Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To evaluate the comparative efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on glycaemic control, body weight, and lipid profile in adults with type 2 diabetes.

DESIGN

Systematic review and network meta-analysis.

DATA SOURCES

PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase from database inception to 19 August 2023.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Eligible randomised controlled trials enrolled adults with type 2 diabetes who received GLP-1RA treatments and compared effects with placebo or any GLP-1RA drug, with a follow-up duration of at least 12 weeks. Trials with a crossover design, non-inferiority studies comparing GLP-1RA and other drug classes without a placebo group, using withdrawn drugs, and non-English studies were deemed ineligible.

RESULTS

76 eligible trials involving 15 GLP-1RA drugs and 39 246 participants were included in this network meta-analysis; all subsequent estimates refer to the comparison with placebo. All 15 GLP-1RAs effectively lowered haemoglobin A_{1c} and fasting plasma glucose concentrations. Tirzepatide induced the largest reduction of haemoglobin A_{1c} concentrations (mean difference −2.10% (95% confidence interval −2.47% to −1.74%), surface under the cumulative ranking curve 94.2%; high confidence of evidence), and fasting plasma glucose concentrations (−3.12 mmol/L (−3.59 to −2.66), 97.2%; high confidence), and proved the most effective GLP-1RA drug for glycaemic control. Furthermore, GLP-1RAs were shown to have strong benefits to weight management for patients with type 2 diabetes. CagriSema (semaglutide with cagrilintide) resulted in the highest weight loss (mean difference −14.03 kg (95% confidence interval −17.05 to −11.00); high confidence of evidence), followed by tirzepatide (−8.47 kg (−9.68 to −7.26); high confidence). Semaglutide was effective in lowering the concentration of low density lipoprotein (−0.16 mmol/L (−0.30 to −0.02)) and total cholesterol (−0.48 mmol/L (−0.84 to −0.11)). Moreover, this study also raises awareness of gastrointestinal adverse events induced by GLP-1RAs, and concerns about safety are especially warranted for high dose administration.

CONCLUSIONS

GLP-1RAs are efficacious in treating adults with type 2 diabetes. Compared with the placebo, tirzepatide was the most effective GLP-1RA drug for glycaemic control by reducing haemoglobin A_{1c} and fasting plasma glucose concentrations. GLP-1RAs also significantly improved weight management for type 2 diabetes, with CagriSema performing the best for weight loss. The results prompt safety concerns for GLP-1RAs, especially with high dose administration, regarding gastrointestinal adverse events.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42022342845.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Glucagon-like peptide-1 receptor agonist (GLP-1RA) is a promising drug class demonstrating proven benefits for adults with type 2 diabetes

Regulatory authorities have approved several GLP-1RA drugs, and novel drugs are continually emerging, resulting in an urgent need for updated evidence synthesis of the comparative effectiveness of various GLP-1RAs

WHAT THIS STUDY ADDS

Compared with the placebo, all 15 GLP-1RAs had significant effects on glycaemic control, and tirzepatide was the most effective in reducing haemoglobin A_{1c} and fasting plasma glucose concentrations

CagriSema induced the highest weight reduction in adults with type 2 diabetes, followed by tirzepatide and retatrutide

Several GLP-1RAs resulted in a significantly higher odds ratio of discontinuation due to adverse events than placebo, raising safety concerns about gastrointestinal adverse events, especially at high doses

Introduction

Diabetes mellitus is a pervasive worldwide epidemic, with global numbers of people affected reaching 476 million, of which 463 million have type 2 diabetes, and an increasing annual growth trend.[1] Pharmacological treatments such as thiazolidinediones, sulfonylureas, and insulins have major drawbacks, including hypoglycaemia and weight gain.[2 3] Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors are two novel drug classes that have attracted widespread attention for their cardiovascular and renal benefits in patients with type 2 diabetes.[4-6] These drug classes have become attractive options for the treatment of type 2 diabetes, particularly in the development of GLP-1RAs, which have been advancing rapidly with important breakthroughs alongside the continuous development of new drugs in recent years.[7-9]

GLP-1RAs attain glycaemic control through mechanisms such as increasing insulin secretion

induced by hyperglycaemia, inhibiting glucagon secretion during hyperglycaemia, slowing gastric emptying, preventing substantial increases in postprandial glucose, and reducing caloric intake and body weight.[10-13] Short acting GLP-1RAs (exenatide and lixisenatide) reduce the effect of nocturnal and fasting glucose but maintain the effect on gastric emptying during long term treatment. Long acting GLP-1RAs (eg, liraglutide, exenatide, and dulaglutide) have more profound effects on nocturnal and fasting glucose and glycated haemoglobin (HbA_{1c}), both in the context of oral hypoglycaemic drugs and in combination with basal insulin. GLP-1RAs have been shown to greatly reduce the body weight of obese people with type 2 diabetes.[8 14] The US Food and Drug Administration has approved several different formulations or doses of GLP-1RAs for the treatment of type 2 diabetes: exenatide, liraglutide, dulaglutide, albiglutide, lixisenatide, semaglutide, and tirzepatide.[15]

Given the wide variety of GLP-1RA drugs, the differences in pharmacokinetics, efficacy, adverse reaction rates, and dosing requirements of each GLP-1RA need to be evaluated independently.[16] Additionally, clinicians need to understand the advantages and disadvantages of each GLP-1RA drug to reach the appropriate clinical decisions. Several network meta-analyses have compared the efficacy of different GLP-1RAs.[17-21] However, the development of GLP-1RA novel drugs is indeed a rapidly evolving area, and many new drugs have emerged this year, including orforglipron, retatrutide, and CagriSema (semaglutide with cagrilintide). Furthermore, an updated evidence synthesis considering several large scale trials published recently is urgently needed.[8 22-24] Thus, these previous studies are no longer sufficient to provide adequate and timely support for patients, physicians, and investigators. Therefore, we aimed to address this issue. We performed a systematic review and network meta-analysis to evaluate and compare GLP-1RAs' efficacy in glycaemic control, weight management, and lipid profile in patients with type 2 diabetes. We have included the most complete and latest available GLP-1RAs, and several novel drugs were pooled and compared in a network meta-analysis for the first time. We provide up-to-date information about GLP-1RA treatment of type 2 diabetes, which can aid policy formulation and drug selection for physicians' clinical practices.

