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ORIGINAL RESEARCH

Long-Term Efficacy Trajectories of GLP-1 Receptor Agonists: A Systematic Review and Network Meta-Analysis

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Purpose: To investigate the long-term efficacy and changing trajectories of glucagon-like peptide-1 receptor agonists (GLP-1RAs) among patients with type 2 diabetes.

Methods: The PubMed, Embase and Cochrane Library databases were searched up to March 2024 to identify randomized controlled trials that assessed the efficacy of GLP-1RAs compared with placebo. To further explore the long-term trajectories of GLP-1RAs, we also conducted subgroup analyses of the placebo-subtracted groups based on the follow-up periods: 12–18 weeks, 24–30 weeks, 48–56 weeks, 68–78 weeks and ≥ 104 weeks.

Results: Fifty-five trials involving 18,876 participants were included in this meta-analysis. GLP-1RAs significantly improved HbA1c levels, body weight, fasting plasma glucose (FPG), systolic blood pressure, and serum lipid levels. GLP-1RAs continuously reduced HbA1c and FPG for at least 104 weeks, with the largest reductions observed at 12–18 weeks (versus placebo, WMD −0.99 [−1.09, −0.89], P < 0.001; −1.56 [−1.82. −1.29], P < 0.001, respectively). However, the reductions in HbA1c and FPG at ≥ 104 weeks were approximately 0.36% and 0.47 mmol/L less than the reductions at 12–18 weeks, respectively. With respect to weight loss, the optimal effect was observed at 24–30 weeks (WMD −2.42 [−2.90, −1.95], P < 0.001), followed by a plateau period. In addition, GLP-1RAs were associated with a greater risk of hypoglycemia and gastrointestinal adverse events.

Conclusion: GLP-1RAs are recommended for long-term treatment of patients with type 2 diabetes due to the persistent improvement in glycemic control and weight loss. However, it is important to account for the weakening effects after 2 years.

Keywords: glucagon-like peptide 1 receptor agonists, type 2 diabetes, network meta-analysis, systematic review

Introduction

Type 2 diabetes mellitus (T2DM) has become a significant global public health concern, especially affecting about 12.02% of people in China according to the latest prediction.[1] Characterized by impaired glucose homeostasis causing persistent hyperglycemia, T2DM is typically accompanied by weight gain, which is a vital determinant of poor glycemic control.[2–4] A cohort study conducted among Americans revealed that people who exhibited weight-gain patterns were more prone to high HbA1c levels than individuals who exhibit weight-loss patterns.[5] Similarly, a recent study conducted in a Chinese population also revealed that patients with T2DM who experienced weight gain ≥3% tended to have higher HbA1c levels.[6] Previous studies have confirmed that weight gain tends to increase insulin resistance and promotes the development of β-cell dysfunction, which is another important factor that contributes to unsatisfactory glucose control.[7,8] Accordingly, the American Diabetes Association (ADA) standard care of diabetes suggests that it is necessary to consider the potential beneficial effects on weight loss when selecting antidiabetic medicines for patients with T2DM and excess body weight.[9]

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Several antidiabetic drugs, especially sulfonylureas and insulin, play a role in controlling blood glucose levels but also lead to increased risks of weight gain and hypoglycemia.[10–12] Consequently, a novel class of glucose-lowering agents, GLP-1 receptor agonists (GLP-1RAs), has attracted considerable attention. GLP-1 is an intestinal peptide hormone that promotes glucose-dependent insulin secretion, slows gastric emptying and reduces food intake.[13] Compared with traditional treatments, GLP-1RAs offer advantages not only in glycemic control but also in weight management, further reducing diabetes-related complications.[14,15] Moreover, a network meta-analysis demonstrated that GLP-1RAs were associated with improvements in insulin resistance and β-cell function, thereby leading to diabetes remission.[16] As such, the latest Chinese guidelines recommend GLP-1RAs for patients with type 2 diabetes mellitus (T2DM) who are overweight or obese.[17]

