectrum of drug dosages. Unlike previous studies, which often emphasize pharmacokinetic or mechanistic insights, our analysis is guided by clinical relevance, addressing the practical application of these therapies in managing Type 2 diabetes, particularly in patients with comorbid conditions such as obesity and hypertension. Through the evaluation of these therapies according to their efficacy and safety profiles, our findings offer critical insights to evidence-based guidelines, equipping clinicians with a more nuanced understanding of optimal therapy selections and potential combinations for tailored patient management.

The comparative effectiveness and safety of these three drug classes have not been thoroughly assessed in relation to each other, given their distinct mechanisms of action. Network meta-analysis (NMA) serves as an ideal statistical approach to address this gap. As a method that allows for the simultaneous comparison and ranking of multiple interventions through both direct and indirect evidence, NMAs consolidate findings from multiple comparators into a single pooled analysis [14]. Consequently, our study employs NMA to evaluate and compare the efficacy and safety of the GIP/GLP-1 dual receptor agonist tirzepatide (TIR), the GLP-1 receptor agonist liraglutide (LIR), and various SGLT-2 inhibitors, including canagliflozin (Can), ertugliflozin (Ert), empagliflozin (Emp), dapagliflozin (Dap), and henagliflozin (Hen), in the treatment of Type 2 diabetes mellitus. Our goal is to provide evidence-based insights that can assist clinicians in formulating optimal hypoglycemic regimens.

Methods

This systematic review and network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure rigorous and transparent reporting of findings. The study protocol was registered on PROSPERO (ID: CRD42024537006), and we adhered to the PRISMA checklist throughout all phases of study selection, data extraction, and analysis to meet the highest reporting standards in systematic reviews and meta-analyses [15].

Search strategy

Systematic searches were conducted across PubMed, EMBASE, and the Cochrane Library from database inception to February 11, 2024, using a defined set of keywords and Boolean operators to identify randomized clinical trials (RCTs) evaluating the efficacy and safety of tirzepatide, liraglutide, canagliflozin, ertugliflozin, empagliflozin, dapagliflozin, and henagliflozin, detailed search strategies tailored to each database are provided in Supplementary File 1. Duplicate records were removed through Endnote 20.

Study selection criteria

Studies were included in this meta-analysis based on the following PICO (Population, Intervention, Comparator, Outcomes) criteria: Population – individuals diagnosed with type 2 diabetes, aged 18 years or older; Intervention – treatment with different doses of tirzepatide (Tir), liraglutide (Lir), canagliflozin (Can), ertugliflozin (Ert), empagliflozin (Emp), dapagliflozin (Dap), or henagliflozin (Hen); Comparator – placebo or any one or more of the included intervention drugs; Outcomes – efficacy outcomes, such as reductions in HbA1c, changes in body weight, and blood pressure, as well as safety outcomes, including adverse events (AEs) and serious adverse events (SAEs).

Studies were excluded if they met any of the following criteria: secondary analysis of published RCTs, ongoing or completed experiments with unpublished results, conference papers, review articles, animal or in vitro studies, editorials, letters, statements, or if the data were incomplete or could not be extracted.

Data collection and quality assessment

Two researchers (X.P.Y and X.F.) independently conducted literature screening, data extraction, and quality assessment. Extracted data included the first author, publication year, intervention measures, sample size, baseline characteristics, changes in monitored indicators, intervention duration, and adverse events. For quality assessment, the RevMan5.4 program and the Cochrane risk of bias tool were used to evaluate each study across seven domains, categorizing each domain as low risk, high risk, or unclear risk [16]. Discrepancies were resolved through discussion between the two researchers (X.P.Y and X.F.), with a third author (Y.J.T), consulted when necessary to reach a consensus.

Data analysis

The statistical analysis was performed utilizing Stata 17.0. Continuous variables employ the mean difference (MD) to gauge the extent of the effect, whereas binary variables utilize the odds ratio (OR) to assess the size of the effect. The confidence interval (CI) is set to 95% CI. Chi-square (χ^2) was used to test the statistical heterogeneity between the evaluation results, and I^2 was used to quantitatively judge the heterogeneity. $P > 0.05$, or $I^2 < 50\%$ means that there is no heterogeneity, and the fixed effect model is used. $P \leq 0.05$, or $I^2 \geq 50\%$ is heterogeneity. The random effect model and sensitivity analysis are employed to establish the origin of heterogeneity. Determine the cumulative ranking curve (SUCRA) to evaluate the therapeutic effects of different therapies and arrange them in order of effectiveness (Table 2).

Results

Study selection and characteristics

Some doses of drugs in the RCTs were seldom used in clinical settings, or the number of subjects was too small. Two researchers (X.P.Y and X.F.) decided to exclude the following intervention measures: tirzepatide 1 mg, tirzepatide 12 mg, liraglutide 0.1 mg, liraglutide 0.3 mg, liraglutide 0.9 mg, canagliflozin 50 mg, empagliflozin 50 mg, and dapagliflozin 2.5 mg. According to the retrieval strategy, a total of 8673 articles were retrieved, and 28 articles [17–44] remained after de-duplication, primary screening, and re-screening, involving 8499 patients. See Fig. 1 for the process and results of literature screening, Fig. 2 for literature quality evaluation, and Table 1 for baseline characteristics. The intervention duration ranged from 4 to 52 weeks, including 4-week RCT1, 8-week RCT1, 5-week RCT1, 14-week RCT1, 24-week RCT8, 26-week RCT8, 28-week RCT1, 40-week RCT1, and 52-week RCT2. The network diagram presented below illustrates all outcome indicators. Each node (blue dot) represents an intervention; the size of each node reflects the number of participants in the intervention, with larger nodes indicating more participants. The connecting line between two points signifies a direct comparison between the two interventions; the thicker the line, the more studies available to compare the two interventions. Out of the 28 documents analyzed, one presented a significant risk in terms of potential blindness and the reliability of the data obtained [31]. Another document [32] included a single-blind component in the experimental process, allowing researchers to adjust medications. See Fig. 3 for the specific evaluation structure.

Efficacy outcomes

HbA1c (main outcome indicator)

In the network meta-analysis of HbA1c, 19 interventions across 26 studies were included, involving different doses of seven hypoglycemic drugs: tirzepatide (5 mg, 10 mg, 15 mg), liraglutide (0.6 mg, 1.2 mg, 1.8 mg), canagliflozin (100 mg, 200 mg, 300 mg), ertugliflozin (5 mg, 15

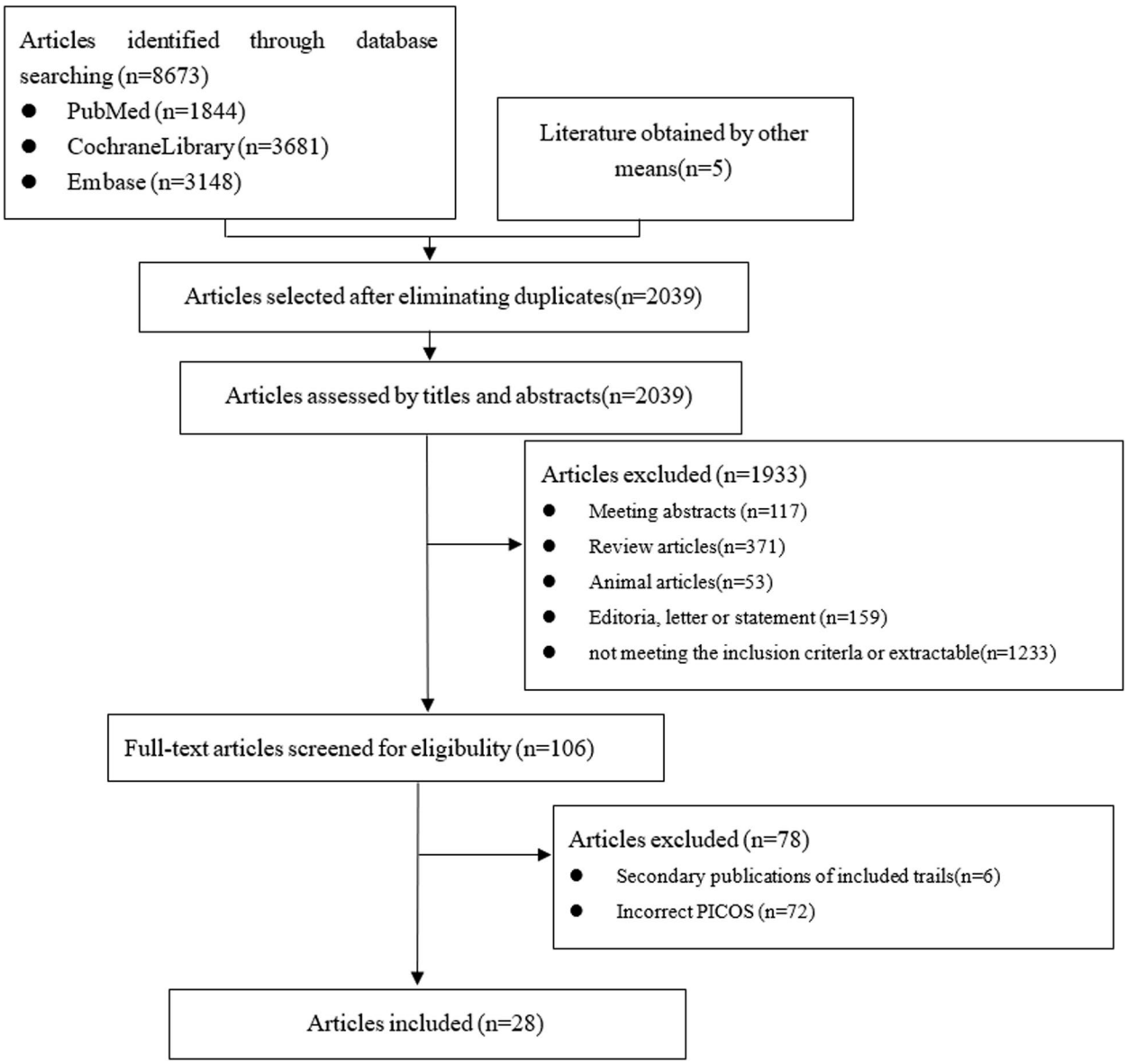

Fig. 1 The process and results of literature screening

mg), empagliflozin (5 mg, 10 mg, 25 mg), dapagliflozin (5 mg, 10 mg), and henagliflozin (5 mg, 10 mg), as well as placebo. The dot diagram is shown in Fig. 3A. The heterogeneity test results showed $\chi^2 = 4.52$, $I^2 = 0\%$, $P = 0.95$ ($P > 0.05$), indicating no significant heterogeneity among the included studies; thus, a fixed-effects model was used for the combined effect.

The league table (Table 3) presents pairwise comparisons between various interventions: all interventions achieved statistically significant improvements compared with placebo. Tirzepatide 15 mg had the most substantial HbA1c reduction (MD [95% CI], −2.24% [−2.52%, −1.96%]), followed by tirzepatide 10 mg (MD [95% CI], −1.99% [−2.29%, −1.69%]), tirzepatide 5 mg (MD [95% CI], −1.82% [−2.11%, −1.53%]), and liraglutide 1.2 mg (MD [95% CI], −1.23% [−1.41%, −1.05%]). The SUCRA rankings for hypoglycemic efficacy are shown in Table 3 and Fig. 4.1 with tirzepatide 15 mg (99.7%) ranked highest, followed by tirzepatide 10 mg (94%), tirzepatide 5 mg (89.6%), liraglutide 1.2 mg (80.6%), and liraglutide 1.8 mg (79.7%).