Methods

The protocol for this systematic review and network meta-analysis has been registered with PROSPERO (CRD42022342845). This study followed the PRISMA (preferred reporting items for systematic reviews and meta-analyses) 2020 and extension statement for network meta-analyses (PRISMA-NMA).[25 26]

Search strategy

We searched PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase for randomised controlled trials of GLP-1RAs in people with type 2 diabetes from database inception to 9 July 2022, and updated the literature search on 17 December 2022 and 19 August 2023. Three reviewers (HY, AZ, and J-YW) searched and screened the eligible studies independently, and inconsistencies were resolved by consulting a fourth reviewer (C-SY). Additionally, we manually searched the websites of the European Association for the Study of Diabetes and American Diabetes Association scientific meetings, as well as ClinicalTrials.gov, to retrieve additional qualified trials or search the database for any additional information on trials that have been identified. Moreover, the references of included articles and relevant systematic reviews have also been screened for potential fit studies. A complete list of search strategies can be found in appendix 1.

Eligibility criteria

Eligible randomised controlled trials enrolled adults (18-65 years old) with type 2 diabetes who received GLP-1RAs, with a follow-up duration of at least 12 weeks. The treatment was either monotherapy of GLP-1RA or added GLP-1RA to non-randomised background hypoglycaemic treatments. The comparator could be a placebo or any GLP-1RA. We included randomised controlled trials from peer reviewed articles and excluded conference abstracts and non-English literature. We excluded trials with a crossover design, non-inferiority studies comparing GLP-1RA to other drug classes without a placebo arm, or using withdrawn drugs.

Screening process

We imported the database retrieved items into EndNote 20.4.1 (Clarivate Analytics, Philadelphia, PA, USA) and removed duplication, juxtaposing them with results from other sources. The screening process consisted of three stages. Firstly, three reviewers (HY, AZ, and J-YW) independently selected the articles according to the title, and any uncertain entries were included. Secondly, all articles selected from the first phase underwent a summary review, and disagreements were resolved through discussion among reviewers and a fourth reviewer (C-SY) was consulted. Thirdly, articles with eligible titles and abstracts were further reviewed in the full text according to predetermined inclusion and exclusion criteria.

Data extraction

For each eligible study, we applied predesigned tables to independently extract the following information: study characteristics (year of publication, country, treatment duration), population (age, sex, sample size, diabetes duration, body mass index), intervention (name and dose), and outcomes. We measured the changes from baseline in outcomes of HbA_{1c} concentrations, fasting blood glucose concentrations, body weight, body mass index, waist circumference, and serum lipid parameters, eg, high density lipoprotein, low density lipoprotein, total cholesterol, and triglyceride levels. We also evaluated the safety of GLP-1RAs in eligible

trials by examining adverse events comprehensively with no predefined restrictions. We abstracted all relevant data reported in the included trials, including treatment discontinuation due to adverse events, all-cause death, cardiovascular disease, non-fatal stroke, kidney failure, severe hypoglycaemia, eye disease requiring intervention, health-related quality of life, serious gastrointestinal events, etc. We used WebPlot Digitizer version 4.3 to estimate the values only if the data were presented graphically.[27] Two independent examiners (HY, AZ) conducted data extraction, which was then checked and arbitrated by a third examiner (J-YW).

Quality assessment of evidence

We used the Cochrane randomised trial Risk of Bias tool (version 2.0) to assess the risk of bias in the included trials, including random sequence generation, assignment hiding, blinding, loss of result data, and selective reporting of results.[28] If the risk of bias was low in all domains, the overall risk of bias in each trial was considered low (scored as 1); if the risk of bias was high in at least one domain, the overall risk of bias in each trial was considered to be high (scored as 3). In any other context, the risk of bias was considered to be some concerns (scored as 2). Two reviewers completed the bias risk assessment independently, and any differences were resolved by a consensus. We performed funnel plots to scrutinise the small study effect bias using estimates of direct evidence and examined each comparison separately. Egger's and Begg's tests were applied to assess funnel plot symmetry quantitatively.[29] We also used the CINeMA (Confidence in Network Meta-Analysis) framework to assess the certainty of the evidence in six key areas, including within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and inconsistency.[30 31] We assessed intransitivity for the CINeMA framework by comparing potential effect modifiers, such as baseline age and HbA_{1c} concentration, between studies that provided direct and indirect evidence for each comparison.

Data synthesis and analysis

The means and standard deviations of changes in the outcomes were converted from milligrams per decilitre (mg/dL) to millimoles per litre (mmol/L), and the variance was calculated using a previously developed program.[32] We applied the following formula to studies missing standard deviation data.[33]

If only P values were reported, we used the METAEFF command program in Stata version 17 (Stata Corp LLC) software to calculate the mean difference and 95% confidence interval from the available data.[34]

$$SD = \sqrt{\frac{(N_1-1)\,SD_1^2 + (N_2-1)\,SD_2^2 + \frac{N_1N_2}{N_1+N_2}(M_1^2+M_2^2-2M_1M_2)}{N_1+N_2-1}}$$

We performed network meta-analyses of randomised controlled trials with Stata and used the Stata command MVMETA[35] to perform multivariate network meta-analyses in the frequentist framework.[36] The relative effects were measured as mean differences for continuous outcomes, including HbA_{1c} concentrations, fasting blood glucose concentrations, body weight, etc, and odds ratios for binary outcomes, such as adverse events. Random effects network meta-analyses were estimated by the restricted maximum likelihood method and were used to account for heterogeneity between studies and calculate the pooled estimates and 95% confidence interval.[37] We assessed heterogeneity with τ^2 (low <0.04; low-moderate 0.04-0.16; moderate-high 0.16-0.36; high >0.36) according to previously published methods.[38-40] The τ^2 was assumed the same for all contrasts in the network meta-analysis, and the correlation was assumed 0.5 in the between-study covariance matrix. We used a node splitting approach to evaluate the agreement between direct and indirect estimates in each closed loop evidence, and a design treatment interaction model to assess the entire network.[41] When continuous variables were missing, we used standard deviations borrowed from other similar randomised controlled trials to calculate the missing standard deviations.