Furthermore, given the chronic nature of T2DM, which requires lifelong treatment, it is equally crucial to assess the efficacy and durability of GLP-1RAs for long-term use.[18,19] There are numerous reviews and empirical studies that have confirmed the sustained benefits of GLP-1RAs on glycemic control and weight loss.[12,20–25] However, most of those studies did not consider the trajectory of effects on glycemic control and weight loss by GLP-1RAs, particularly the magnitude and duration of potential attenuation. Understanding these precise trajectories is crucial for clinicians to optimize monitoring and treatment strategies. Yao et al[22] compared the efficacy only based on subgroup analysis with follow-up durations of 3–6, 6–12 and >12 months. Their study reported that the efficacy of GLP-1RAs was affected by the treatment duration, and the effects of tirzepatide on glycemic control and weight loss strengthened over time. In addition, several GLP-1RAs, such as semaglutide, liraglutide and dulaglutide, had a decreasing efforts on body weight. However, the article only briefly compared the efficacy of main endpoints across different follow-up time points. Additionally, their analysis did not further investigate the trajectories beyond 12 months or quantify the potential attenuation of effects during this period.

Therefore, we conducted this meta-analysis to assess the long-term efficacy and safety of GLP-1RAs in patients with T2DM. Furthermore, we described the trajectory of the effects of GLP-1RAs on glycemic control and body weight by comparing the placebo-subtracted differences between different follow-up periods.

Materials and Methods

This study was conducted following the Cochrane Collaboration Guidelines and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement. We registered the protocol in PROSPERO (CRD42024533999).

Data Sources and Searches

This study is a systematic review and meta-analysis evaluating the duration of efficacy and safety of GLP-1 receptor agonists for the treatment of type 2 diabetes. An extensive search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed from database inception to March 2024. The detailed search strategies can be found in Table S1.

Study Selection

We selected fully published randomized controlled trials (RCTs) in adults with T2DM for whom the treatment period was at least 24 weeks. Eligible trials compared the efficacy and safety between GLP-1RAs approved by the FDA and placebo. The maintenance doses of interest were as follows: dulaglutide 1.5 mg once weekly (QW), exenatide 10 μg twice daily (BID), exenatide 2 mg QW, semaglutide 14 mg once daily (QD), semaglutide 1 mg QW, liraglutide 1.8 mg QD, albiglutide 30 mg QW, lixisenatide 20 μg QD and tirzepatide 15 mg QW.[26,27]

Studies were excluded if they (1) were observational, open-label or crossover study designs or secondary analyses of the included trials; (2) lacked information on the interventions and outcomes of interest; or (3) were published in a non-English language. Fixed-dose combinations of GLP-1 receptor agonists and other antidiabetic drugs were also perceived as ineligible.

The primary efficacy measures for this network meta-analysis were the changes from baseline in HbA1c or body weight. The secondary efficacy endpoints included changes in fasting plasma glucose (FPG), systolic blood pressure

(SBP), diastolic blood pressure (DBP), and serum lipid levels (including triglyceride, total cholesterol, HDL cholesterol and LDL cholesterol) from baseline. The safety endpoints were the incidence of hypoglycemic episodes (including severe hypoglycemia), gastrointestinal events, acute pancreatitis, and thyroid cancer.

Data Extraction and Quality Assessment

Our study summarized numerous RCTs with follow-up durations ranging from 24 weeks to 3 years. Owing to the significant variability and limited number of trials conducted over 2 years, we chose 104 weeks as the longest analysis time point. Moreover, we merged data from more than 104 weeks and discussed them together within 104 weeks. As such, we analyzed five time points in the subgroup analysis: 12–18, 24–30, 48–56, 68–78 and ≥104 weeks.

Two authors independently performed the literature search and extracted study data on the basis of the predesigned criteria, and any discrepancies were resolved by a third reviewer. The following data were extracted from each article: first author, year of study, trial registration number, patients' demographic characteristics, study duration, study arms, and outcomes of interest. Changes from baseline at each time point were collected directly from the articles when available or calculated from the baseline and follow-up values. Furthermore, we derived the values of other follow-ups from graphs provided by using the WebPlotDigitizer program available online (https://wpd.starrydata2.org/). In the case of more than one report pertaining to the same study, we selected the report with the most complete and informative data. The quality of the studies included was assessed via the Cochrane risk of bias tool.[28] Two researchers independently assessed the risk of bias in the trials, and disagreements were resolved through consensus.