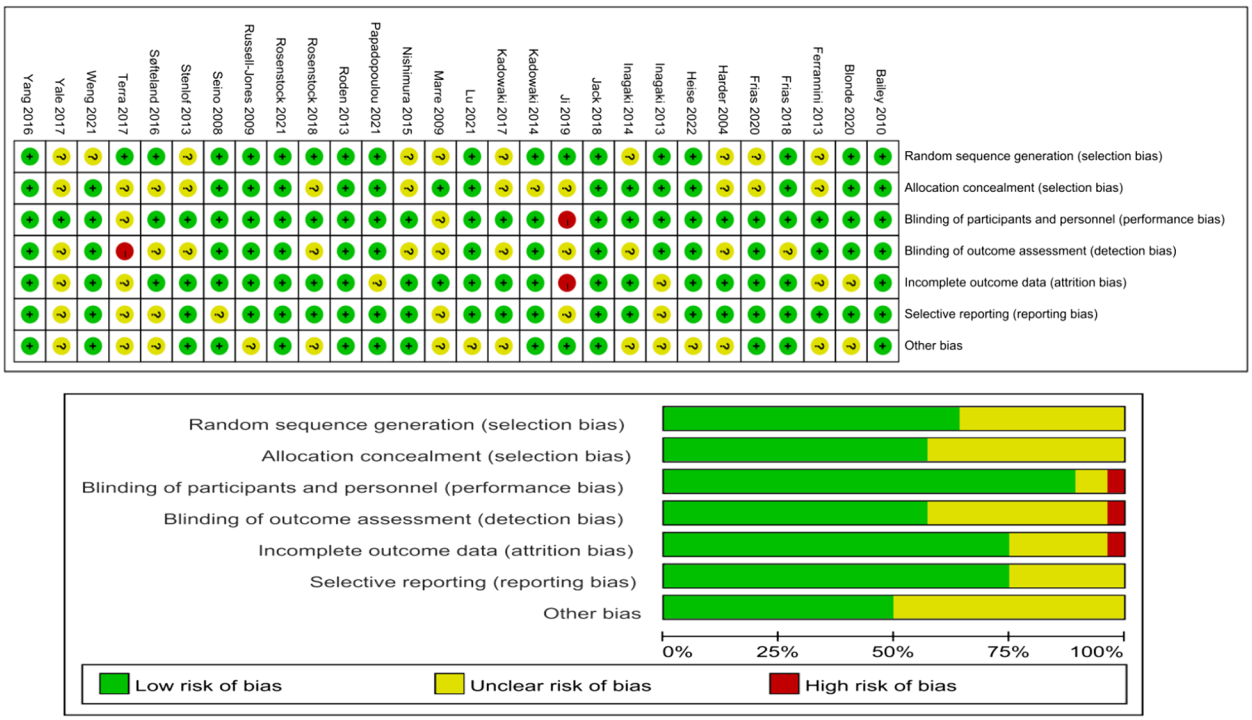

Fig. 2 Literature quality evaluation

Weight (secondary outcome indicator)

The network meta-analysis of body weight included 19 interventions from 27 studies with various doses of seven hypoglycemic drugs: tirzepatide (5 mg, 10 mg, 15 mg), liraglutide (0.6 mg, 1.2 mg, 1.8 mg), canagliflozin (100 mg, 200 mg, 300 mg), ertugliflozin (5 mg, 15 mg), empagliflozin (5 mg, 10 mg, 25 mg), dapagliflozin (5 mg, 10 mg), and henagliflozin (5 mg, 10 mg). Placebo was also included in the analysis. The dot diagram is shown in Fig. 3B. Heterogeneity test results for this analysis were $\chi 2 = 10.09$, $I^2 = 0\%$, $P = 0.523$ ($P > 0.05$), suggesting homogeneity among studies, supporting the use of a fixed-effects model.

The league table (Table 4) shows the effectiveness of each intervention in weight reduction compared to placebo. Tirzepatide 15 mg exhibited the most significant weight reduction (MD [95% CI], −8.74 kg [−9.83 kg, −7.66 kg]), followed by tirzepatide 10 mg (MD [95% CI], −7.13 kg [−8.40 kg, −5.86 kg]). SUCRA rankings for weight loss are indicated in Table 4 and Fig. 4.2, with tirzepatide 15 mg at the top (100%), followed by tirzepatide 10 mg (94.4%), tirzepatide 5 mg (88.9%), canagliflozin 300 mg (78.4%), and empagliflozin 10 mg (65.6%).

SBP (secondary outcome indicator)

The network meta-analysis of systolic blood pressure (SBP) included 13 interventions from nine studies. These interventions consisted of various doses of five hypoglycemic drugs. The heterogeneity test results indicated $\chi^2 = 5.04$, $I^2 = 0\%$, $P = 0.538$ ($P > 0.05$), suggesting no significant heterogeneity, and a fixed-effects model was applied.

The league table (Table 5) displays each intervention's impact on reducing SBP compared to placebo. Canagliflozin 300 mg showed the most substantial SBP reduction (MD [95% CI], −5.96 mmHg [−7.96 mmHg, −3.96 mmHg]). SUCRA results in Table 5 and Fig. 4.3, rank canagliflozin 300 mg highest (82.1%), followed by dapagliflozin 5 mg (76.1%) and henagliflozin 10 mg (70%).

DBP (secondary outcome indicator)

In the network meta-analysis of diastolic blood pressure (DBP), 11 interventions from eight studies were included, comprising various doses of four hypoglycemic drugs. The heterogeneity test showed $\chi 2 = 5.6$, $I^2 = 0\%$, $P = 0.47$ ($P > 0.05$), indicating no heterogeneity among studies, supporting a fixed-effects model.

The league table (Table 6) shows the DBP reduction effectiveness of each intervention compared to placebo, with henagliflozin 5 mg achieving the best DBP reduction (MD [95% CI], −2.46 mmHg [−3.82 mmHg, −1.10 mmHg]). Table 6 and Fig. 4.4 provides SUCRA results, with henagliflozin 5 mg at the top (78.5%), followed by

Table 1 Baseline data

Study	Gender(M/F)	Age	N	Treatment	Duration (weeks)	Outcomes
Rosenstock, et al. (2021) [17]	56/59	53.6 ± 12.8	115	Placebo	40	HbA1c,Weight,AE, SAE
	56/65	54.1 ± 11.9	121	Tir 5mg		
	72/49	55.8 ± 10.4	121	Tir 10mg		
	63/58	52.9 ± 12.3	121	Tir 15mg		
Frias, et al. (2020) [18]	12/14	56.0 ± 10.13	26	Placebo	12	HbA1c,Weight,AE, SAE
	16/13	55.5 ± 8.54	29	Tir 15mg		
Frias, et al. (2018) [19]	29/22	56.6 ± 8.9	51	Placebo	26	HbA1c,Weight,AE, SAE
	34/21	57.9 ± 8.2	55	Tir 5mg		
	30/21	56.5 ± 9.9	51	Tir 10mg		
	22/31	56.0 ± 7.6	53	Tir 15mg		
Heise, et al. (2022) [20]	21/7	60.4 ± 7.6	28	Placebo	28	Weight,AE, SAE
	31/14	61.1 ± 7.1	45	Tir 15mg		
Blonde, et al. (2020) [21]	58/42	56.0 ± 9.9	100	Placebo	26	HbA1c,Weight,AE, SAE
	125/78	54.7 ± 10.1	203	Lir 1.8mg		
Harder, et al. (2004) [22]	1/11	60.1 ± 6.7	12	Placebo	8	HbA1c,Weight
	11/10	59.9 ± 11.0	21	Lir 0.6mg		
Seino, et al. (2008) [23]	29/17	57.5 ± 8.7	46	Placebo	14	HbA1c,Weight
	28/17	60 ± 7.0	45	Lir 0.6mg		
Marre, et al. (2009) [24]	54/60	54.7 ± 10.0	114	Placebo	26	HbA1c,Weight, SAE
	126/107	55.7 ± 9.9	233	Lir 0.6mg		
	102/126	57.7 ± 9.0	228	Lir 1.2mg		
	124/110	55.6 ± 10.0	234	Lir 1.8mg		
Russell-Jones, et al. (2009) [25]	56/59	57.5 ± 9.6	115	Placebo	26	HbA1c,Weight,AE, SAE
	132/100	57.6 ± 9.5	232	Lir 1.8mg		
Yale, et al. (2017) [26]	41/28	64.3 ± 7.76	69	Placebo	52	HbA1c,Weight,AE, SAE
	37/37	64.3 ± 8.49	74	Can 100mg		
	42/30	65.8 ± 7.88	72	Can 300mg		
Kadowaki, et al. (2017) [27]	53/15	56.0 ± 9.5	68	Placebo	24	HbA1c,Weight,AE, SAE
	54/16	58.4 ± 8.9	70	Can 100mg		
Inagaki, et al. (2013) [28]	54/21	57.7 ± 11.0	75	Placebo	12	HbA1c,Weight,SBP,DBP,AE, SAE
	52/22	57.7 ± 10.5	74	Can 100mg		
	49/27	57.0 ± 10.7	76	Can 200mg		
	55/20	57.1 ± 10.1	75	Can 300mg		
Inagaki, et al. (2014) [29]	60/33	58.2 ± 11.0	93	Placebo	24	HbA1c,Weight,SBP,DBP,AE, SAE
	60/33	58.4 ± 10.4	93	Can 100mg		
	72/16	57.4 ± 11.1	88	Can 200mg		
Stenlof, et al. (2013) [30]	88/104	55.7 ± 10.9	192	Placebo	26	HbA1c,Weight,SBP,DBP,AE, SAE
	81/114	55.1 ± 10.8	195	Can 100mg		
	89/108	55.3 ± 10.2	197	Can 300mg		
Ji, et al. (2019) [31]	88/79	56.9 ± 9.0	167	Placebo	26	HbA1c,Weight,SBP,DBP,AE, SAE
	95/65	56.1 ± 9.0	160	Ert 5mg		
	98/71	56.3 ± 9.3	169	Ert 15mg		
Terra, et al. (2017) [32]	82/71	56.1 ± 10.9	153	Placebo	26	HbA1c,Weight,AE, SAE
	89/67	56.8 ± 11.4	156	Ert 5mg		
	90/62	56.2 ± 10.8	152	Ert 15mg		
Rosenstock, et al. (2018) [44]	98/111	56.5 ± 8.7	209	Placebo	26	HbA1c,Weight,AE, SAE
	97/110	56.6 ± 8.1	207	Ert 5mg		
	93/112	56.9 ± 9.4	205	Ert 15mg		

Table 1 (continued)

Study	Gender(M/F)	Age	N	Treatment	Duration (weeks)	Outcomes
Dagogo-Jack S, et al. (2018) [33]	100/53	58.3 ± 9.2	153	Placebo	52	HbA1c,Weight,AE, SAE
	81/75	59.2 ± 9.3	156	Ert 5mg		
	82/71	59.7 ± 8.6	153	Ert 15mg		
Kadowaki, et al. (2014) [34]	80/29	58.7 ± 8.7	109	Placebo	12	HbA1c,Weight,SBP,DBP,AE, SAE
	84/26	57.3 ± 11.2	110	Emp 5mg		
	77/32	57.9 ± 9.4	109	Emp 10mg		
	84/25	57.2 ± 9.7	109	Emp 25mg		
Søfteland, et al. (2017) [35]	60/48	55.9 ± 9.7	108	Placebo	24	HbA1c,Weight,AE, SAE
	66/43	54.3 ± 9.6	109	Emp 10mg		
	71/39	55.4 ± 9.9	110	Emp 25mg		
Nishimura, et al. (2015) [36]	17/4	60.7 ± 10.8	21	Placebo	4	AE, SAE
	14/6	64.8 ± 5.9	20	Emp 10mg		
	16/3	62.6 ± 7.8	19	Emp 25mg		
Ferrannini, et al. (2013) [37]	45/37	58.0(28–80)	82	Placebo	12	HbA1c,Weight,AE
	46/35	59.0(37–78)	81	Emp 5mg		
	40/41	58.0(30–76)	81	Emp 10mg		
	41/41	57.0(30–79)	82	Emp 25mg		
Roden, et al. (2013) [38]	123/105	54.9 ± 10.9	228	Placebo	24	HbA1c,Weight,SBP,DBP,AE, SAE
	142/82	56.2 ± 11.6	224	Emp 10mg		
	145/79	53.8 ± 11.6	224	Emp 25mg		
Papadopoulou, et al. (2021) [39]	21/21	60.6 ± 9.4	42	Placebo	12	HbA1c,Weight
	23/20	61.7 ± 6.7	43	Dap 10mg		
Yang, et al. (2016) [40]	86/59	53.5 ± 9.2	145	Placebo	24	HbA1c,Weight,SBP,AE, SAE
	67/80	53.1 ± 9.1	147	Dap 5mg		
	88/64	54.6 ± 9.5	152	Dap 10mg		
Bailey, et al. (2010) [41]	76/67	53.7 ± 10.3	143	Placebo	24	HbA1c,Weight,AE, SAE
	69/68	54.3 ± 9.4	137	Dap 5mg		
	77/58	52.7 ± 9.9	135	Dap 10mg		
Weng, et al. (2021) [42]	93/68	55.3 ± 9.5	161	Placebo	24	HbA1c,Weight,SBP,DBP,AE, SAE
	103/59	54.3 ± 9.5	162	Hen 5mg		
	101/59	54.7 ± 10.7	160	Hen 10mg		
Lu, et al. (2021) [43]	100/51	52.4 ± 10.2	151	Placebo	24	HbA1c,Weight,SBP,DBP,AE, SAE
	88/62	53.3 ± 9.6	150	Hen 5mg		
	115/36	52.2 ± 9.4	151	Hen 10mg		

canagliflozin 300 mg (72.6%) and henagliflozin 10 mg (72.5%).

AE (secondary outcome indicator)

The network meta-analysis of adverse events (AEs) included 19 interventions from 24 studies. The heterogeneity test results for AEs showed $\chi^2 = 4.4$, $I^2 = 0\%$, $P = 0.819$ ($P > 0.05$), indicating homogeneity.

The league table (Table 7) demonstrated liraglutide 1.8 mg with the highest AE risk (OR [95% CI]: 2.57 [1.78, 3.70]), while empagliflozin 10 mg showed a lower AE risk compared to placebo. SUCRA rankings, provided in Table 7 and Fig. 4.5, indicate liraglutide 1.8 mg at the highest AE risk (98.6%), followed by tirzepatide 15 mg (79.3%), tirzepatide 10 mg (76.6%), tirzepatide 5 mg (74.4%), and henagliflozin 10 mg (70.4%).

SAE (secondary outcome indicator)

The network meta-analysis for serious adverse events (SAE) included 19 interventions in 24 studies, with heterogeneity test results $\chi 2 = 2.90$, $I^2 = 0\%$, $P = 0.968$ ($P > 0.05$), suggesting homogeneity across studies and justifying a fixed-effects model.