We used Stata to create a network diagram and ranked GLP-1RAs with different doses based on the surface under the cumulative ranking curve (SUCRA) to evaluate their efficacy of type 2 diabetes.[42] Additionally, to evaluate whether baseline characteristics affected the findings, we conducted meta-regressions of potential effect modifiers, including the duration of type 2 diabetes, age, and background hypoglycaemic treatments. We also conducted subgroup analyses of different doses of each GLP-1RA, follow-up duration, and single versus dual or triple agonists.

Patient and public involvement

No patient representatives or members of the public were directly involved in the planning, design, conduct, or reporting of this study, and no primary data were collected. As a result of limited funding, we were not able to engage with consumer groups.

Results

Literature selection and study characteristics

We retrieved 16316 citations, assessed 483 full text articles, and updated the literature search twice to ensure that the search results were up to date. Based on our inclusion criteria, 76 randomised controlled trials of 39246 adults proved eligible (fig 1). Included trials involved 58 countries and regions, and sample sizes ranged from 29 to 1878 people. The duration of the intervention varied between 12 weeks and 78 weeks. Mean age was 56.79 years (standard deviation 9.59), mean proportion of men was 54.06%, and mean duration of diabetes was 8.47 years (standard deviation 6.46). At baseline, patients had a mean body mass index of 31.73 (standard deviation 6.55) and HbA_{1c} of 8.13% (65 mmol/mol; standard deviation 0.93) (appendix 2,

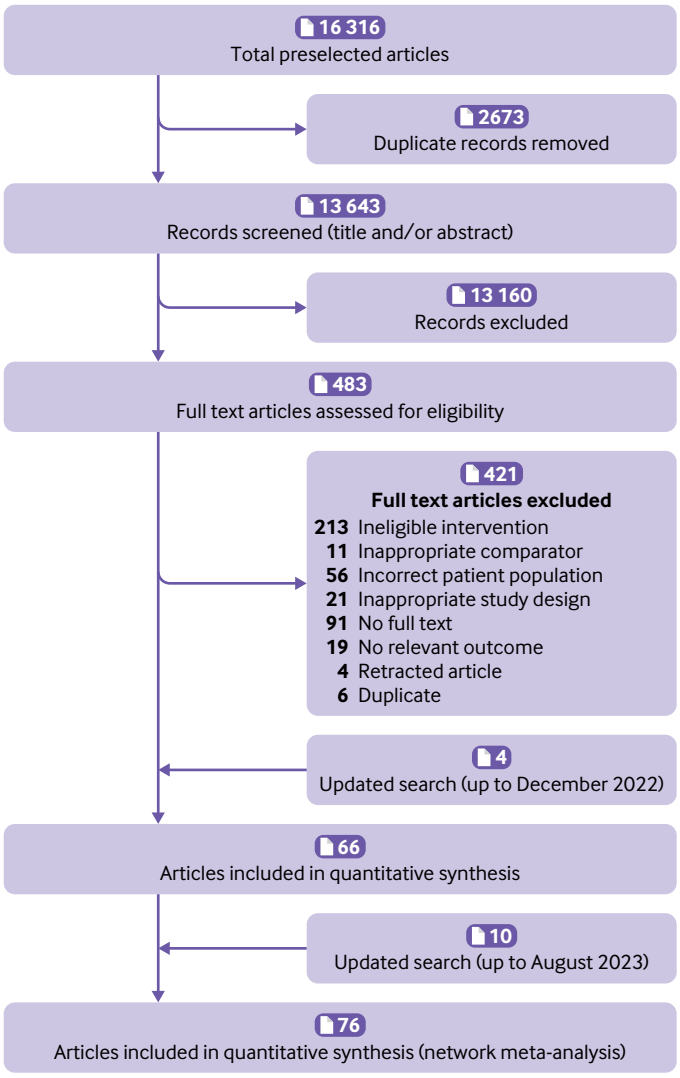

Fig 1 | Flow diagram of preferred reporting items identified, included, and excluded for systematic reviews and meta-analyses (PRISMA)

table S2.1). Based on our retrieved publications, 16 GLP-1RAs were identified, and taspoglutide was excluded because it was out of development due to strong gastrointestinal adverse effects.[43 44] Thus, 15 GLP-1RA drugs were compared in the network, including eight regulatory authorities approved drugs and seven candidate drugs (appendix 2, table S2.2).

Risk of bias, certainty of evidence, and consistency

The risk of bias for each trial is shown in appendix 4. Key limitations were likely that some studies did not report sufficient details on the implementation of blindness among participants, investigators, and outcome evaluators. In 76 trials, 68 studies (89%) had a low risk of random-sequence generation bias, 66 studies (87%) had a low risk of deviations from intended interventions, 67 studies (88%) had a low risk of missing outcome data, and 68 studies (89%) had a low risk for the measurement of the outcome domain. Selection reporting bias was found in 56 studies (74%). Overall, 10 studies (13%) had a high risk of bias. For our consistency evaluation (ie, alignment of direct and indirect evidence), side-splitting results suggested inconsistency in several comparisons; however, no strong statistical evidence of global inconsistency was reported for most outcomes. Consistency assessments also prompted vigilance over waist circumference data (P=0.07), which warrants more rigorous randomised controlled trials in the future. The τ^2 result did not identify any high heterogeneity in the network, and most comparisons were low or low-moderate levels of heterogeneity (appendix 5). After assessing the level of evidence using CINeMA, most of the results of the pairwise comparisons were of moderate or high confidence (appendix 9). All networks met the principle of transitivity, endowing the validity of indirect comparisons (appendix 9, table S9.1). Furthermore, we found no evidence of asymmetry in the funnel plots (appendix 10).

Glycaemic control

For HbA_{1c} reduction, the network meta-analysis comprised 56 trials involving 26 343 people. All 15 GLP-1RA drugs showed significant efficacy in reducing HbA_{1c} levels compared with placebo in adults with type 2 diabetes (fig 2, fig 3). Tirzepatide (mean difference −2.10% (95% confidence interval −2.47% to −1.74%), SUCRA 94.2%; high confidence of evidence) induced the most significant HbA_{1c} reduction, followed by mazdutide (−2.09% (95% confidence interval −3.10% to −1.09%), SUCRA 90.4%; high confidence of evidence) and CagriSema (−1.80% (−2.87% to −0.73%), SUCRA 80.9%; high confidence of evidence). We compared different GLP-1RAs for down regulating HbA_{1c} (appendix 8, table S8.1). CINeMA indicated that the overall quality of HbA_{1c} evidence was mainly moderate or high (appendix 9, table S9.2).