Data Synthesis and Statistical Analysis

First, random-effects pairwise meta-analyses were carried out for direct comparisons. We conducted subgroup analyses on the basis of different GLP-1RAs and follow-ups. Subsequently, frequentist random effects network meta-analyses were performed to assess the transitivity assumption regarding efficacy between different follow-ups. The efficacy of placebo-subtracted differences was discussed separately in the network meta-analysis. Meta-regression analysis was performed using Stata 17.0 to explore heterogeneity sources ($I^2 > 50\%$). Pre-selected primary moderators included drug type, background therapy, and baseline characteristics (age, diabetes duration, proportion of females, weight, BMI and HbA1c).

Results

Study Characteristics

A total of 12,891 articles were initially retrieved via the search strategy (Figure 1). After the removal of 5,608 duplicate articles, 7,283 articles remained for title and abstract screening. A total of 7,189 articles were excluded on the basis of titles and abstracts, and thus, 94 articles remained for full-text screening. After assessing the full texts, 39 additional articles were excluded due to the following reasons: unable to obtain the full text (n=3), incorrect interventions (n=3), non-placebo-controlled trials (n=1), unsuitable study designs (n=5), irrelevant outcomes (n=19) and secondary publications of included trials (n=8). Ultimately, fifty-five trials (18,876 participants) were included in this meta-analysis. We included seven trials examining dulaglutide QW, ten trials examining exenatide BID, one trial examining exenatide QW, five trials examining semaglutide QD, four trials examining semaglutide QW, twelve trials examining liraglutide QD, five trials examining albiglutide QW, ten trials examining lixisenatide QD and four trials examining tirzepatide QW.

The characteristics of the included studies are presented in Table S2. The durations of the studies varied widely, including thirty-eight studies with durations of 24–30 weeks, two studies with durations of 40 weeks, six studies with durations of 52–56 weeks, four studies with durations of 68–76 weeks, and five studies with durations of ≥104 weeks. As shown in Figures S1 and 2, the included trials all had an low risk of bias.

Efficacy Outcomes

Pooled Analysis

The results regarding the efficacy of the treatment compared with the placebo are presented in Table 1. All GLP-1RAs had a positive effect on reducing HbA1c (WMD −1.00, 95% CI [−1.11, −0.90], $P < 0.001$) and FPG levels (WMD −1.37