Table 2 SUCRA sorting summary

Treatment	Outcomes					
	HbA1c	Weight	SBP	DBP	AE	SAE
Placebo	0	9.5	2.5	8.3	31.1	60.8
Tir5mg	89.6	88.9	NA	NA	74.4	68.6
Tir10mg	94	94.4	NA	NA	76.6	58.3
Tir15mg	99.7	100	NA	NA	79.3	31.4
Lir0.6mg	43.8	0.9	NA	NA	NA	41.2
Lir1.2mg	80.6	6.5	NA	NA	NA	48.5
Lir1.8mg	79.7	16.9	NA	NA	98.6	60.9
Can100mg	54	48.8	55.1	69.7	56.1	49.1
Can200mg	59.4	52.5	66.1	65.3	66.7	44.3
Can300mg	67.5	78.4	82.1	72.6	56.7	34.2
Ert5mg	24.9	60.2	68.1	46.8	19.9	82.9
Ert15mg	42	60.8	46.3	46.1	32.7	65.6
Emp5mg	20.6	41.3	12.3	15.3	10.7	25.5
Emp10mg	30.2	65.6	28.1	28.4	6.8	66.2
Emp25mg	44.2	61.8	33	46.6	11.4	47.5
Dap5mg	9.4	39.6	76.1	NA	43.4	36.3
Dap10mg	14	60.7	50.3	NA	58.3	28.8
Hen5mg	45.9	30.8	59.8	78.5	56.8	65.2
Hen10mg	50.5	32.3	70	72.5	70.4	34.7