Evaluated by fasting blood glucose, the network meta-analysis enrolled 47 randomised controlled trials with 17 163 subjects, confirming the placebo controlled effectiveness of all the 15 GLP-1RAs (fig 4, fig 5). Tirzepatide (mean difference −3.12 mmol/L (−3.59 to −2.66), SUCRA 97.2%; high confidence of evidence) proved the most effective in reducing fasting blood glucose concentrations. Detailed comparisons of fasting blood glucose concentrations are presented (appendix 8, table S8.2).

Body weight

This analysis included 53 trials with 21 349 participants for body weight changes. CagriSema (mean difference −14.03 kg (−17.05 to −11.00); high confidence of evidence) was identified to be the most effective GLP-1RA drug in lowering body weight (fig 6, fig 7). Tirzepatide, retatrutide, orforglipron, semaglutide, and liraglutide also displayed significant weight loss effects compared with placebo. More detailed comparisons of body weight were provided in SUCRA data (appendix 7, figure S7.3 and table S7.3) and a table (appendix 8, table S8.3).

For body mass index, figure S6.1 shows the network meta-analysis results of all qualified trials after

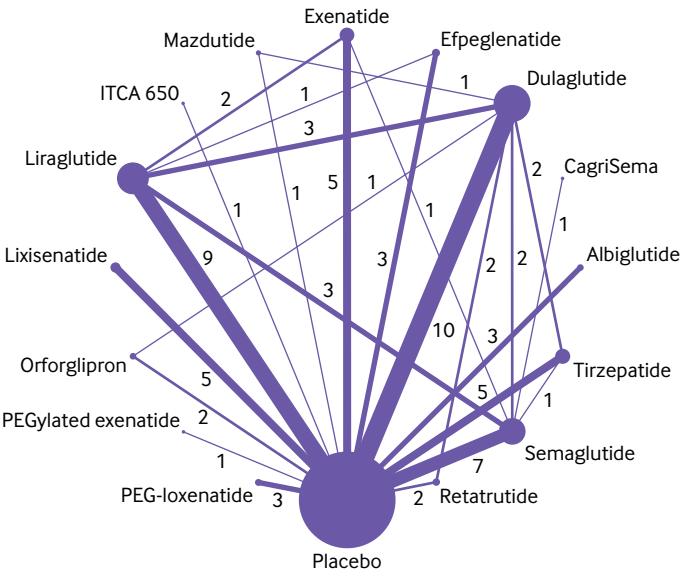

Fig 2 | Network of available comparisons of GLP-1RAs and placebo for HbA_{1c}. The size of the nodes is proportional to the number of trial participants, and the thickness of the line connecting the nodes is proportional to the randomised number of trial participants directly comparing the two treatments. Numbers represent the number of trials contributing to each treatment comparison. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide; ITCA 650=a combination of drug and device containing exenatide in osmotic mini pump

inconsistency analysis. Tirzepatide (−2.85 (−3.70 to −2.01)), orforglipron (−2.06 (−3.22 to −0.91)), semaglutide (−1.28 (−1.73 to −0.83)), liraglutide (−0.81 (−1.26 to −0.36)) effectively lowered the body mass index levels compared with placebo. More detailed information on body mass index can be found in appendix 7 (figure S7.4 and table S7.4) and appendix 8 (table S8.4). Moreover, tirzepatide (−6.77 cm (−8.97 to −4.57)), semaglutide (−3.74 cm (−5.25 to −2.24)), and liraglutide (−2.30 cm (−3.78 to −0.82)) were shown to be effective in reducing waist circumference (figure S6.2, figure S7.5, table S7.5, and table S8.5).

Lipid profiles

Effects of GLP-1RAs on serum lipid concentrations were evaluated by high density lipoprotein, low density lipoprotein, total cholesterol, and triglycerides. Network meta-analysis showed that PEG-loxenatide (mean difference 0.16 mmol/L (95% confidence interval 0.00 to 0.31)) was the only GLP-1RA drug that significantly increased high density lipoprotein concentrations compared with placebo (figure S6.3, figure S7.6, table S7.6, and table S8.6). Semaglutide was also the only GLP-1RA that effectively lowered the levels of low density lipoprotein (mean difference −0.16 mmol/L (95% confidence interval −0.30 to −0.02); figure S6.4), and total cholesterol (−0.48 mmol/L (−0.84 to −0.11); figure S6.5). For triglycerides, ITCA 650 (−1.59 mmol/L (−2.86 to −0.32)) and tirzepatide (−0.89 mmol/L (−1.64 to −0.13) showed significant effects compared with placebo (figure S6.6).

Adverse events

We also conducted network meta-analyses to evaluate adverse events of GLP-1RA drugs, and the