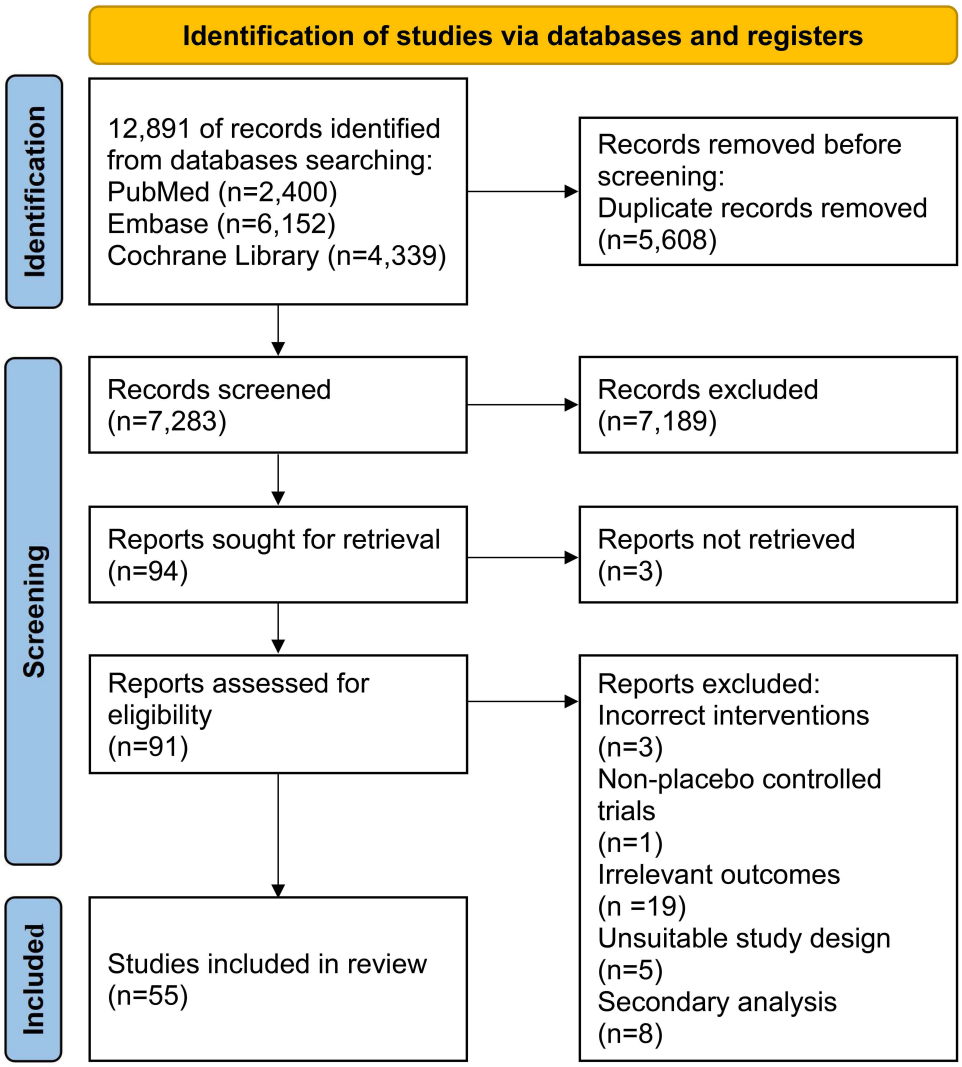

Figure 1 Flow diagram of study selection.

[−1.55, −1.18], P < 0.001). With the exception of albiglutide (WMD 0.58 [0.18, 0.97], P = 0.004), all the other GLP-1RAs significantly reduced body weight (P < 0.001). There were no data on the effects of lixisenatide on blood pressure. GLP-1RAs had an overall effect on reducing SBP (WMD −3.53 [−4.27, −2.80], P < 0.001); however, only exenatide BID

Table 1 Summary of Results of Efficacy Changes Comparing GLP-1RAs with Placebo in T2DM Patients

Comparison		No. of Comparisons	Participants (GLP-1RAs/ Placebo)	Overall Effect		Heterogeneity		
Outcomes	Subgroups			Pooled Results WMD (95% CI)	P	Tau^2	I^2, %	P
% HbA1c	Overall	58	10,941/8269	−1.00 [−1.11, −0.90]	< 0.001	0.14	91	< 0.001
	Dulaglutide 1.5 mg QW	7	1312/866	−1.02 [−1.18, −0.86]	< 0.001	0.03	72	0.002
	Exenatide 10 μg BID	10	1281/1028	−0.80 [−0.96, −0.63]	< 0.001	0.04	68	< 0.001
	Exenatide 2 mg QW	1	231/230	−0.73 [−0.95, −0.51]	< 0.001	NA	NA	NA
	Semaglutide 14 mg QD	5	852/714	−1.28 [−1.40, −1.16]	< 0.001	0.01	35	0.190
	Semaglutide 1.0 mg QW	4	815/816	−1.47 [−1.68, −1.25]	< 0.001	0.04	78	0.004
	Liraglutide 1.8 mg QD	12	2106/1564	−1.02 [−1.15, −0.89]	< 0.001	0.03	69	<0.001
	Albiglutide 30 mg QW	5	976/542	−0.90 [−1.11, −0.70]	< 0.001	0.04	72	0.006
	Lixisenatide 20 μg QD	10	2763/1908	−0.54 [−0.65, −0.43]	< 0.001	0.01	49	0.040
	Tirzepatide 15 mg QW	4	605/601	−1.94 [−2.23, −1.66]	< 0.001	0.06	77	0.005

(*Continued*)

Table 1 (Continued).