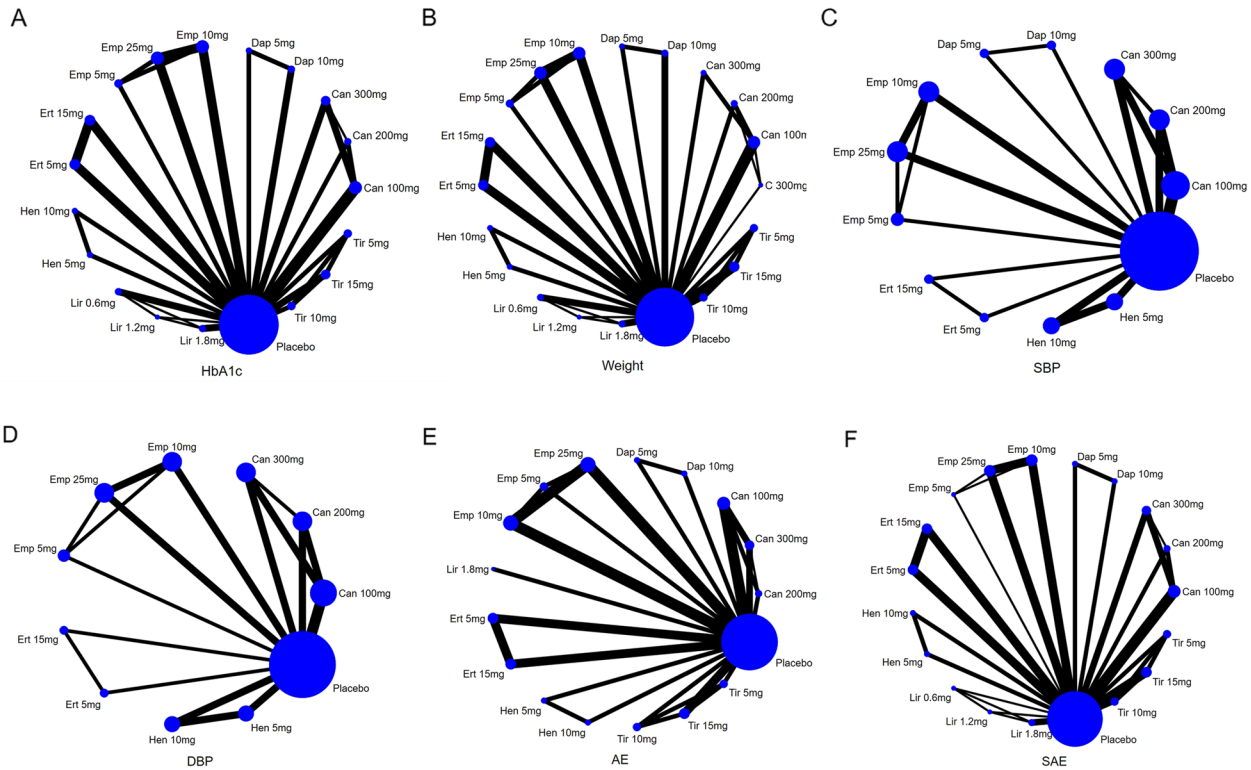

Fig. 3 The specific evaluation structure

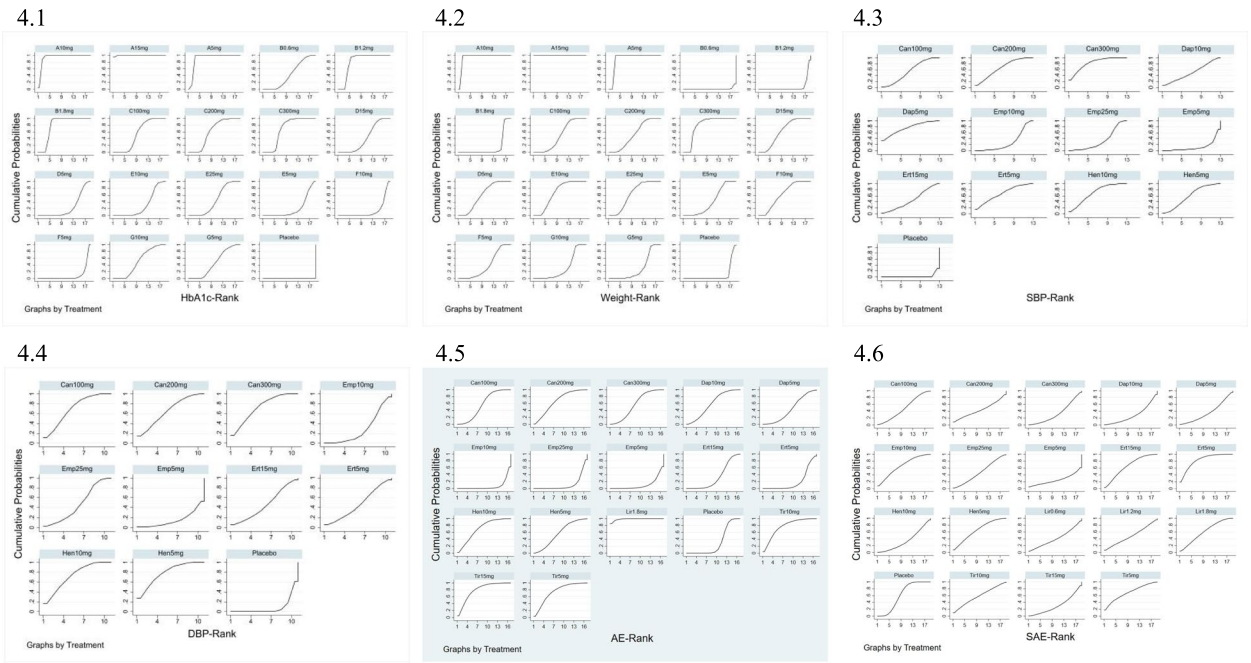

Fig. 4 SUCRA plots for each outcome indicator

Table 3 League table for HbA1c

Placebo	_Hen5mg_	_Hen10mg_	_Dap5mg_	_Dap10mg_	_Emp5mg_	_Emp25mg_	_Emp10mg_	_Ert5mg_	_Ert15mg_	_Can300mg_	_Can200mg_	_Can100mg_	_Lir1.8mg_	_Lir1.2mg_	_Lir0.6mg_	_Tir5mg_	_Tir15mg_	_Tir10mg_
Placebo	-0.83 (-1.06,-)	-0.86 (-1.09,-)	-0.49 (-0.70,-)	-0.55 (-0.75,-)	-0.63 (-0.86,-)	-0.81 (-0.98,-)	-0.71 (-0.88,-)	-0.67 (-0.85,-)	-0.79 (-0.97,-)	-1.00 (-1.18,-)	-0.93 (-1.13,-)	-0.88 (-1.03,-)	-1.23 (-1.41,-)	-1.26 (-1.50,-)	-0.81 (-1.03,-)	-1.82 (-2.11,-)	-2.24 (-2.52,-)	-1.99 (-2.29,-)
0.83 (0.59,1.06)	Hen5mg	-0.03 (-0.26,0.20)	0.34 (0.02,0.66)	0.27 (-0.03,0.58)	0.20 (-0.13,0.53)	0.02 (-0.27,0.31)	0.11 (-0.18,0.40)	0.15 (-0.14,0.44)	0.03 (-0.26,0.33)	-0.17 (-0.47,0.12)	-0.10 (-0.42,0.21)	-0.06 (-0.34,0.22)	-0.40 (-0.70,-)	-0.43 (-0.77,-)	0.02 (-0.30,0.34)	-0.99 (-1.37,-)	-1.41 (-1.78,-)	-1.16 (-1.54,-)
0.86 (0.62,1.09)	0.03 (-0.20,0.26)	Hen10mg	0.37 (0.05,0.69)	0.30 (-0.00,0.61)	0.23 (-0.10,0.56)	0.05 (-0.24,0.34)	0.14 (-0.15,0.44)	0.18 (-0.11,0.48)	0.06 (-0.23,0.36)	-0.14 (-0.44,0.15)	-0.07 (-0.39,0.24)	-0.03 (-0.31,0.26)	-0.38 (-0.67,-)	-0.40 (-0.74,-)	0.05 (-0.28,0.37)	-0.96 (-1.34,-)	-1.38 (-1.75,-)	-1.13 (-1.51,-)
0.49 (0.27,0.70)	-0.34 (-0.66,-)	-0.37 (-0.69,-)	Dap5mg	-0.07 (-0.29,0.15)	-0.14 (-0.46,0.18)	-0.32 (-0.60,-)	-0.23 (-0.50,0.05)	-0.19 (-0.47,0.09)	-0.31 (-0.59,-)	-0.51 (-0.80,-)	-0.44 (-0.74,-)	-0.40 (-0.66,-)	-0.74 (-1.03,-)	-0.77 (-1.10,-)	-0.32 (-0.63,-)	-1.33 (-1.69,-)	-1.75 (-2.11,-)	-1.50 (-1.87,-)
0.55 (0.36,0.75)	-0.27 (-0.58,0.03)	-0.30 (-0.61,0.00)	0.07 (-0.15,0.29)	Dap10mg	-0.07 (-0.37,0.23)	-0.25 (-0.51,0.00)	-0.16 (-0.41,0.10)	-0.12 (-0.38,0.14)	-0.24 (-0.50,0.02)	-0.45 (-0.71,-)	-0.38 (-0.66,-)	-0.33 (-0.57,-)	-0.68 (-0.94,-)	-0.70 (-1.01,-)	-0.25 (-0.55,0.04)	-1.26 (-1.61,-)	-1.69 (-2.02,-)	-1.43 (-1.79,-)
0.63 (0.39,0.86)	-0.20 (-0.53,0.13)	-0.23 (-0.56,0.10)	0.14 (-0.18,0.46)	0.07 (-0.23,0.37)	Emp5mg	-0.18 (-0.41,0.05)	-0.09 (-0.32,0.14)	-0.05 (-0.34,0.24)	-0.17 (-0.46,0.12)	-0.38 (-0.67,-)	-0.30 (-0.61,0.00)	-0.26 (-0.53,0.02)	-0.61 (-0.90,-)	-0.63 (-0.97,-)	-0.18 (-0.50,0.14)	-1.19 (-1.56,-)	-1.61 (-1.98,-)	-1.36 (-1.74,-)
0.81 (0.64,0.98)	-0.02 (-0.31,0.27)	-0.05 (-0.34,0.24)	0.32 (0.04,0.60)	0.25 (0.00,0.51)	0.18 (-0.05,0.41)	Emp25mg	0.09 (-0.08,0.26)	0.13 (-0.11,0.37)	0.01 (-0.23,0.26)	-0.19 (-0.44,0.05)	-0.12 (-0.39,0.14)	-0.08 (-0.30,0.15)	-0.43 (-0.67,-)	-0.45 (-0.75,-)	-0.00 (-0.28,0.28)	-1.01 (-1.35,-)	-1.43 (-1.76,-)	-1.18 (-1.53,-)
0.71 (0.54,0.88)	-0.11 (-0.40,0.18)	-0.14 (-0.44,0.15)	0.23 (-0.05,0.50)	0.16 (-0.10,0.41)	0.09 (-0.14,0.32)	-0.09 (-0.26,0.08)	Emp10mg	0.04 (-0.20,0.28)	-0.08 (-0.32,0.16)	-0.29 (-0.53,-)	-0.22 (-0.48,0.05)	-0.17 (-0.40,0.06)	-0.52 (-0.77,-)	-0.55 (-0.84,-)	-0.10 (-0.38,0.18)	-1.11 (-1.44,-)	-1.53 (-1.85,-)	-1.28 (-1.62,-)
0.67 (0.50,0.85)	-0.15 (-0.44,0.14)	-0.18 (-0.48,0.11)	0.19 (-0.09,0.47)	0.12 (-0.14,0.38)	0.05 (-0.24,0.34)	-0.13 (-0.37,0.11)	-0.04 (-0.28,0.20)	Ert5mg	-0.12 (-0.29,0.05)	-0.33 (-0.58,-)	-0.26 (-0.52,0.01)	-0.21 (-0.44,0.02)	-0.56 (-0.81,-)	-0.59 (-0.88,-)	-0.13 (-0.42,0.15)	-1.15 (-1.48,-)	-1.57 (-1.89,-)	-1.31 (-1.66,-)
0.79 (0.62,0.97)	-0.03 (-0.33,0.26)	-0.06 (-0.36,0.23)	0.31 (0.03,0.59)	0.24 (0.02,0.50)	0.17 (-0.12,0.46)	-0.01 (-0.26,0.23)	0.08 (-0.16,0.32)	0.12 (-0.05,0.29)	Ert15mg	-0.21 (-0.46,0.04)	-0.14 (-0.41,0.13)	-0.09 (-0.32,0.14)	-0.44 (-0.69,-)	-0.47 (-0.76,-)	-0.02 (-0.30,0.27)	-1.03 (-1.36,-)	-1.45 (-1.77,-)	-1.20 (-1.54,-)
1.00 (0.82,1.18)	0.17 (-0.12,0.47)	0.14 (-0.15,0.44)	0.51 (0.23,0.80)	0.45 (0.18,0.71)	0.38 (0.08,0.67)	0.19 (-0.05,0.44)	0.29 (0.04,0.53)	0.33 (0.08,0.58)	0.21 (-0.04,0.46)	Can300mg	0.07 (-0.16,0.30)	0.12 (-0.06,0.30)	-0.23 (-0.49,0.02)	-0.26 (-0.56,0.04)	0.19 (-0.09,0.48)	-0.82 (-1.16,-)	-1.24 (-1.57,-)	-0.99 (-1.34,-)
0.93 (0.73,1.13)	0.10 (-0.21,0.42)	0.07 (-0.24,0.39)	0.44 (0.15,0.74)	0.38 (0.10,0.66)	0.30 (-0.00,0.61)	0.12 (-0.14,0.39)	0.22 (-0.05,0.48)	0.26 (-0.01,0.52)	0.14 (-0.13,0.41)	-0.07 (-0.30,0.16)	Can200mg	0.05 (-0.16,0.25)	-0.30 (-0.57,-)	-0.33 (-0.64,-)	0.12 (-0.18,0.42)	-0.89 (-1.24,-)	-1.31 (-1.65,-)	-1.06 (-1.42,-)
0.88 (0.73,1.03)	0.06 (-0.22,0.34)	0.03 (-0.26,0.31)	0.40 (0.13,0.66)	0.33 (0.08,0.57)	0.26 (-0.02,0.53)	0.08 (-0.15,0.30)	0.17 (-0.06,0.40)	0.21 (-0.02,0.44)	0.09 (-0.14,0.32)	-0.12 (-0.30,0.06)	-0.05 (-0.25,0.16)	Can100mg	-0.35 (-0.58,-)	-0.38 (-0.66,-)	0.07 (-0.19,0.34)	-0.94 (-1.26,-)	-1.36 (-1.67,-)	-1.11 (-1.44,-)
1.23 (1.05,1.41)	0.40 (0.11,0.70)	0.38 (0.08,0.67)	0.74 (0.46,1.03)	0.68 (0.41,0.94)	0.61 (0.31,0.90)	0.43 (0.18,0.67)	0.52 (0.27,0.77)	0.56 (0.31,0.81)	0.44 (0.19,0.69)	0.23 (-0.02,0.49)	0.30 (0.03,0.57)	0.35 (0.11,0.58)	Lir1.8mg	-0.03 (-0.27,0.22)	0.42 (0.19,0.66)	-0.59 (-0.93,-)	-1.01 (-1.34,-)	-0.76 (-1.11,-)
1.26 (1.02,1.50)	0.43 (0.10,0.77)	0.40 (0.06,0.74)	0.77 (0.45,1.10)	0.70 (0.40,1.01)	0.63 (0.30,0.97)	0.45 (0.16,0.75)	0.55 (0.25,0.84)	0.59 (0.29,0.88)	0.47 (0.17,0.76)	0.26 (-0.04,0.56)	0.33 (0.01,0.64)	0.38 (0.09,0.66)	0.03 (-0.22,0.27)	Lir1.2mg	0.45 (0.20,0.70)	-0.56 (-0.94,-)	-0.98 (-1.35,-)	-0.73 (-1.11,-)
0.81 (0.59,1.03)	-0.02 (-0.34,0.30)	-0.05 (-0.37,0.28)	0.32 (0.01,0.63)	0.25 (-0.04,0.55)	0.18 (-0.14,0.50)	0.00 (-0.28,0.28)	0.10 (-0.18,0.38)	0.13 (-0.15,0.42)	0.02 (-0.27,0.30)	-0.19 (-0.48,0.09)	-0.12 (-0.42,0.18)	-0.07 (-0.34,0.19)	-0.42 (-0.66,-)	-0.45 (-0.70,-)	Lir0.6mg	-1.01 (-1.38,-)	-1.43 (-1.79,-)	-1.18 (-1.55,-)
1.82 (1.53,2.11)	0.99 (0.62,1.37)	0.96 (0.59,1.34)	1.33 (0.97,1.69)	1.26 (0.92,1.61)	1.19 (0.82,1.56)	1.01 (0.68,1.35)	1.11 (0.77,1.44)	1.15 (0.81,1.48)	1.03 (0.69,1.36)	0.82 (0.48,1.16)	0.89 (0.54,1.24)	0.94 (0.61,1.26)	0.59 (0.25,0.93)	0.56 (0.18,0.94)	1.01 (0.65,1.38)	Tir5mg	-0.42 (-0.71,-)	-0.17 (-0.46,0.12)
2.24 (1.96,2.52)	1.41 (1.05,1.78)	1.38 (1.02,1.75)	1.75 (1.40,2.11)	1.69 (1.35,2.02)	1.61 (1.25,1.98)	1.43 (1.11,1.76)	1.53 (1.20,1.85)	1.57 (1.24,1.89)	1.45 (1.12,1.77)	1.24 (0.91,1.57)	1.31 (0.97,1.65)	1.36 (1.04,1.67)	1.01 (0.68,1.34)	0.98 (0.61,1.35)	1.43 (1.08,1.79)	0.42 (0.13,0.71)	Tir15mg	0.25 (-0.04,0.55)
1.99 (1.69,2.29)	1.16 (0.78,1.54)	1.13 (0.75,1.51)	1.50 (1.13,1.87)	1.43 (1.08,1.79)	1.36 (0.99,1.74)	1.18 (0.84,1.53)	1.28 (0.93,1.62)	1.31 (0.97,1.66)	1.20 (0.85,1.54)	0.99 (0.64,1.34)	1.06 (0.70,1.42)	1.11 (0.77,1.44)	0.76 (0.41,1.11)	0.73 (0.35,1.11)	1.18 (0.81,1.55)	0.17 (-0.12,0.46)	-0.25 (-0.55,0.04)	Tir10mg

Purple indicates interventions; green signifies statistically significant differences in pairwise comparisons; gray indicates no statistical significance

The league table (Table 8) indicated no significant difference in SAE risk between any interventions and placebo. The top three SUCRA values for SAE likelihood in Table 8 and Fig. 4.6, were ertugliflozin 5 mg (82.9%), tirzepatide 5 mg (68.6%), and empagliflozin 10 mg (66.2%), while the lowest values were tirzepatide 15 mg (31.4%), dapagliflozin 10 mg (28.8%), and empagliflozin 5 mg (25.5%).

Publication bias

Funnel plots were utilized to analyze the differences in average changes across all assessment variables