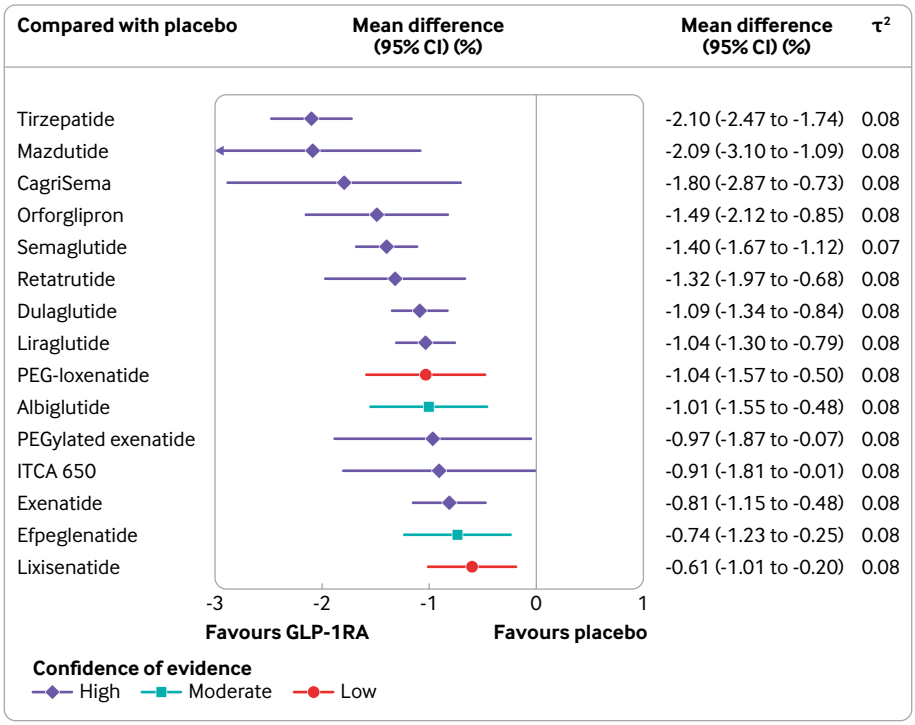

Fig 3 | Forest plot of network effect sizes between GLP-1RAs and placebo for HbA_{1c} measured in percentage. According to the network confidence meta-analysis (CINeMA) framework, the certainty of evidence is visually represented in the forest map, with varying colours indicating different confidence levels. The complete CINeMA assessments are shown in appendix 9. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide; ITCA 650=a combination of drug and device containing exenatide in osmotic mini pump

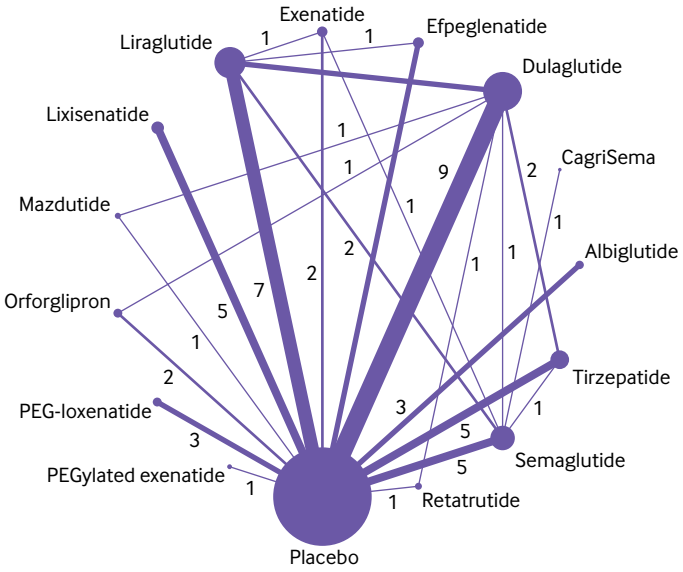

Fig 4 | Network of available comparisons between GLP-1RAs and placebo for fasting blood glucose. The size of the nodes is proportional to the number of trial participants, and the thickness of the line connecting the nodes is proportional to the randomised number of trial participants directly comparing the two treatments. Numbers represent the number of trials contributing to each treatment comparison. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide

results implied safety concerns. The following GLP-1RAs showed a significantly higher odds ratio of discontinuation due to adverse events compared with placebo: lixisenatide (odds ratio 2.86 (95% confidence interval 1.48 to 5.51)), semaglutide (2.61 (1.56 to 4.37)), exenatide (2.39 (1.14 to 4.98)), tirzepatide (2.30 (1.30 to 4.09)), and liraglutide (2.15 (1.26 to 3.69)) (fig 8A). Regarding specific adverse reactions, the most reported were gastrointestinal events. CagriSema (6.60 (1.16 to 37.76)), tirzepatide (2.88 (2.09 to 3.96)), retatrutide (2.53 (1.17 to 5.46)), orforglipron (2.43 (1.25 to 4.74)), semaglutide (2.37 (1.84 to 3.06)), efpeglenatide (2.32 (1.21 to 4.43)), dulaglutide (2.08 (1.62 to 2.66)), liraglutide (1.99 (1.56 to 2.56)), and exenatide (1.43 (1.03 to 1.99)) were positively associated with diarrhoea compared with placebo (fig 8B). Nausea is another frequently reported gastrointestinal side effect. Except for albiglutide, PEG-loxenatide, and mazdutide, all the other 12 GLP-1RAs induced significantly elevated odds ratio of nausea (fig 8C). Ten GLP-1RAs induced a significantly higher risk of vomiting than placebo: ITCA 650, CagriSema, orforglipron, efpeglenatide, tirzepatide, lixisenatide, semaglutide, liraglutide, exenatide, and dulaglutide (fig 8D).

Sensitivity analyses and meta-regressions

According to our eligibility criteria, trials comparing GLP-1RAs with other antidiabetic drug classes without a placebo arm were not included in the pooled estimates. To further examine the robustness of the results, we performed sensitivity analyses by adding all pre-excluded trials comparing GLP-1RAs with other glucose-lowering drug classes. As shown in appendix 11, sensitivity analyses proved consistent with the primary results, confirming the robustness of our findings.

The impact of potential baseline effect modifiers on the primary outcomes was assessed through meta-regression analyses. Patient age, diabetes duration,