Comparison		No. of Comparisons	Participants (GLP-1RAs/ Placebo)	Overall Effect		Heterogeneity		
Outcomes	**Subgroups**			**Pooled Results WMD (95% CI)**	**P**	**Tau²**	**I², %**	**P**
Weight	Overall	58	10,941/8269	−2.24 [−2.71, −1.77]	< 0.001	3.06	94	< 0.001
(kg)	Dulaglutide 1.5 mg QW	7	1312/866	−1.64 [−2.19, −1.09]	< 0.001	0.34	68	0.005
	Exenatide 10 μg BID	10	1281/1028	−1.80 [−2.41, −1.20]	< 0.001	0.63	72	< 0.001
	Exenatide 2 mg QW	1	231/230	−1.50 [−2.21, −0.79]	< 0.001	NA	NA	NA
	Semaglutide 14 mg QD	5	852/714	−2.93 [−3.71, −2.14]	< 0.001	0.62	79	< 0.001
	Semaglutide 1.0 mg QW	4	815/816	−4.07 [−4.65, −3.49]	< 0.001	0.14	40	0.170
	Liraglutide 1.8 mg QD	12	2106/1564	−2.01 [−2.61, −1.41]	< 0.001	0.84	77	< 0.001
	Albiglutide 30 mg QW	5	976/542	0.58 [0.18, 0.97]	0.004	0.00	0	0.440
	Lixisenatide 20 μg QD	10	2763/1908	−0.84 [−1.10, −0.58]	< 0.001	0.06	37	0.120
	Tirzepatide 15 mg QW	4	605/601	−8.80 [−9.62, −7.99]	< 0.001	0.25	37	0.190
FPG	Overall	53	10,657/8011	−1.37 [−1.55, −1.18]	< 0.001	0.40	86	< 0.001
(mmol/L)	Dulaglutide 1.5 mg QW	6	1258/815	−1.50 [−1.95, −1.05]	< 0.001	0.25	85	< 0.001
	Exenatide 10 μg BID	9	1253/1010	−0.98 [−1.32, −0.65]	< 0.001	0.16	63	0.005
	Exenatide 2 mg QW	1	231/230	−0.67 [−1.17, −0.17]	0.009	NA	NA	NA
	Semaglutide 14 mg QD	5	852/714	−1.76 [−1.96, −1.56]	< 0.001	0.00	0	0.530
	Semaglutide 1.0 mg QW	4	815/816	−1.86 [−2.09, −1.63]	< 0.001	0.01	18	0.300
	Liraglutide 1.8 mg QD	11	1960/1426	−1.61 [−1.89, −1.34]	< 0.001	0.11	59	0.006
	Albiglutide 30 mg QW	5	976/542	−1.56 [−1.87, −1.25]	< 0.001	0.03	23	0.270
	Lixisenatide 20 μg QD	10	2760/1908	−0.54 [−0.72, −0.37]	< 0.001	0.00	0	0.550
	Tirzepatide 15 mg QW	3	552/550	−2.58 [−3.30, −1.85]	< 0.001	0.33	83	0.002
SBP	Overall	36	6347/4931	−3.53 [−4.27, −2.80]	< 0.001	2.35	49	< 0.001
(mmHg)	Dulaglutide 1.5 mg QW	4	876/429	−2.60 [−4.09, −1.10]	< 0.001	0.00	0	0.650
	Exenatide 10 μg BID	5	698/492	−3.98 [−5.92, −2.04]	0.001	1.42	29	0.230
	Exenatide 2 mg QW	1	231/230	−1.90 [−4.39, 0.59]	0.140	NA	NA	NA
	Semaglutide 14 mg QD	5	852/714	−3.43 [−6.47, −0.38]	0.002	9.43	79	< 0.001
	Semaglutide 1.0 mg QW	4	815/816	−4.66 [−6.79, −2.52]	< 0.001	2.64	57	0.070
	Liraglutide 1.8 mg QD	11	1872/1450	−2.68 [−3.92, −1.44]	< 0.001	1.60	38	0.100
	Albiglutide 30 mg QW	2	398/199	−3.61 [−5.96, −1.25]	0.003	0.00	0	0.710
	Tirzepatide 15 mg QW	4	605/601	−5.51 [−7.03, −3.99]	< 0.001	0.00	0	0.500
DBP	Overall	33	5680/4580	−0.90 [−1.31, −0.50]	< 0.001	0.38	28	0.070
(mmHg)	Dulaglutide 1.5 mg QW	4	876/429	−0.69 [−1.65, 0.27]	0.160	0.00	0	0.450
	Exenatide 10 μg BID	5	698/492	−2.00 [−3.14, −0.86]	< 0.001	0.41	24	0.260
	Exenatide 2 mg QW	1	231/230	0.10 [−1.56, 1.76]	0.910	NA	NA	NA
	Semaglutide 14 mg QD	5	852/714	−1.01 [−2.17, 0.15]	0.090	0.74	43	0.130
	Semaglutide 1.0 mg QW	4	815/816	−0.19 [−1.07, 0.69]	0.680	0.05	6	0.360
	Liraglutide 1.8 mg QD	10	1712/1411	−0.18 [−0.82, 0.47]	0.590	0.00	0	0.640
	Albiglutide 30 mg QW	1	101/99	−0.90 [−3.31, 1.51]	0.460	NA	NA	NA
	Tirzepatide 15 mg QW	4	605/601	−2.19 [−3.09, −1.28]	< 0.001	0.00	0	0.890
TG	Overall	17	2803/2201	−0.26 [−0.39, −0.14]	< 0.001	0.04	91	< 0.001
(mmol/L)	Dulaglutide 1.5 mg QW	2	333/192	−0.41 [−0.68, −0.14]	0.003	0.01	17	0.270
	Exenatide 10 μg BID	2	372/239	0.02 [−0.19, 0.23]	0.860	0.02	58	0.120
	Exenatide 2 mg QW	1	231/230	0.02 [0.01, 0.03]	0.001	NA	NA	NA
	Liraglutide 1.8 mg QD	6	865/740	−0.21 [−0.34, −0.09]	< 0.001	0.00	0	0.600
	Albiglutide 30 mg QW	2	397/199	−0.19 [−0.42, 0.03]	0.100	0.00	0	0.450
	Tirzepatide 15 mg QW	4	605/601	−0.49 [−0.68, −0.30]	< 0.001	0.03	78	0.004
TC	Overall	18	2896/2234	−0.19 [−0.27, −0.11]	< 0.001	0.02	61	< 0.001
(mmol/L)	Dulaglutide 1.5 mg QW	2	333/192	−0.30 [−0.60, −0.01]	0.040	0.03	61	0.110
	Exenatide 10 μg BID	3	465/272	−0.11 [−0.20, −0.02]	0.020	0.00	0	0.950
	Exenatide 2 mg QW	1	231/230	−0.05 [−0.27, 0.17]	0.660	NA	NA	NA
	Liraglutide 1.8 mg QD	6	865/740	−0.10 [−0.22, 0.03]	0.130	0.01	29	0.220
	Albiglutide 30 mg QW	2	397/199	−0.11 [−0.33, 0.11]	0.320	0.01	47	0.170
	Tirzepatide 15 mg QW	4	605/601	−0.40 [−0.59, −0.20]	< 0.001	0.03	72	0.010