Table 4 League table for weight

Placebo	_Hen5mg_	_Hen10mg_	_Dap5mg_	_Dap10mg_	_Emp5mg_	_Emp25mg_	_Emp10mg_	_Ert5mg_	_Ert15mg_	_Can300mg_	_Can200mg_	_Can100mg_	_Lir1.8mg_	_Lir1.2mg_	_Lir0.6mg_	_Tir5mg_	_Tir15mg_	_Tir10mg_
Placebo	-1.26 (-1.95,-0.57)	-1.31 (-2.00,-0.61)	-1.53 (-2.15,-0.91)	-1.93 (-2.55,-1.31)	-1.57 (-2.16,-0.98)	-1.94 (-2.39,-1.49)	-2.00 (-2.44,-1.55)	-1.92 (-2.44,-1.39)	-1.93 (-2.44,-1.41)	-2.31 (-2.79,-1.83)	-1.79 (-2.35,-1.23)	-1.73 (-2.13,-1.33)	-0.51 (-1.05,0.04)	0.18 (-0.46,0.81)	0.55 (-0.04,1.15)	-5.38 (-6.65,-4.11)	-8.74 (-9.83,-7.66)	-7.13 (-8.40,-5.86)
1.26 (0.57,1.95)	Hen5mg	-0.04 (-0.73,0.65)	-0.27 (-1.19,0.66)	-0.66 (-1.59,0.27)	-0.30 (-1.21,0.60)	-0.68 (-1.50,0.14)	-0.73 (-1.55,0.09)	-0.65 (-1.52,0.21)	-0.66 (-1.52,0.20)	-1.05 (-1.88,-0.21)	-0.52 (-1.41,0.37)	-0.46 (-1.26,0.33)	0.76 (-0.12,1.64)	1.44 (0.50,2.38)	1.82 (0.90,2.73)	-4.12 (-5.56,-2.67)	-7.48 (-8.76,-6.19)	-5.86 (-7.31,-4.42)
1.31 (0.61,2.00)	0.04 (-0.65,0.73)	Hen10mg	-0.22 (-1.15,0.70)	-0.62 (-1.55,0.31)	-0.26 (-1.17,0.65)	-0.64 (-1.46,0.19)	-0.69 (-1.52,0.13)	-0.61 (-1.48,0.26)	-0.62 (-1.49,0.24)	-1.00 (-1.84,-0.16)	-0.48 (-1.37,0.41)	-0.42 (-1.22,0.38)	0.80 (-0.08,1.68)	1.48 (0.55,2.42)	1.86 (0.95,2.77)	-4.07 (-5.52,-2.63)	-7.44 (-8.72,-6.15)	-5.82 (-7.27,-4.38)
1.53 (0.91,2.15)	0.27 (-0.66,1.19)	0.22 (-0.70,1.15)	Dap5mg	-0.40 (-1.01,0.22)	-0.04 (-0.89,0.82)	-0.41 (-1.18,0.35)	-0.47 (-1.23,0.30)	-0.39 (-1.20,0.42)	-0.40 (-1.21,0.41)	-0.78 (-1.56,0.00)	-0.26 (-1.09,0.58)	-0.20 (-0.93,0.54)	1.02 (0.20,1.84)	1.71 (0.82,2.59)	2.08 (1.23,2.94)	-3.85 (-5.26,-2.44)	-7.21 (-8.46,-5.96)	-5.60 (-7.01,-4.19)
1.93 (1.31,2.55)	0.66 (0.27,1.59)	0.62 (0.31,1.55)	0.40 (-0.22,1.01)	Dap10mg	0.36 (0.50,1.21)	-0.01 (-0.78,0.75)	-0.07 (-0.83,0.69)	0.01 (-0.80,0.82)	-0.00 (-0.81,0.81)	-0.38 (-1.16,0.40)	0.14 (-0.70,0.97)	0.20 (-0.54,0.93)	1.42 (0.59,2.25)	2.10 (1.22,2.99)	2.48 (1.62,3.34)	-3.45 (-4.87,-2.04)	-6.82 (-8.07,-5.57)	-5.20 (-6.61,-3.79)
1.57 (0.98,2.16)	0.30 (-0.60,1.21)	0.26 (-0.65,1.17)	0.04 (-0.82,0.89)	-0.36 (-1.21,0.50)	Emp5mg	-0.37 (-0.96,0.21)	-0.43 (-1.02,0.16)	-0.35 (-1.14,0.44)	-0.36 (-1.14,0.42)	-0.74 (-1.50,0.01)	-0.22 (-1.04,0.59)	-0.16 (-0.87,0.55)	1.06 (0.25,1.87)	1.74 (0.88,2.61)	2.12 (1.28,2.96)	-3.81 (-5.21,-2.41)	-7.18 (-8.41,-5.94)	-5.56 (-6.96,-4.16)
1.94 (1.49,2.39)	0.68 (0.14,1.50)	0.64 (0.19,1.46)	0.41 (-0.35,1.18)	0.01 (-0.75,0.78)	0.37 (-0.21,0.96)	Emp25mg	-0.06 (-0.50,0.39)	0.02 (-0.66,0.71)	0.01 (-0.67,0.70)	-0.37 (-1.02,0.28)	0.15 (-0.56,0.87)	0.21 (-0.39,0.81)	1.43 (0.72,2.14)	2.12 (1.34,2.90)	2.49 (1.74,3.24)	-3.44 (-4.78,-2.10)	-6.80 (-7.97,-5.63)	-5.19 (-6.53,-3.84)
2.00 (1.55,2.44)	0.73 (0.09,1.55)	0.69 (0.13,1.52)	0.47 (-0.30,1.23)	0.07 (-0.69,0.83)	0.43 (-0.16,1.02)	0.06 (-0.39,0.50)	Emp10mg	0.08 (-0.61,0.77)	0.07 (-0.61,0.75)	-0.31 (-0.96,0.34)	0.21 (-0.51,0.93)	0.27 (-0.33,0.87)	1.49 (0.79,2.20)	2.18 (1.40,2.95)	2.55 (1.81,3.29)	-3.38 (-4.73,-2.04)	-6.74 (-7.92,-5.57)	-5.13 (-6.47,-3.79)
1.92 (1.39,2.44)	0.65 (0.21,1.52)	0.61 (0.26,1.48)	0.39 (-0.42,1.20)	-0.01 (-0.82,0.80)	0.35 (-0.44,1.14)	-0.02 (-0.71,0.66)	-0.08 (-0.77,0.61)	Ert5mg	-0.01 (-0.53,0.51)	-0.39 (-1.10,0.32)	0.13 (-0.64,0.90)	0.19 (-0.47,0.85)	1.41 (0.66,2.17)	2.10 (1.27,2.92)	2.47 (1.68,3.26)	-3.46 (-4.84,-2.09)	-6.82 (-8.03,-5.62)	-5.21 (-6.58,-3.84)
1.93 (1.41,2.44)	0.66 (0.20,1.52)	0.62 (0.24,1.49)	0.40 (-0.41,1.21)	0.00 (-0.81,0.81)	0.36 (-0.42,1.14)	-0.01 (-0.70,0.67)	-0.07 (-0.75,0.61)	0.01 (-0.51,0.53)	Ert15mg	-0.38 (-1.09,0.32)	0.14 (-0.63,0.90)	0.20 (-0.46,0.85)	1.42 (0.66,2.18)	2.10 (1.28,2.93)	2.48 (1.69,3.27)	-3.45 (-4.82,-2.08)	-6.82 (-8.02,-5.61)	-5.20 (-6.57,-3.83)
2.31 (1.83,2.79)	1.05 (0.21,1.88)	1.00 (0.16,1.84)	0.78 (0.00,1.56)	0.38 (-0.40,1.16)	0.74 (0.01,1.50)	0.37 (-0.28,1.02)	0.31 (-0.34,0.96)	0.39 (-0.32,1.10)	0.38 (-0.32,1.09)	Can300mg	0.52 (-0.10,1.15)	0.58 (0.09,1.07)	1.80 (1.08,2.52)	2.49 (1.70,3.28)	2.86 (2.10,3.62)	-3.07 (-4.43,-1.71)	-6.43 (-7.62,-5.25)	-4.82 (-6.17,-3.46)
1.79 (1.23,2.35)	0.52 (0.37,1.41)	0.48 (0.41,1.37)	0.26 (-0.58,1.09)	-0.14 (-0.97,0.70)	0.22 (-0.59,1.04)	-0.15 (-0.87,0.56)	-0.21 (-0.93,0.51)	-0.13 (-0.90,0.64)	-0.14 (-0.90,0.63)	-0.52 (-1.15,0.10)	Can200mg	0.06 (-0.50,0.62)	1.28 (0.51,2.06)	1.97 (1.12,2.81)	2.34 (1.52,3.15)	-3.59 (-4.98,-2.20)	-6.96 (-8.18,-5.73)	-5.34 (-6.73,-3.95)
1.73 (1.33,2.13)	0.46 (0.33,1.26)	0.42 (0.38,1.22)	0.20 (-0.54,0.93)	-0.20 (-0.93,0.54)	0.16 (-0.55,0.87)	-0.21 (-0.81,0.39)	-0.27 (-0.87,0.33)	-0.19 (-0.85,0.47)	-0.20 (-0.85,0.46)	-0.58 (-1.07,-0.09)	-0.06 (-0.62,0.50)	Can100mg	1.22 (0.55,1.89)	1.91 (1.16,2.65)	2.28 (1.57,2.99)	-3.65 (-4.98,-2.32)	-7.01 (-8.17,-5.86)	-5.40 (-6.73,-4.07)
0.51 (0.04,1.05)	-0.76 (-1.64,0.12)	-0.80 (-1.68,0.08)	-1.02 (-1.84,-0.20)	-1.42 (-2.25,-0.59)	-1.06 (-1.87,-0.25)	-1.43 (-2.14,-0.72)	-1.49 (-2.20,-0.79)	-1.41 (-2.17,-0.66)	-1.42 (-2.18,-0.66)	-1.80 (-2.52,-1.08)	-1.28 (-2.06,-0.51)	-1.22 (-1.89,-0.55)	Lir1.8mg	0.68 (0.05,1.32)	1.06 (0.44,1.67)	-4.87 (-6.26,-3.48)	-8.24 (-9.45,-7.02)	-6.62 (-8.00,-5.24)
-0.18 (-0.81,0.46)	-1.44 (-2.38,-0.50)	-1.48 (-2.42,-0.55)	-1.71 (-2.59,-0.82)	-2.10 (-2.99,-1.22)	-1.74 (-2.61,-0.88)	-2.12 (-2.90,-1.34)	-2.18 (-2.95,-1.40)	-2.10 (-2.92,-1.27)	-2.10 (-2.93,-1.28)	-2.49 (-3.28,-1.70)	-1.97 (-2.81,-1.12)	-1.91 (-2.65,-1.16)	-0.68 (-1.32,-0.05)	Lir1.2mg	0.37 (-0.28,1.03)	-5.56 (-6.98,-4.13)	-8.92 (-10.18,-)	-7.31 (-8.72,-5.89)
-0.55 (-1.15,0.04)	-1.82 (-2.73,-0.90)	-1.86 (-2.77,-0.95)	-2.08 (-2.94,-1.23)	-2.48 (-3.34,-1.62)	-2.12 (-2.96,-1.28)	-2.49 (-3.24,-1.74)	-2.55 (-3.29,-1.81)	-2.47 (-3.26,-1.68)	-2.48 (-3.27,-1.69)	-2.86 (-3.62,-2.10)	-2.34 (-3.15,-1.52)	-2.28 (-2.99,-1.57)	-1.06 (-1.67,-0.44)	-0.37 (-1.03,0.28)	Lir0.6mg	-5.93 (-7.34,-4.52)	-9.29 (-10.53,-	-7.68 (-9.08,-6.28)
5.38 (4.11,6.65)	4.12 (2.67,5.56)	4.07 (2.63,5.52)	3.85 (2.44,5.26)	3.45 (2.04,4.87)	3.81 (2.41,5.21)	3.44 (2.10,4.78)	3.38 (2.04,4.73)	3.46 (2.09,4.84)	3.45 (2.08,4.82)	3.07 (1.71,4.43)	3.59 (2.20,4.98)	3.65 (2.32,4.98)	4.87 (3.48,6.26)	5.56 (4.13,6.98)	5.93 (4.52,7.34)	Tir5mg	-3.36 (-4.60,-2.13)	-1.75 (-3.03,-0.47)
8.74 (7.66,9.83)	7.48 (6.19,8.76)	7.44 (6.15,8.72)	7.21 (5.96,8.46)	6.82 (5.57,8.07)	7.18 (5.94,8.41)	6.80 (5.63,7.97)	6.74 (5.57,7.92)	6.82 (5.62,8.03)	6.82 (5.61,8.02)	6.43 (5.25,7.62)	6.96 (5.73,8.18)	7.01 (5.86,8.17)	8.24 (7.02,9.45)	8.92 (7.66,10.18	9.29 (8.06,10.53	3.36 (2.13,4.60)	Tir15mg	1.61 (0.38,2.85)
7.13 (5.86,8.40)	5.86 (4.42,7.31)	5.82 (4.38,7.27)	5.60 (4.19,7.01)	5.20 (3.79,6.61)	5.56 (4.16,6.96)	5.19 (3.84,6.53)	5.13 (3.79,6.47)	5.21 (3.84,6.58)	5.20 (3.83,6.57)	4.82 (3.46,6.17)	5.34 (3.95,6.73)	5.40 (4.07,6.73)	6.62 (5.24,8.00)	7.31 (5.89,8.72)	7.68 (6.28,9.08)	1.75 (0.47,3.03)	-1.61 (-2.85,-0.38)	Tir10mg

Purple indicates interventions; green signifies statistically significant differences in pairwise comparisons; gray indicates no statistical significance

Table 5 League table for SBP

Placebo	_Hen5mg_	_Hen10mg_	_Ert5mg_	_Ert15mg_	_Emp5mg_	_Emp25mg_	_Emp10mg_	_Dap5mg_	_Dap10mg_	_Can300mg_	_Can200mg_	_Can100mg_
Placebo	-4.85 (-6.63,-3.07)	-5.33 (-7.14,-3.52)	-5.30 (-8.09,-2.51)	-4.10 (-6.89,-1.31)	-1.11 (-4.95,2.73)	-3.36 (-5.60,-1.12)	-3.04 (-5.27,-0.80)	-5.90 (-9.33,-2.47)	-4.30 (-7.72,-0.88)	-5.96 (-7.96,-3.96)	-5.17 (-7.41,-2.92)	-4.65 (-6.42,-2.88)
4.85 (3.07,6.63)	Hen5mg	-0.48 (-2.28,1.32)	-0.45 (-3.76,2.86)	0.75 (-2.56,4.06)	3.74 (-0.49,7.97)	1.49 (-1.36,4.35)	1.81 (-1.05,4.68)	-1.05 (-4.91,2.81)	0.55 (-3.31,4.41)	-1.11 (-3.79,1.57)	-0.32 (-3.18,2.55)	0.20 (-2.32,2.71)
5.33 (3.52,7.14)	0.48 (-1.32,2.28)	Hen10mg	0.03 (-3.29,3.36)	1.23 (-2.09,4.56)	4.22 (-0.02,8.46)	1.97 (-0.91,4.86)	2.29 (-0.57,5.16)	-0.57 (-4.44,3.31)	1.03 (-2.84,4.90)	-0.63 (-3.31,2.06)	0.17 (-2.70,3.03)	0.68 (-1.84,3.20)
5.30 (2.51,8.09)	0.45 (-2.86,3.76)	-0.03 (-3.36,3.29)	Ert5mg	1.20 (-1.54,3.94)	4.19 (-0.55,8.94)	1.94 (-1.63,5.52)	2.26 (-1.31,5.84)	-0.60 (-5.02,3.82)	1.00 (-3.42,5.42)	-0.66 (-4.09,2.77)	0.13 (-3.45,3.71)	0.65 (-2.66,3.95)
4.10 (1.31,6.89)	-0.75 (-4.06,2.56)	-1.23 (-4.56,2.09)	-1.20 (-3.94,1.54)	Ert15mg	2.99 (-1.75,7.74)	0.74 (-2.83,4.32)	1.06 (-2.51,4.64)	-1.80 (-6.22,2.62)	-0.20 (-4.62,4.22)	-1.86 (-5.29,1.57)	-1.07 (-4.65,2.51)	-0.55 (-3.86,2.75)
1.11 (-2.73,4.95)	-3.74 (-7.97,0.49)	-4.22 (-8.46,0.02)	-4.19 (-8.94,0.55)	-2.99 (-7.74,1.75)	Emp5mg	-2.25 (-6.10,1.60)	-1.93 (-5.75,1.90)	-4.79 (-9.94,0.35)	-3.19 (-8.33,1.95)	-4.85 (-9.17,-0.53)	-4.06 (-8.50,0.38)	-3.54 (-7.77,0.68)
3.36 (1.12,5.60)	-1.49 (-4.35,1.36)	-1.97 (-4.86,0.91)	-1.94 (-5.52,1.63)	-0.74 (-4.32,2.83)	2.25 (-1.60,6.10)	Emp25mg	0.32 (-1.93,2.57)	-2.54 (-6.64,1.55)	-0.94 (-5.03,3.15)	-2.60 (-5.61,0.40)	-1.81 (-4.98,1.36)	-1.30 (-4.15,1.56)
3.04 (0.80,5.27)	-1.81 (-4.68,1.05)	-2.29 (-5.16,0.57)	-2.26 (-5.84,1.31)	-1.06 (-4.64,2.51)	1.93 (-1.90,5.75)	-0.32 (-2.57,1.93)	Emp10mg	-2.86 (-6.96,1.23)	-1.26 (-5.35,2.83)	-2.92 (-5.91,0.06)	-2.13 (-5.28,1.02)	-1.62 (-4.45,1.22)
5.90 (2.47,9.33)	1.05 (-2.81,4.91)	0.57 (-3.31,4.44)	0.60 (-3.82,5.02)	1.80 (-2.62,6.22)	4.79 (-0.35,9.94)	2.54 (-1.55,6.64)	2.86 (-1.23,6.96)	Dap5mg	1.60 (-2.00,5.20)	-0.06 (-4.03,3.90)	0.73 (-3.36,4.83)	1.25 (-2.61,5.10)
4.30 (0.88,7.72)	-0.55 (-4.41,3.31)	-1.03 (-4.90,2.84)	-1.00 (-5.42,3.42)	0.20 (-4.22,4.62)	3.19 (-1.95,8.33)	0.94 (-3.15,5.03)	1.26 (-2.83,5.35)	-1.60 (-5.20,2.00)	Dap10mg	-1.66 (-5.62,2.30)	-0.87 (-4.96,3.23)	-0.35 (-4.21,3.50)
5.96 (3.96,7.96)	1.11 (-1.57,3.79)	0.63 (-2.06,3.31)	0.66 (-2.77,4.09)	1.86 (-1.57,5.29)	4.85 (0.53,9.17)	2.60 (-0.40,5.61)	2.92 (-0.06,5.91)	0.06 (-3.90,4.03)	1.66 (-2.30,5.62)	Can300mg	0.80 (-1.73,3.32)	1.31 (-0.68,3.30)
5.17 (2.92,7.41)	0.32 (-2.55,3.18)	-0.17 (-3.03,2.70)	-0.13 (-3.71,3.45)	1.07 (-2.51,4.65)	4.06 (-0.38,8.50)	1.81 (-1.36,4.98)	2.13 (-1.02,5.28)	-0.73 (-4.83,3.36)	0.87 (-3.23,4.96)	-0.80 (-3.32,1.73)	Can200mg	0.51 (-1.72,2.75)
4.65 (2.88,6.42)	-0.20 (-2.71,2.32)	-0.68 (-3.20,1.84)	-0.65 (-3.95,2.66)	0.55 (-2.75,3.86)	3.54 (-0.68,7.77)	1.30 (-1.56,4.15)	1.62 (-1.22,4.45)	-1.25 (-5.10,2.61)	0.35 (-3.50,4.21)	-1.31 (-3.30,0.68)	-0.51 (-2.75,1.72)	Can100mg

Purple indicates interventions; green signifies statistically significant differences in pairwise comparisons; gray indicates no statistical significance

between the treatment and placebo groups. Most of the data points in all of the funnel plots were situated on either side of the vertical axis. They were fundamentally symmetric and may have some level of publication bias. Certain instances exhibit varying levels of asymmetry, indicating the potential presence of publication bias (Fig. 5).