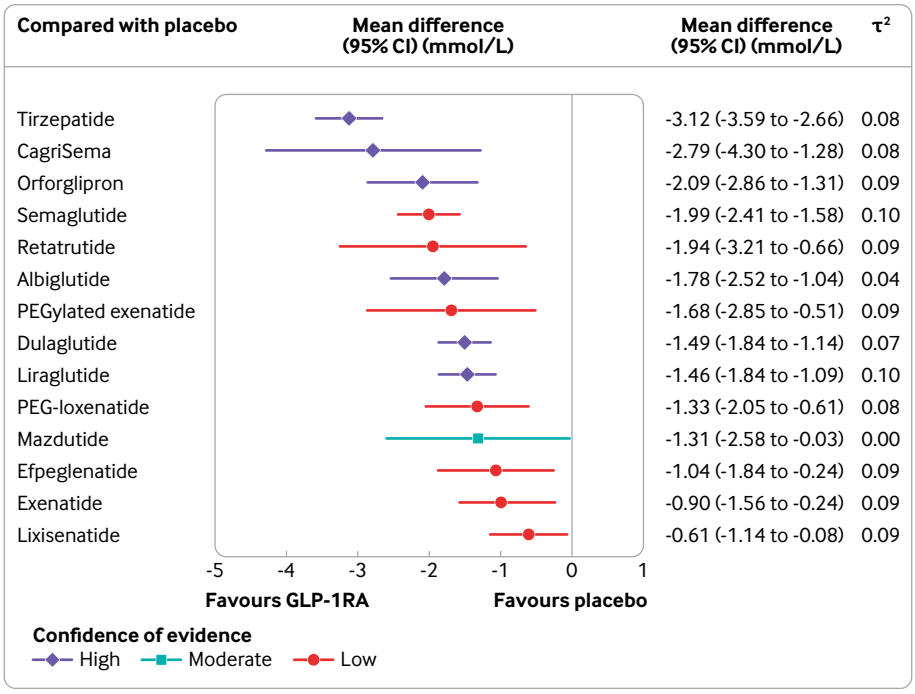

Fig 5 | Forest plot of network effect sizes between GLP-1RAs and placebo for fasting blood glucose. Certainty of evidence is visually represented in the forest map, with varying colours indicating different confidence levels. The complete CINeMA assessments are shown in appendix 9. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide

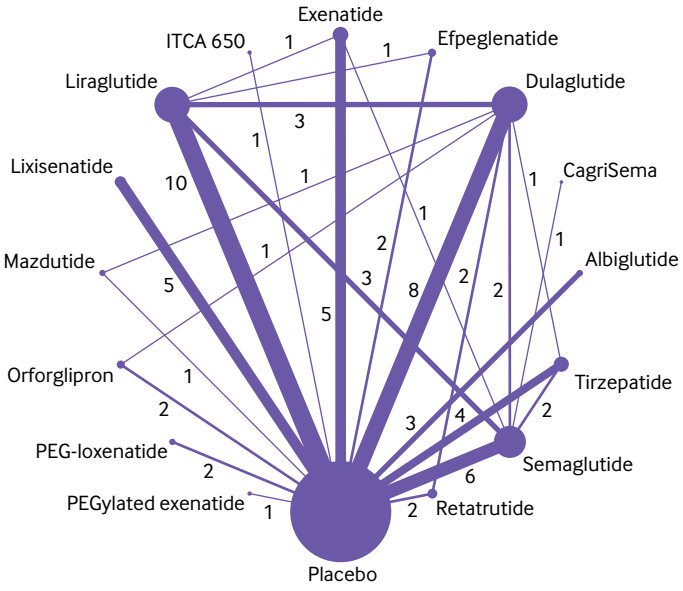

Fig 6 | Network of available comparisons between GLP-1RAs and placebo for weight loss. The size of the nodes is proportional to the number of trial participants, and the thickness of the line connecting the nodes is proportional to the randomised number of trial participants directly comparing the two treatments. Numbers represent the number of trials contributing to each treatment comparison. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide; ITCA 650=a combination of drug and device containing exenatide in osmotic mini pump

and background treatment were evaluated, and no significant effect on the primary outcomes was found (appendix 12).

Subgroup analyses

Subgroup analyses of each GLP-1RA with multiple doses

Among the 15 GLP-1RAs, 11 involved multiple doses in the included trials. Thus, we performed subgroup analyses to further investigate the differences in efficacy between various doses of each drug (appendix 14). Tizepatide showed outstanding potency according to our pooled results and was available in four doses: 1 mg, 5 mg, 10 mg, and 15 mg, administrated with subcutaneous injections once a week. Significantly positive correlations were observed between the dose and efficacy indicated by HbA_{1c} concentrations, fasting blood glucose concentrations, body weight, body mass index, and waist circumference (figure S14.1). Similarly, the effects of dulaglutide also displayed a dose-dependent manner (figure S14.4). However, the effects of certain drugs were not directly proportional to doses, as observed in the assessment of concentrations of HbA_{1c} and fasting blood glucose with liraglutide (figure S14.3). Detailed information is presented in appendix 14.

In terms of safety, tirzepatide at the doses of 15 mg induced a significantly higher risk of discontinuation due to adverse events (odds ratio 2.26 (95% confidence interval 1.35 to 3.77)). The odds ratios of gastrointestinal side effects were observed to be higher with the increasing doses of tirzepatide, semaglutide, dulaglutide, lixisenatide, retatrutide, etc (appendix 17), which raised a warning for high dose administration of GLP-1RA drugs.

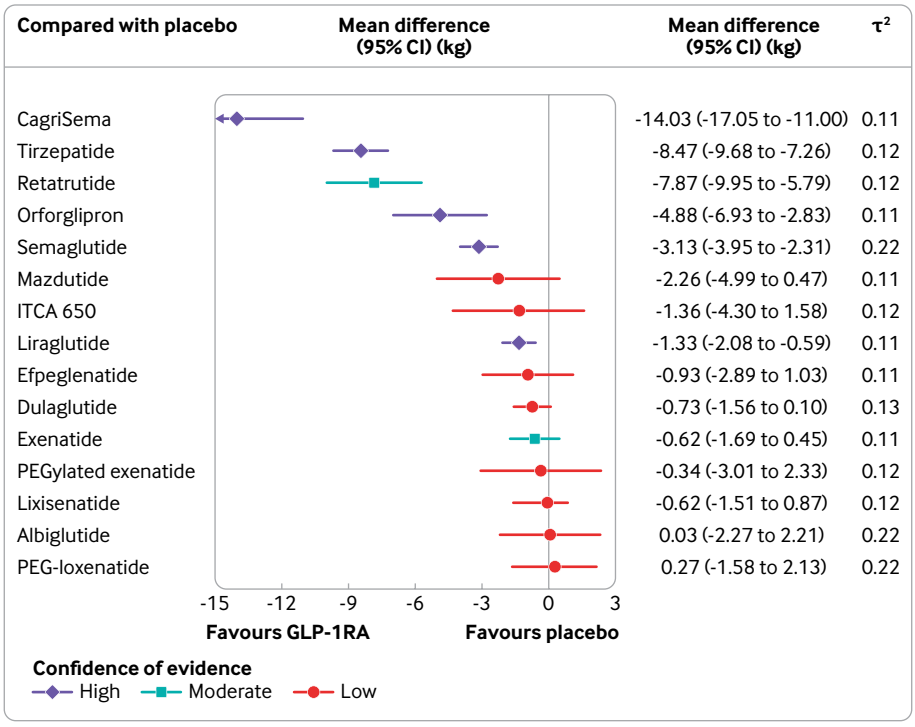

Fig 7 | Forest plot of network effect sizes between GLP-1RAs and placebo for weight loss. Certainty of evidence is visually represented in the forest map, with varying colours indicating different confidence levels. The complete CINeMA assessments are shown in appendix 9. GLP-1RA=glucagon-like peptide-1 receptor agonist; PEG-loxenatide=polyethylene glycol loxenatide; ITCA 650=a combination of drug and device containing exenatide in osmotic mini pump