(*Continued*)

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Table 1 (Continued).

Comparison		No. of Comparisons	Participants (GLP-1RAs/ Placebo)	Overall Effect		Heterogeneity		
Outcomes	Subgroups			Pooled Results WMD (95% CI)	P	Tau^2	I^2, %	P
HDL-C	Overall	18	2758/2057	0.01 [−0.01, 0.03]	0.480	0.00	57	0.002
(mmol/L)	Dulaglutide 1.5 mg QW	2	333/192	0.02 [−0.01, 0.06]	0.220	0.00	0	0.530
	Exenatide 10 μg BID	4	537/307	−0.01 [−0.04, 0.03]	0.760	0.00	35	0.200
	Exenatide 2 mg QW	1	231/230	−0.04 [−0.09, 0.01]	0.150	NA	NA	NA
	Liraglutide 1.8 mg QD	5	655/528	−0.00 [−0.04, 0.03]	0.970	0.00	42	0.140
	Albiglutide 30 mg QW	2	397/199	−0.01 [−0.05, 0.03]	0.660	0.00	27	0.240
	Tirzepatide 15 mg QW	4	605/601	0.05 [−0.01, 0.11]	0.11	0.00	82	< 0.001
LDL-C	Overall	17	2686/2022	−0.11 [−0.17, −0.05]	< 0.001	0.01	44	0.030
(mmol/L)	Dulaglutide 1.5 mg QW	2	333/192	−0.15 [−0.28, −0.02]	0.020	0.00	5	0.310
	Exenatide 10 μg BID	3	465/272	−0.06 [−0.14, 0.01]	0.100	0.00	0	0.800
	Exenatide 2 mg QW	1	231/230	−0.04 [−0.23, 0.15]	0.690	NA	NA	NA
	Liraglutide 1.8 mg QD	5	655/528	−0.04 [−0.13, 0.05]	0.420	0.00	0	0.720
	Albiglutide 30 mg QW	2	397/199	−0.06 [−0.20, 0.08]	0.380	0.00	14	0.280
	Tirzepatide 15 mg QW	4	605/601	−0.26 [−0.43, −0.09]	0.003	0.02	72	0.010