Quality assessment of included studies

Of the 28 studies, the majority were judged to have low risk of bias in random sequence generation and allocation concealment, with 16 studies meeting these criteria. However, 12 studies presented unclear risk of bias

Table 6 League table for DBP

Placebo	_Hen5mg_	_Hen10mg_	_Ert5mg_	_Ert15mg_	_Emp5mg_	_Emp25mg_	_Emp10mg_	_Can300mg_	_Can200mg_	_Can100mg_
Placebo	−2.46 (−3.82, −1.10)	−2.27 (−3.59, −0.95)	−1.40 (−3.31, 0.51)	−1.40 (−3.33, 0.53)	0.06 (−2.32, 2.44)	−1.39 (−2.80, 0.03)	−0.81 (−2.23, 0.62)	−2.26 (−3.61, −0.91)	−2.04 (−3.60, −0.48)	−2.17 (−3.40, −0.94)
2.46 (1.10, 3.82)	Hen5mg	0.19 (−1.17, 1.55)	1.06 (−1.28, 3.40)	1.06 (−1.30, 3.42)	2.52 (0.22, 5.25)	1.07 (−0.89, 3.03)	1.65 (−0.31, 3.62)	0.20 (−1.72, 2.11)	0.42 (−1.64, 2.49)	0.29 (−1.54, 2.12)
2.27 (0.95, 3.59)	−0.19 (−1.55, 1.17)	Hen10mg	0.87 (−1.45, 3.19)	0.87 (−1.47, 3.21)	2.33 (−0.40, 5.05)	0.88 (−1.06, 2.82)	1.46 (−0.48, 3.41)	0.01 (−1.89, 1.90)	0.23 (−1.82, 2.28)	0.10 (−1.71, 1.91)
1.40 (−0.51, 3.31)	−1.06 (−3.40, 1.28)	−0.87 (−3.19, 1.45)	Ert5mg	0.00 (−1.87, 1.87)	1.46 (−1.59, 4.51)	0.01 (−2.36, 2.39)	0.59 (−1.79, 2.97)	−0.86 (−3.20, 1.47)	−0.64 (−3.10, 1.83)	−0.77 (−3.04, 1.50)
1.40 (−0.53, 3.33)	−1.06 (−3.42, 1.30)	−0.87 (−3.21, 1.47)	−0.00 (−1.87, 1.87)	Ert15mg	1.46 (−1.61, 4.52)	0.01 (−2.39, 2.41)	0.59 (−1.81, 3.00)	−0.86 (−3.22, 1.50)	−0.64 (−3.12, 1.85)	−0.77 (−3.06, 1.52)
−0.06 (−2.44, 2.32)	−2.52 (−5.25, 0.22)	−2.33 (−5.05, 0.40)	−1.46 (−4.51, 1.59)	−1.46 (−4.52, 1.61)	Emp5mg	−1.45 (−3.83, 0.94)	−0.86 (−3.23, 1.51)	−2.32 (−5.05, 0.41)	−2.09 (−4.93, 0.74)	−2.23 (−4.90, 0.44)
1.39 (−0.03, 2.80)	−1.07 (−3.03, 0.89)	−0.88 (−2.82, 1.06)	−0.01 (−2.39, 2.36)	−0.01 (−2.41, 2.39)	1.45 (−0.94, 3.83)	Emp25mg	0.58 (−0.84, 2.01)	−0.87 (−2.83, 1.08)	−0.65 (−2.76, 1.46)	−0.78 (−2.66, 1.09)
0.81 (−0.62, 2.23)	−1.65 (−3.62, 0.31)	−1.46 (−3.41, 0.48)	−0.59 (−2.97, 1.79)	−0.59 (−3.00, 1.81)	0.86 (−1.51, 3.23)	−0.58 (−2.01, 0.84)	Emp10mg	−1.46 (−3.40, 0.49)	−1.23 (−3.32, 0.85)	−1.37 (−3.22, 0.49)
2.26 (0.91, 3.61)	−0.20 (−2.11, 1.72)	−0.01 (−1.90, 1.89)	0.86 (−1.47, 3.20)	0.86 (−1.50, 3.22)	2.32 (−0.41, 5.05)	0.87 (−1.08, 2.83)	1.46 (−0.49, 3.40)	Can300mg	0.23 (−1.49, 1.94)	0.09 (−1.26, 1.44)
2.04 (0.48, 3.60)	−0.42 (−2.49, 1.64)	−0.23 (−2.28, 1.82)	0.64 (−1.83, 3.10)	0.64 (−1.85, 3.12)	2.09 (−0.74, 4.93)	0.65 (−1.46, 2.76)	1.23 (−0.85, 3.32)	−0.23 (−1.94, 1.49)	Can200mg	−0.13 (−1.68, 1.41)
2.17 (0.94, 3.40)	−0.29 (−2.12, 1.54)	−0.10 (−1.91, 1.71)	0.77 (−1.50, 3.04)	0.77 (−1.52, 3.06)	2.23 (−0.44, 4.90)	0.78 (−1.09, 2.66)	1.37 (−0.49, 3.22)	−0.09 (−1.44, 1.26)	0.13 (−1.41, 1.68)	Can100mg

Purple indicates interventions; green signifies statistically significant differences in pairwise comparisons; gray indicates no statistical significance

Table 7 League table for AE

Placebo	_Tir5mg_	_Tir10mg_	_Tir15mg_	_Lir1.8mg_	_Can100mg_	_Can200mg_	_Can300mg_	_Ert5mg_	_Ert15mg_	_Emp5mg_	_Emp10mg_	_Emp25mg_	_Dap5mg_	_Dap10mg_	_Hen5mg_	_Hen10mg_
Placebo	1.56 (0.98, 2.47)	1.60 (1.00, 2.57)	1.66 (1.06, 2.60)	2.57 (1.78, 3.70)	1.25 (0.95, 1.64)	1.40 (0.92, 2.13)	1.26 (0.92, 1.73)	0.90 (0.71, 1.13)	1.01 (0.80, 1.27)	0.76 (0.51, 1.13)	0.75 (0.57, 0.98)	0.79 (0.61, 1.04)	1.11 (0.77, 1.60)	1.27 (0.88, 1.83)	1.26 (0.85, 1.88)	1.45 (0.96, 2.19)
0.64 (0.40, 1.02)	Tir5mg	1.03 (0.63, 1.67)	1.07 (0.66, 1.72)	1.65 (0.91, 2.98)	0.81 (0.47, 1.38)	0.90 (0.48, 1.68)	0.81 (0.46, 1.42)	0.58 (0.34, 0.97)	0.65 (0.38, 1.09)	0.49 (0.27, 0.90)	0.48 (0.28, 0.82)	0.51 (0.30, 0.87)	0.72 (0.40, 1.29)	0.82 (0.45, 1.47)	0.81 (0.44, 1.50)	0.93 (0.50, 1.73)
0.63 (0.39, 1.00)	0.97 (0.60, 1.58)	Tir10mg	1.04 (0.64, 1.68)	1.61 (0.88, 2.93)	0.78 (0.45, 1.36)	0.88 (0.47, 1.65)	0.79 (0.44, 1.39)	0.56 (0.33, 0.95)	0.63 (0.37, 1.07)	0.48 (0.26, 0.88)	0.47 (0.27, 0.81)	0.50 (0.29, 0.86)	0.70 (0.38, 1.26)	0.79 (0.44, 1.44)	0.79 (0.42, 1.47)	0.91 (0.48, 1.70)
0.60 (0.38, 0.94)	0.94 (0.58, 1.51)	0.96 (0.60, 1.56)	Tir15mg	1.55 (0.87, 2.76)	0.75 (0.44, 1.28)	0.85 (0.46, 1.56)	0.76 (0.44, 1.32)	0.54 (0.33, 0.90)	0.61 (0.36, 1.01)	0.46 (0.25, 0.84)	0.45 (0.27, 0.76)	0.48 (0.28, 0.81)	0.67 (0.38, 1.19)	0.76 (0.43, 1.36)	0.76 (0.41, 1.39)	0.87 (0.47, 1.61)
0.39 (0.27, 0.56)	0.61 (0.34, 1.09)	0.62 (0.34, 1.13)	0.65 (0.36, 1.15)	Lir1.8mg	0.49 (0.31, 0.77)	0.55 (0.31, 0.95)	0.49 (0.30, 0.79)	0.35 (0.23, 0.54)	0.39 (0.25, 0.60)	0.30 (0.17, 0.51)	0.29 (0.19, 0.46)	0.31 (0.20, 0.49)	0.43 (0.26, 0.73)	0.49 (0.29, 0.83)	0.49 (0.29, 0.84)	0.56 (0.33, 0.98)
0.80 (0.61, 1.05)	1.24 (0.72, 2.13)	1.28 (0.74, 2.21)	1.33 (0.78, 2.26)	2.05 (1.30, 3.23)	Can100mg	1.12 (0.74, 1.70)	1.01 (0.74, 1.37)	0.72 (0.50, 1.03)	0.80 (0.56, 1.15)	0.61 (0.38, 0.98)	0.60 (0.41, 0.87)	0.63 (0.43, 0.93)	0.89 (0.56, 1.40)	1.01 (0.64, 1.60)	1.01 (0.62, 1.63)	1.16 (0.71, 1.89)
0.71 (0.47, 1.08)	1.11 (0.59, 2.07)	1.14 (0.61, 2.14)	1.18 (0.64, 2.19)	1.83 (1.05, 3.19)	0.89 (0.59, 1.35)	Can200mg	0.90 (0.57, 1.42)	0.64 (0.40, 1.03)	0.72 (0.44, 1.16)	0.54 (0.31, 0.96)	0.53 (0.32, 0.87)	0.57 (0.34, 0.93)	0.79 (0.46, 1.38)	0.90 (0.52, 1.58)	0.90 (0.50, 1.60)	1.03 (0.57, 1.85)
0.79 (0.58, 1.09)	1.24 (0.70, 2.17)	1.27 (0.72, 2.25)	1.32 (0.76, 2.29)	2.04 (1.26, 3.31)	0.99 (0.73, 1.36)	1.11 (0.71, 1.76)	Can300mg	0.71 (0.48, 1.06)	0.80 (0.54, 1.18)	0.61 (0.37, 1.00)	0.59 (0.39, 0.90)	0.63 (0.42, 0.95)	0.88 (0.55, 1.43)	1.01 (0.62, 1.63)	1.00 (0.60, 1.67)	1.15 (0.69, 1.93)
1.11 (0.88, 1.41)	1.73 (1.03, 2.91)	1.78 (1.05, 3.02)	1.85 (1.11, 3.07)	2.86 (1.85, 4.42)	1.39 (0.98, 1.99)	1.56 (0.97, 2.52)	1.40 (0.95, 2.08)	Ert5mg	1.12 (0.89, 1.41)	0.85 (0.54, 1.34)	0.83 (0.58, 1.19)	0.88 (0.62, 1.26)	1.24 (0.80, 1.91)	1.41 (0.92, 2.18)	1.41 (0.89, 2.23)	1.61 (1.01, 2.59)
0.99 (0.79, 1.26)	1.55 (0.92, 2.60)	1.59 (0.94, 2.70)	1.65 (0.99, 2.75)	2.56 (1.65, 3.95)	1.25 (0.87, 1.78)	1.40 (0.87, 2.25)	1.25 (0.85, 1.85)	0.89 (0.71, 1.13)	Ert15mg	0.76 (0.48, 1.20)	0.74 (0.52, 1.06)	0.79 (0.55, 1.13)	1.11 (0.72, 1.71)	1.26 (0.82, 1.95)	1.26 (0.79, 1.99)	1.44 (0.90, 2.31)
1.31 (0.88, 1.95)	2.04 (1.11, 3.75)	2.10 (1.13, 3.89)	2.18 (1.20, 3.96)	3.37 (1.97, 5.78)	1.64 (1.02, 2.65)	1.84 (1.04, 3.27)	1.65 (1.00, 2.74)	1.18 (0.74, 1.86)	1.32 (0.83, 2.09)	Emp5mg	0.98 (0.66, 1.46)	1.04 (0.70, 1.55)	1.46 (0.85, 2.50)	1.67 (0.97, 2.85)	1.66 (0.94, 2.91)	1.90 (1.07, 3.36)
1.34 (1.02, 1.74)	2.08 (1.22, 3.55)	2.14 (1.24, 3.68)	2.22 (1.32, 3.74)	3.43 (2.18, 5.40)	1.67 (1.14, 2.45)	1.88 (1.14, 3.08)	1.68 (1.11, 2.54)	1.20 (0.84, 1.71)	1.34 (0.94, 1.92)	1.02 (0.69, 1.52)	Emp10mg	1.06 (0.81, 1.39)	1.49 (0.95, 2.33)	1.70 (1.08, 2.67)	1.69 (1.04, 2.73)	1.94 (1.19, 3.16)
1.26 (0.96, 1.65)	1.96 (1.14, 3.36)	2.01 (1.16, 3.49)	2.09 (1.23, 3.56)	3.24 (2.06, 5.10)	1.58 (1.08, 2.31)	1.77 (1.08, 2.90)	1.59 (1.05, 2.40)	1.13 (0.79, 1.61)	1.27 (0.89, 1.81)	0.96 (0.64, 1.43)	0.94 (0.72, 1.23)	Emp25mg	1.40 (0.89, 2.20)	1.60 (1.02, 2.52)	1.59 (0.98, 2.57)	1.83 (1.12, 2.98)
0.90 (0.62, 1.29)	1.40 (0.78, 2.52)	1.44 (0.79, 2.61)	1.49 (0.84, 2.66)	2.31 (1.38, 3.87)	1.13 (0.71, 1.77)	1.26 (0.73, 2.19)	1.13 (0.70, 1.83)	0.81 (0.52, 1.24)	0.90 (0.59, 1.39)	0.69 (0.40, 1.17)	0.67 (0.43, 1.06)	0.71 (0.45, 1.12)	Dap5mg	1.14 (0.79, 1.65)	1.13 (0.66, 1.95)	1.30 (0.75, 2.26)
0.79 (0.55, 1.14)	1.23 (0.68, 2.21)	1.26 (0.69, 2.29)	1.31 (0.73, 2.33)	2.02 (1.21, 3.40)	0.99 (0.63, 1.56)	1.11 (0.63, 1.93)	0.99 (0.61, 1.61)	0.71 (0.46, 1.09)	0.79 (0.51, 1.22)	0.60 (0.35, 1.03)	0.59 (0.37, 0.93)	0.63 (0.40, 0.99)	0.88 (0.61, 1.27)	Dap10mg	0.99 (0.58, 1.71)	1.14 (0.66, 1.98)
0.79 (0.53, 1.18)	1.23 (0.67, 2.28)	1.27 (0.68, 2.36)	1.32 (0.72, 2.41)	2.04 (1.18, 3.50)	0.99 (0.61, 1.61)	1.11 (0.62, 1.98)	1.00 (0.60, 1.66)	0.71 (0.45, 1.13)	0.80 (0.50, 1.26)	0.60 (0.34, 1.06)	0.59 (0.37, 0.96)	0.63 (0.39, 1.02)	0.88 (0.51, 1.51)	1.01 (0.58, 1.73)	Hen5mg	1.15 (0.76, 1.74)
0.69 (0.46, 1.04)	1.07 (0.58, 2.00)	1.10 (0.59, 2.07)	1.15 (0.62, 2.11)	1.77 (1.02, 3.07)	0.86 (0.53, 1.41)	0.97 (0.54, 1.74)	0.87 (0.52, 1.46)	0.62 (0.39, 0.99)	0.69 (0.43, 1.11)	0.53 (0.30, 0.93)	0.52 (0.32, 0.84)	0.55 (0.34, 0.89)	0.77 (0.44, 1.33)	0.88 (0.51, 1.52)	0.87 (0.57, 1.32)	Hen10mg