Subgroup analyses of follow-up durations

The efficacy of GLP-1RA drugs can be affected by the follow-up duration. We categorised follow-up durations into short term (3-6 months), medium term (6-12 months), and long term (>12 months), and conducted subgroup analyses to address this issue. The efficacy of tirzepatide in lowering concentrations of HbA_{1c} and fasting blood glucose, and lowering body weight was directly proportional to the length of follow-up duration (appendix 15). Semaglutide and exenatide kept relatively steady efficacy on HbA_{1c} with different follow-up durations.

Of note, several GLP-1RAs showed a gradual decline in effects on body weight throughout the long term intervention. In comparison to placebo, semaglutide resulted in a reduction of body weight from a mean difference of −3.28 kg (95% confidence interval −4.20 to −2.37) with medium term intervention to −2.75 kg (−4.60 to −0.89) with long term intervention. Liraglutide and dulaglutide also showed a similar trend (appendix 15). These results indicate potential limitations of GLP-1RAs for sustained long term weight loss efforts.

Subgroup analyses of single versus dual or triple agonists

We conducted subgroup analyses of single versus dual or triple agonists. The specific drug classification can be found in table S2.2. Evidence synthesis indicated

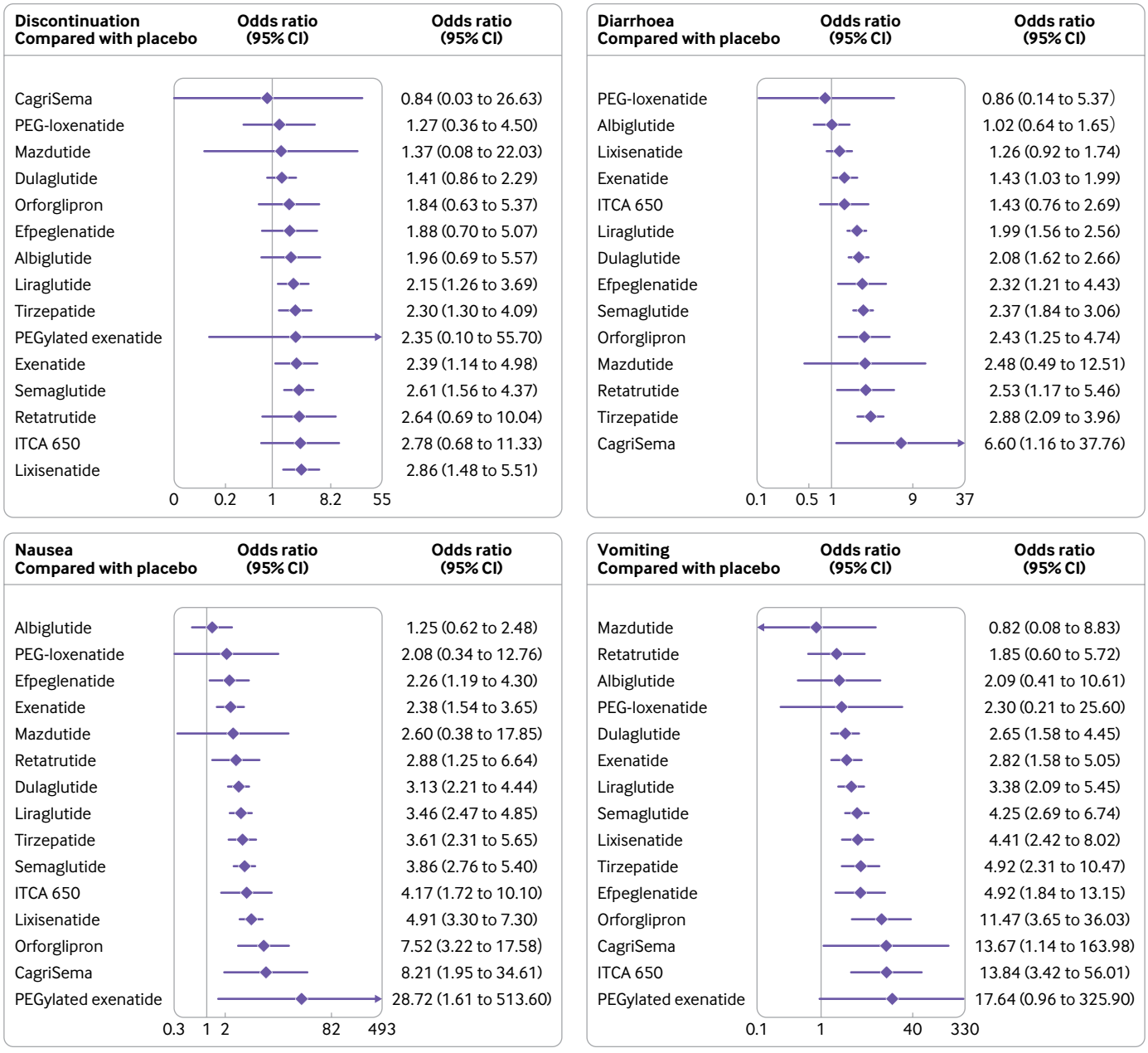

Fig 8 | Estimates in network meta-analysis for common adverse events of glucagon-like peptide-1 receptor agonists compared with placebo. (A) discontinuation; (B) diarrhoea; (C) nausea; (D) vomiting. Effect sizes are presented as odds ratios with 95% confidence intervals (CIs). PEG=polyethylene glycol

that dual agonists (tirzepatide, mazdutide, and CagriSema) and triple agonists (retatrutide) displayed overall better efficacy than regular GLP-1RA drugs in reducing HbA_{1c} concentrations, fasting blood glucose concentrations, and body weight (appendix 16). These four dual or triple agonists are all newly developed in the past few years, showing a new trend of drug development in this field.