Notes: Follow-up at primary endpoints as a priority.
Abbreviations: HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GLP-1RAs, glucagon-like peptide 1 receptor agonists; T2DM, type 2 diabetes mellitus; WMD, weighted mean differences; CI, confidence internal; NA, not available.

and tirzepatide were superior in reducing DBP compared with placebos (P < 0.001). Moreover, there were no data on the effects of lixisenatide or semaglutide on changes in serum lipid levels. GLP-1RAs – mainly tirzepatide – had weak effects on reducing triglyceride, total cholesterol and LDL cholesterol (LDL-C) levels (P < 0.01). No significant differences in improving HDL cholesterol (HDL-C) levels were detected between the GLP-1RA group and the placebo group (P = 0.480). In summary, GLP-1RAs improved HbA1c levels, body weight, FPG levels, blood pressure and serum lipid levels.

As shown in Table S3, meta-regression revealed that proportion of females was a significant moderator (β = −0.017, 95% CI −0.005 to −0.030, p=0.007). None of the pre-selected covariates showed significant effects on HbA1c and weight changes.

Subgroup Analysis Based on Follow-Up Duration

As shown in Table 2, a subgroup analysis based on the follow-up duration was conducted: 12–18 weeks, 24–30 weeks, 48–56 weeks, 68–78 weeks, and ≥104 weeks. We investigated changes in HbA1c levels, body weight, FPG levels, and systolic blood pressure from baseline to each follow-up point between the treatment group and the placebo group. Compared with the placebo group, GLP-1RAs significantly reduced HbA1c levels, FPG levels and SBP at each follow-up point (P<0.001). Considering that albiglutide had no effect on weight loss at any follow-up point (Figure S3), we excluded this agent from the subsequent analyses. Thus, the overall effect of GLP-1RAs on weight loss slightly changed to WMD −2.42 kg (95% CI [−2.89, −1.95], P < 0.001). Compared with placebos, GLP-1RAs were more effective for weight loss at 12–18, 24–30 and 48–56 weeks (P < 0.05, respectively) but were equally effective at 68–78 weeks (WMD −5.66 [−11.36, 0.03], P = 0.050). In addition, we also provided the results of subgroup analysis on serum lipids by follow-up in Table S4.

Placebo-Subtracted Differences

To further explore the long-term effects of GLP-1RAs on T2DM, we synchronously compared the placebo-subtracted group at each follow-up point via network meta-analysis. The network maps of efficacy at each follow-up point are shown in Figure S4. The results of the surface under the cumulative ranking curve (SUCRA) and mean rank analyses are shown in Figure S5 and Table S5.

Table 2 Subgroup Analysis on Efficacy Changes by Follow-Up Comparing GLP-1RAs with Placebo in T2DM Patients