Purple indicates interventions; green signifies statistically significant differences in pairwise comparisons; gray indicates no statistical significance

Table 8 League table for SAE

Placebo	_Tir5mg_	_Tir10mg_	_Tir15mg_	_Lir0_6mg_	_Lir1_2mg_	_Lir1_8mg_	_Can100mg_	_Can200mg_	_Can300mg_	_Ert5mg_	_Ert15mg_	_Emp5mg_	_Emp10mg_	_Emp25mg_	_Dap5mg_	_Dap10mg_	_Hen5mg_	_Hen10mg_
Placebo	1.28 (0.36, 4.50)	0.98 (0.27, 3.53)	0.56 (0.17, 1.84)	0.65 (0.17, 2.44)	0.77 (0.21, 2.79)	0.98 (0.41, 2.35)	0.83 (0.39, 1.77)	0.71 (0.33, 1.53)	0.62 (0.26, 1.50)	1.55 (0.79, 3.06)	1.13 (0.55, 2.32)	0.36 (0.04, 3.27)	1.15 (0.49, 2.68)	0.82 (0.33, 2.02)	0.62 (0.22, 1.77)	0.52 (0.18, 1.55)	1.90 (0.86, 4.19)	0.85 (0.34, 2.10)
0.78 (0.22, 2.76)	Tir5mg	0.77 (0.20, 2.97)	0.44 (0.11, 1.82)	0.51 (0.08, 3.21)	0.60 (0.10, 3.71)	0.77 (0.16, 3.61)	0.65 (0.15, 2.83)	0.56 (0.07, 4.56)	0.49 (0.11, 2.26)	1.22 (0.29, 5.12)	0.89 (0.21, 3.78)	0.28 (0.02, 3.59)	0.90 (0.20, 4.09)	0.64 (0.14, 3.02)	0.49 (0.10, 2.51)	0.41 (0.08, 2.16)	1.49 (0.33, 6.59)	0.66 (0.14, 3.14)
1.02 (0.28, 3.67)	1.30 (0.34, 5.02)	Tir10mg	0.57 (0.14, 2.31)	0.66 (0.10, 4.17)	0.78 (0.13, 4.83)	1.00 (0.21, 4.71)	0.85 (0.19, 3.75)	0.73 (0.09, 6.01)	0.63 (0.13, 3.00)	1.59 (0.37, 6.75)	1.16 (0.27, 5.01)	0.37 (0.03, 4.71)	1.17 (0.25, 5.43)	0.84 (0.17, 4.00)	0.64 (0.12, 3.32)	0.54 (0.10, 2.86)	1.93 (0.43, 8.72)	0.86 (0.18, 4.15)
1.78 (0.54, 5.84)	2.27 (0.55, 9.41)	1.75 (0.43, 7.04)	Tir15mg	1.15 (0.19, 6.85)	1.36 (0.23, 7.92)	1.74 (0.40, 7.64)	1.48 (0.36, 6.05)	1.27 (0.16, 9.94)	1.11 (0.25, 4.86)	2.77 (0.71, 10.87)	2.02 (0.50, 8.09)	0.64 (0.05, 7.86)	2.04 (0.47, 8.80)	1.46 (0.33, 6.48)	1.11 (0.23, 5.40)	0.93 (0.19, 4.66)	3.38 (0.81, 14.09)	1.51 (0.34, 6.73)
1.55 (0.41, 5.85)	1.98 (0.31, 12.53)	1.52 (0.24, 9.63)	0.87 (0.15, 5.18)	Lir0.6mg	1.19 (0.34, 4.08)	1.52 (0.49, 4.65)	1.29 (0.28, 5.97)	1.11 (0.13, 9.42)	0.96 (0.19, 4.78)	2.41 (0.55, 10.58)	1.76 (0.39, 7.98)	0.56 (0.04, 7.31)	1.78 (0.36, 8.72)	1.27 (0.25, 6.35)	0.97 (0.18, 5.24)	0.81 (0.15, 4.50)	2.94 (0.62, 13.80)	1.31 (0.26, 6.57)
1.31 (0.36, 4.76)	1.67 (0.27, 10.31)	1.28 (0.21, 7.92)	0.73 (0.13, 4.26)	0.84 (0.25, 2.90)	Lir1.2mg	1.28 (0.43, 3.76)	1.08 (0.24, 4.88)	0.93 (0.11, 7.77)	0.81 (0.17, 3.92)	2.03 (0.48, 8.65)	1.48 (0.34, 6.53)	0.47 (0.04, 6.06)	1.50 (0.31, 7.14)	1.07 (0.22, 5.20)	0.82 (0.15, 4.30)	0.69 (0.13, 3.69)	2.48 (0.54, 11.30)	1.11 (0.23, 5.38)
1.02 (0.43, 2.45)	1.30 (0.28, 6.14)	1.00 (0.21, 4.73)	0.57 (0.13, 2.51)	0.66 (0.21, 2.02)	0.78 (0.27, 2.30)	Lir1.8mg	0.85 (0.26, 2.71)	0.72 (0.11, 4.85)	0.64 (0.18, 2.22)	1.59 (0.53, 4.75)	1.16 (0.37, 3.61)	0.37 (0.03, 3.94)	1.17 (0.34, 4.02)	0.84 (0.24, 2.95)	0.64 (0.16, 2.49)	0.54 (0.13, 2.15)	1.94 (0.59, 6.31)	0.87 (0.25, 3.06)
1.20 (0.56, 2.57)	1.54 (0.35, 6.68)	1.18 (0.27, 5.23)	0.68 (0.17, 2.77)	0.78 (0.17, 3.61)	0.92 (0.20, 4.15)	1.18 (0.37, 3.77)	Can100mg	0.86 (0.16, 4.74)	0.75 (0.31, 1.84)	1.87 (0.65, 5.18)	1.37 (0.48, 3.87)	0.44 (0.04, 4.47)	1.38 (0.44, 4.31)	0.99 (0.30, 3.20)	0.75 (0.21, 2.73)	0.63 (0.17, 2.37)	2.28 (0.76, 6.84)	1.02 (0.31, 3.33)
1.40 (0.26, 7.52)	1.79 (0.22, 14.60)	1.37 (0.17, 11.36)	0.79 (0.10, 6.16)	0.90 (0.11, 7.71)	1.07 (0.13, 8.95)	1.37 (0.21, 9.13)	1.16 (0.21, 6.42)	Can200mg	0.87 (0.15, 5.15)	2.18 (0.36, 13.32)	1.59 (0.26, 9.87)	0.51 (0.03, 8.08)	1.61 (0.24, 10.55)	1.15 (0.17, 7.72)	0.88 (0.12, 6.32)	0.74 (0.10, 5.42)	2.66 (0.41, 17.02)	1.19 (0.18, 8.01)
1.61 (0.67, 3.87)	2.05 (0.44, 9.51)	1.58 (0.33, 7.45)	0.90 (0.21, 3.96)	1.04 (0.21, 5.14)	1.23 (0.26, 5.93)	1.57 (0.45, 5.48)	1.33 (0.54, 3.28)	1.15 (0.19, 6.77)	Can300mg	2.50 (0.82, 7.59)	1.82 (0.59, 5.66)	0.58 (0.05, 6.22)	1.84 (0.54, 6.24)	1.32 (0.37, 4.63)	1.00 (0.26, 3.92)	0.84 (0.21, 3.40)	3.05 (0.93, 9.96)	1.36 (0.39, 4.82)
0.64 (0.33, 1.26)	0.82 (0.20, 3.45)	0.63 (0.15, 2.68)	0.36 (0.09, 1.42)	0.42 (0.09, 1.82)	0.49 (0.12, 2.10)	0.63 (0.21, 1.88)	0.53 (0.19, 1.48)	0.46 (0.08, 2.81)	0.40 (0.13, 1.22)	Ert5mg	0.73 (0.38, 1.41)	0.23 (0.02, 2.33)	0.74 (0.25, 2.19)	0.53 (0.17, 1.63)	0.40 (0.09, 1.72)	0.34 (0.09, 1.21)	1.22 (0.43, 3.46)	0.55 (0.18, 1.69)
0.88 (0.43, 1.80)	1.12 (0.26, 4.79)	0.86 (0.20, 3.75)	0.49 (0.12, 1.98)	0.57 (0.13, 2.58)	0.67 (0.15, 2.97)	0.86 (0.28, 2.68)	0.73 (0.26, 2.07)	0.63 (0.10, 3.90)	0.55 (0.18, 1.70)	1.37 (0.71, 2.65)	Ert15mg	0.32 (0.03, 3.23)	1.01 (0.33, 3.06)	0.72 (0.23, 2.28)	0.55 (0.16, 1.95)	0.46 (0.13, 1.69)	1.67 (0.57, 4.86)	0.75 (0.24, 2.37)
2.77 (0.31, 25.03)	3.53 (0.28, 44.72)	2.71 (0.21, 34.68)	1.55 (0.13, 18.98)	1.79 (0.14, 23.33)	2.12 (0.17, 27.19)	2.71 (0.25, 28.93)	2.30 (0.22, 23.61)	1.97 (0.12, 31.50)	1.72 (0.16, 18.46)	4.30 (0.43, 43.05)	3.14 (0.31, 31.81)	Emp5mg	3.17 (0.33, 30.14)	2.27 (0.25, 20.61)	1.73 (0.15, 19.76)	1.45 (0.12, 16.88)	5.25 (0.50, 54.51)	2.35 (0.22, 25.40)
0.87 (0.37, 2.04)	1.11 (0.24, 5.06)	0.86 (0.18, 3.97)	0.49 (0.11, 2.11)	0.56 (0.11, 2.76)	0.67 (0.14, 3.18)	0.85 (0.25, 2.93)	0.72 (0.23, 2.26)	0.62 (0.09, 4.08)	0.54 (0.16, 1.84)	1.36 (0.46, 4.03)	0.99 (0.33, 3.00)	0.32 (0.03, 2.99)	Emp10mg	0.71 (0.28, 1.79)	0.54 (0.14, 2.09)	0.46 (0.12, 1.81)	1.65 (0.52, 5.29)	0.74 (0.21, 2.56)
1.22 (0.50, 3.01)	1.56 (0.33, 7.32)	1.20 (0.25, 5.73)	0.69 (0.15, 3.04)	0.79 (0.16, 3.94)	0.93 (0.19, 4.54)	1.19 (0.34, 4.22)	1.01 (0.31, 3.29)	0.87 (0.13, 5.86)	0.76 (0.22, 2.67)	1.90 (0.61, 5.86)	1.38 (0.44, 4.37)	0.44 (0.05, 4.01)	1.40 (0.56, 3.52)	Emp25mg	0.76 (0.19, 3.02)	0.64 (0.16, 2.62)	2.31 (0.70, 7.69)	1.04 (0.29, 3.71)
1.60 (0.57, 4.53)	2.04 (0.40, 10.47)	1.57 (0.30, 8.17)	0.90 (0.19, 4.36)	1.03 (0.19, 5.59)	1.23 (0.23, 6.45)	1.57 (0.40, 6.11)	1.33 (0.37, 4.82)	1.14 (0.16, 8.23)	1.00 (0.25, 3.89)	2.49 (0.72, 8.61)	1.82 (0.51, 6.42)	0.58 (0.05, 6.61)	1.84 (0.48, 7.03)	1.31 (0.33, 5.19)	Dap5mg	0.84 (0.26, 2.71)	3.03 (0.82, 11.23)	1.36 (0.34, 5.39)
1.91 (0.65, 5.61)	2.43 (0.46, 12.79)	1.87 (0.35, 9.98)	1.07 (0.21, 5.33)	1.23 (0.22, 6.81)	1.46 (0.27, 7.86)	1.87 (0.46, 7.49)	1.58 (0.42, 5.92)	1.36 (0.18, 10.01)	1.19 (0.29, 4.78)	2.96 (0.83, 10.59)	2.16 (0.59, 7.90)	0.69 (0.06, 8.00)	2.19 (0.55, 8.64)	1.56 (0.38, 6.37)	1.19 (0.37, 3.84)	Dap10mg	3.61 (0.95, 13.80)	1.62 (0.39, 6.62)
0.53 (0.24, 1.17)	0.67 (0.15, 2.99)	0.52 (0.11, 2.33)	0.30 (0.07, 1.24)	0.34 (0.07, 1.60)	0.40 (0.09, 1.84)	0.52 (0.16, 1.68)	0.44 (0.15, 1.31)	0.38 (0.06, 2.41)	0.33 (0.10, 1.07)	0.82 (0.29, 2.33)	0.60 (0.21, 1.74)	0.19 (0.02, 1.98)	0.60 (0.19, 1.93)	0.43 (0.12, 1.44)	0.32 (0.09, 1.22)	0.28 (0.07, 1.06)	Hen5mg	0.45 (0.20, 1.02)
1.18 (0.48, 2.92)	1.50 (0.32, 7.10)	1.16 (0.24, 5.55)	0.66 (0.15, 2.95)	0.76 (0.15, 3.80)	0.90 (0.19, 4.38)	1.15 (0.33, 4.07)	0.98 (0.30, 3.19)	0.84 (0.12, 5.67)	0.73 (0.21, 2.59)	1.83 (0.59, 5.68)	1.34 (0.42, 4.24)	0.43 (0.04, 4.61)	1.35 (0.39, 4.68)	0.97 (0.27, 3.47)	0.74 (0.19, 2.93)	0.62 (0.15, 2.53)	2.23 (0.98, 5.11)	Hen10mg