Discussion

Principal findings

This network meta-analysis comprehensively evaluated and compared the efficacy and safety of 15 GLP-1RAs in adults with type 2 diabetes, including the latest novel drugs (orforglipron, retatrutide, and CagriSema, etc). The effectiveness of glycaemic control, body weight, lipid profile, and adverse events were accessed through 76 eligible randomised controlled trials involving 39 246 participants. For glycaemic control, all 15 GLP-1RA drugs had significant effects in reducing HbA_{1c} concentrations and fasting blood glucose concentrations compared with placebo, according to our pooled data. Tirzepatide was the best performing GLP-1RA at lowering concentrations of HbA_{1c} and fasting blood glucose with high confidence of evidence. CagriSema was identified as the most effective GLP-1RA compared with placebo in reducing body weight in adults with type 2 diabetes.

Strengths and limitations of this study

To our knowledge, the present study is the most comprehensive and up-to-date systematic review and network meta-analysis assessing a complete range of almost all available GLP-1RAs including the latest drugs on adults with type 2 diabetes. Our rigorous method applying quality assessment approach of CINeMA confers credibility to the findings. Nevertheless, our study has some limitations. Firstly, the included trials involve varied population characteristics and follow-up durations, although the consistency of results across studies reduced this concern, and it may result in imprecise effect estimates. Secondly, participants had little control over diet and exercise in the trials, which may influence blood glucose metabolism and body weight. Thirdly, some trials did not provide sufficient information to precisely assess the randomisation, allocation concealment, and blinding for investigators, despite trying to contact the authors. Fourthly, some drugs involved few articles, and results must be interpreted with caution when compared with other drugs and in subgroup analyses. However, we performed sensitivity analyses by excluding one study at a time and did not find a single study that affected the final results. Finally, although most of the included studies were of high quality, some trials had a potential risk of bias, such as open label design and pharmaceutical industry funding.

Comparisons with other studies

No previous network meta-analyses had compared such wide ranging GLP-1RAs in people with type 2 diabetes but had only involved limited GLP-1RA drugs.[17-21] Therefore, a thorough and up-to-date examination was missing. We have included the most complete and latest GLP-1RA data to aid drug selection for physicians' clinical practices. Our findings are relevant to a previous network meta-analysis that evaluated multiple types of glucose lowering drugs in patients with type 2 diabetes with HbA_{1c} as the endpoint and concluded that GLP-1RAs were the most effective in lowering HbA_{1c} concentrations.[6] Therefore, our study went further to explore among various GLP-1RA drugs which one works the best, compare the efficiency variation between different doses, and access safety profiles. Additionally, most similar studies ignored exploring the dose-effect mode of GLP-1RAs, and only measured the effects of one GLP-1RA drug or compared limited doses,[45] and a more in-depth investigation was warranted. Therefore, we performed a network meta-analysis to evaluate almost all available GLP-1RAs with various doses, ranked their efficacy and safety, and explored the pattern between dosage and efficacy through subgroup analysis to provide beneficial information to support clinical decision making. We also conducted subgroup analyses and meta-regressions on the treatment duration, single or dual/triple agonists, diabetes duration, age, and background hypoglycaemic treatments, to explore the effect of those modifiers on the findings. Discontinuation of trials due to adverse events and other detrimental outcomes may lead to bias in the assessment of the final results. Therefore, we analysed the population that discontinued treatment because of adverse reactions, rather than the overall discontinued population.

Policy implications

This study validated the potency of GLP-1RA drugs in treating adults with type 2 diabetes. Among various available GLP-1RAs, tirzepatide proved the most effective in glycaemic control. Through a subgroup analysis, we also identified a dose-dependent fashion in tirzepatide reducing HbA_{1c} and fasting blood glucose, and the dose of 15 mg once weekly via subcutaneous injection showed the best efficacy. Patients with type 2 diabetes usually have co-morbid obesity, and our data validated that various GLP-1RA drugs had weight loss effects, especially CagriSema, tirzepatide, and retatrutide, thus enriching the clinical therapeutic approaches. Notably, GLP-1RAs can be used to reach the desired short term outcome in diabetes management: effective glucose lowering without weight gain. In treating type 2 diabetes, meeting glycaemic targets is compromised by the limitations of available treatments, with some antidiabetic drugs (eg, insulin) associated with weight gain.[46] In this context, GLP-1RAs, as a novel strategy, can adequately address this clinical dilemma by promoting glycaemic homeostasis while reducing weight gain. Moreover, this study also raises awareness of the risks of gastrointestinal adverse events induced by GLP-1RAs, and safety concern is especially warranted for high dose administration.

Conclusions

Results for GLP-1RAs showed that these drugs were much more effective than placebo in treating adults with type 2 diabetes. Tirzepatide was the most effective GLP-1RA drug on glycaemic control by reducing HbA_{1c} and fasting blood glucose. GLP-1RA also significantly improved weight management for type 2 diabetes, with CagriSema performing the best on weight loss. Our study also prompts safety concerns for GLP-1RAs with regard to gastrointestinal adverse events.

Contributors: HY and AZ contributed equally to this work. HY and J-YW conceived the initial research idea and obtained funding for this study. HY, AZ, J-YW, and C-SY did the relevant literature searches and screened the articles for inclusion. HY, AZ, DL, and YW extracted the data for analysis and conducted the quality assessment of eligible studies. HY and AZ performed the meta-analysis and produced forest plots and summary results under the supervision of J-YW and C-SY. HY, AZ and J-YW drafted the protocol and the manuscript. C-ZW and C-SY contributed to designing the searches and contributed to the manuscript by providing review comments and edits. J-YW is the study guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required.

Data sharing: All data are publicly available.

The lead author (J-YW) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: We plan to share the findings with appropriate audiences, such as academia, clinicians, policymakers, and the general public, through various channels, including scientific conferences, press releases, and social media.

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