Purple indicates interventions; green signifies statistically significant differences in pairwise comparisons; gray indicates no statistical significance

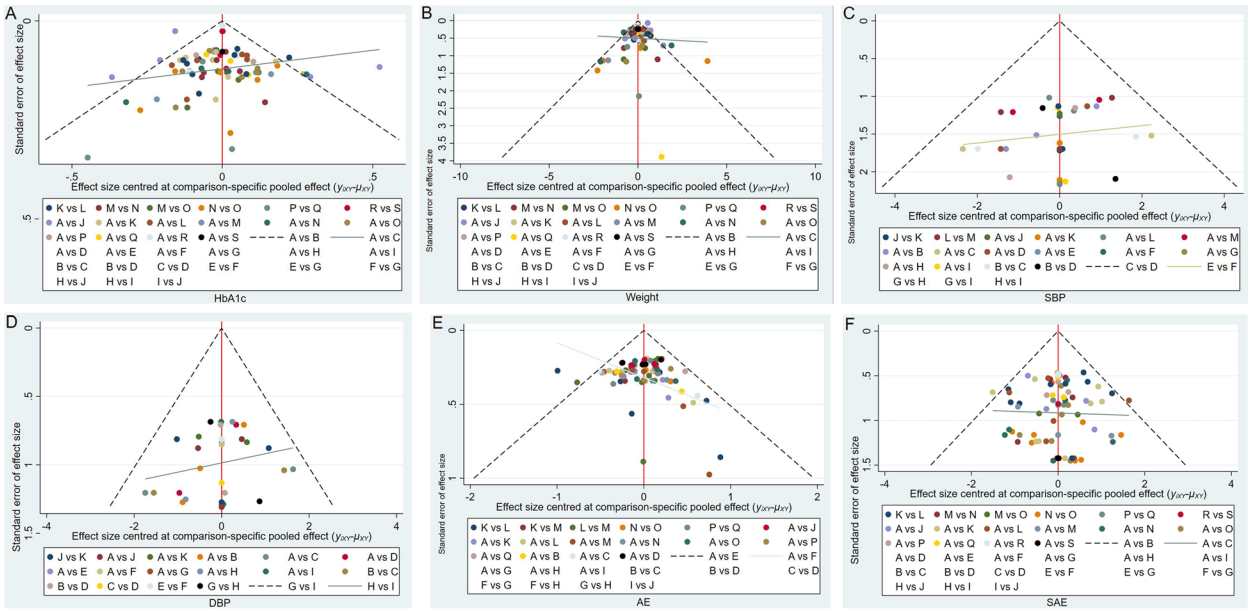

Fig. 5 Publication bias

in blinding of outcome assessments due to insufficient details provided on blinding procedures. Notably, one study exhibited a high risk of bias in the blinding of participants and personnel, impacting the reliability of the findings. In terms of incomplete outcome data and selective reporting, most studies were rated as low risk, with only one showing a high risk due to missing data and lack of reported outcomes. Figure 2 illustrates the quality assessment results across all domains, allowing readers to visually interpret the strengths and limitations of each study's methodological rigor. The overall quality of the included studies supports the robustness of the findings; however, the limitations in blinding procedures should be considered when interpreting the results.

Discussion

In this meta-analysis, among the 28 trials analyzed, tirzepatide at doses of 5 mg, 10 mg, and 15 mg demonstrated the most significant HbA1c reduction and weight loss, aligning with the findings by Ding et al. [5]. As the first dual agonist of GIP and GLP-1 receptors, tirzepatide employs a dual-target mechanism that enables stronger hypoglycemic and weight-reducing effects than other existing hypoglycemic agents, with high tolerability and safety. These qualities underscore its value in comprehensive diabetes management.

Obesity and type 2 diabetes share a fundamental pathophysiological mechanism. Research indicates that a weight reduction of 15% or greater can markedly enhance blood sugar regulation in individuals with diabetes, with some attaining a state of "remission" that is not achievable through alternative hypoglycemic treatments [45]. The incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) regulate blood sugar levels, and tirzepatide targets both GIP and GLP-1 receptors. This dual action helps regulate insulin secretion through GLP-1, delays gastric emptying to reduce appetite, and inhibits gastric acid secretion and motility via GIP, offering an appetite-suppressing effect while potentially preserving islet function.

This study indicates that tirzepatide, particularly at doses of 15 mg and 10 mg, shows a higher likelihood of adverse events (AEs) compared to other medications. Tirzepatide 5 mg, however, is associated with a higher probability of serious adverse events (SAEs). Gastrointestinal reactions, such as nausea, vomiting, and diarrhea, are the main AEs of tirzepatide and align with those observed with GLP-1 receptor agonists. In our analysis, liraglutide 1.8 mg has the highest probability of AEs, underscoring a consideration for clinicians when choosing hypoglycemic agents, as hypoglycemia risk is a significant concern. For instance, although insulin effectively lowers blood glucose, its hypoglycemic risk limits its use. In contrast, tirzepatide has a remarkably low hypoglycemia risk when used alone, as indicated by its action mechanism and existing research [17–20]. This low risk enhances confidence in tirzepatide's use for blood sugar control, contributing to high compliance with HbA1c targets in the tirzepatide group.

Liraglutide, particularly at 1.2 mg and 1.8 mg, shows strong efficacy among GLP-1 receptor agonists, outperforming SGLT2 inhibitors in HbA1c reduction and ranking second to tirzepatide. Evidence shows that liraglutide presents unique benefits relative to other hypoglycemic agents, though its safety profile includes a high probability of AEs, particularly gastrointestinal side effects. Most studies report these adverse effects as mild to moderate, usually diminishing over time with continued treatment.

For systolic and diastolic blood pressure reduction, tirzepatide and liraglutide data were limited in the analyzed studies, leading us to focus on SGLT2 inhibitors for these outcomes. Among SGLT2 inhibitors, canagliflozin performed best in lowering both systolic and diastolic blood pressure, followed by henagliflozin. The cardioprotective effects of SGLT2 inhibitors are well-documented and provide considerable benefits for diabetic patients with hypertension [9, 10, 46]. The cardiovascular effects of SGLT2 inhibitors may be linked to osmotic diuresis, reduced renal glucose reabsorption, and inhibition of the renin–angiotensin–aldosterone system, contributing to lower blood pressure [47, 48]. For example, Zhou et al. [49] and Hussein et al. [48] showed, through meta-analyses, that SGLT2 inhibitors are associated with reduced risks of cardiovascular death and heart failure hospitalization compared to GLP-1 receptor agonists, while GLP-1 receptor agonists demonstrated stronger HbA1c and weight reduction effects.

While tirzepatide may appeal to type 2 diabetic patients seeking weight loss, current evidence on its cardiovascular and renal outcomes is limited. Ongoing studies, expected to conclude in 2025, will provide further insights into these outcomes [50].

This network meta-analysis offers a thorough comparison of tirzepatide, liraglutide, and SGLT2 inhibitors, presenting insights into their comparative efficacy and safety profiles, particularly highlighting tirzepatide's potential for HbA1c reduction and weight loss. Furthermore, using a network meta-analytic framework enables a robust assessment of multiple treatments within a single analysis, facilitating direct and indirect comparisons. Despite these strengths, the study has limitations. First, the number of included studies was small, potentially affecting the generalizability and power of the results. Second, non-English studies were excluded, introducing potential publication bias, and limiting comprehensiveness. Third, the included studies had varying follow-up durations, which might affect the consistency of long-term outcome assessments. Additionally, we could not assess cardiovascular outcomes for GLP-1 receptor agonists or evaluate other GLP-1RAs besides liraglutide, restricting conclusions on their cardiovascular effects.

Conclusion

Among the seven medications analyzed in this study, tirzepatide exhibits the most significant anti-diabetic and weight loss effects. This is especially beneficial for individuals experiencing obesity or excess weight who are also managing type 2 diabetes. The cardiovascular advantages of tirzepatide are now being investigated. The hypoglycemic effect of Liraglutide1.2mg dosage form above 1.2 mg is better than SGLT2i. SGLT2i has a certain antihypertensive effect and is suitable for patients with diabetes complicated with hypertension or other cardiovascular diseases. The results of this study may provide some reference for clinicians to choose new drugs for diabetes. Nonetheless, considering the limitations identified in this study, it is imperative that additional randomized controlled trials are conducted, featuring larger sample sizes, extended follow-up periods, and rigorous quality standards to substantiate the findings further.

Supplementary Information

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Supplementary Material 1

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Authors' contributions

Yunjie Teng: Data curation, Formal Analysis, Methodology, Software, Writing – original draft. Xue Fan: Data curation, Software, Writing – original draft. Rui Yu: Formal Analysis, Methodology, Writin–original draft. Xiaoping Yang: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. All authors contributed to the manuscript and approved the last version for submission.

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Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This is a systematic review and meta-analysis, ethics approval and consent to participate are not applicable.

Consent for publication

Not applicable. This study does not involve human participants.

Competing interests

The authors declare no competing interests.

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