Comparison		No. of Comparisons	Participants (GLP-1RAs/ Placebo)	Overall Effect		Heterogeneity		
Outcomes	Subgroups			Pooled Results WMD (95% CI)	P	Tau^2	I^2, %	P
% HbA1c	12-18 weeks	53	10,010/7333	−0.99 [−1.09, −0.89]	< 0.001	0.13	92	< 0.001
	24-30 weeks	57	10,719/8047	−1.00 [−1.11, −0.89]	< 0.001	0.15	91	< 0.001
	48-56 weeks	12	2854/2071	−1.07 [−1.35, −0.80]	< 0.001	0.22	96	< 0.001
	68-78 weeks	4	1333/978	−0.99 [−1.50, −0.47]	< 0.001	0.26	96	< 0.001
	≥104 weeks	4	816/465	−0.44 [−0.58, −0.29]	< 0.001	0.01	45	0.140
Weight (kg)	12-18 weeks	43	8084/6422	−2.18 [−2.58, −1.79]	< 0.001	1.51	93	< 0.001
	24-30 weeks	53	9960/7711	−2.42 [−2.90, −1.95]	< 0.001	2.84	94	< 0.001
	48-56 weeks	8	2038/1606	−3.85 [−6.02, −1.69]	< 0.001	9.14	97	< 0.001
	68-78 weeks	3	1036/878	−5.66 [−11.36, 0.03]	0.050	24.98	99	< 0.001
FPG (mmol/L)	12-18 weeks	30	6638/4557	−1.56 [−1.82, −1.29]	< 0.001	0.48	90	< 0.001
	24-30 weeks	55	10,797/8148	−1.35 [−1.54, −1.16]	< 0.001	0.40	86	< 0.001
	48-56 weeks	11	2452/1669	−1.68 [−2.14, −1.22]	< 0.001	0.53	90	< 0.001
	68-78 weeks	4	1253/736	−1.23 [−2.17, −0.29]	0.010	0.86	94	< 0.001
	≥104 weeks	4	816/465	−1.18 [−1.41, −0.96]	< 0.001	0.00	0	0.660
SBP (mmHg)	12-18 weeks	7	1193/1254	−3.61 [−4.65, −2.57]	< 0.001	0.00	0	0.980
	24-30 weeks	33	5638/4417	−3.46 [−4.26, −2.66]	< 0.001	2.69	52	< 0.001
	48-56 weeks	8	1809/1331	−3.36 [−4.32, −2.39]	< 0.001	0.00	0	0.930
	68-78 weeks	2	714/718	−3.83 [−6.07, −1.59]	< 0.001	1.23	47	0.170

Abbreviations: HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; SBP, systolic blood pressure; GLP-1RAs, glucagon-like peptide 1 receptor agonists; T2DM, type 2 diabetes mellitus; WMD, weighted mean differences; CI, confidence internal; NA, not available.

The results of the network meta-analysis examining placebo-subtracted differences in lowering HbA1c are presented in Figure 2A and Table 3A. There were no significant differences between the follow-up durations of 12–18, 24–30, 48–56 and 68–78 weeks. The optimal effect of GLP-1RAs on reducing HbA1c levels was observed at 12–18 weeks. However, the effect tended to deteriorate, and significant deterioration began at 104 weeks. At ≥ 104 weeks, the efficacy was lower than at the other follow-up points (WMD 0.36, 95% CI [0.22, 0.49]; 0.37 [0.24, 0.50]; 0.34 [0.20, 0.48]; 0.32 [0.15, 0.49], respectively).

The results of placebo-subtracted differences in decreasing body weight are presented in Figure 2B and Table 3A. The efficacy at 12–18 weeks was less effective than that at 24–30, 48–56 and 68–78 weeks (WMD 0.65 [0.32, 0.97]; 1.20 [0.51, 1.90]; 1.85 [0.79, 2.91], respectively). No significant differences were found between the efficacy at 24–30 and 48–56 weeks or between 48–56 and 76–83 weeks. In other words, the weight loss effects of GLP-1RAs showed an increasing trend and were strongest at 24–30 weeks, followed by a plateau period.

Similarly, the greatest reduction in FPG levels occurred at 12–18 weeks, followed by obvious deterioration after 104 weeks. There were no significant differences detected between the follow-up points of 12–18, 24–30, 48–56 and 68–76 weeks (Figure 2C and Table 3B). Compared with the efficacy at ≥ 104 weeks, greater efficacy was observed at 12–18, 24–30 and 48–56 weeks (WMD −0.47 [−0.81, −0.13]; −0.39 [−0.73, −0.05]; −0.41 [−0.76, −0.05], respectively), while equal efficacy was observed at 76–83 weeks (−0.21 [−0.66, 0.23]). As shown in Figure 2D and Table 3B, placebo-subtracted differences indicated that the reduction in SBP was strongest at 12–18 weeks and remained stable thereafter.

In addition, we explored the placebo-subtracted differences based on treatment protocols, such as different medication methods and background treatments (Tables S6–11). We observed similar trends in glycemic control and weight loss for weekly GLP-1RAs. For daily GLP-1RAs, slight difference in the trend of HbA1c and FPG reduction were exhibited, with the declining effects advanced to 48–56 weeks. Regardless of whether monotherapy, GLP-1RAs combined with one antidiabetic drug or other two-drug treatments were used, the effects of GLP-1RA on reducing HbA1c and FPG levels at ≥ 104 weeks were less effective. With respect to weight loss, the optimal effect was observed at 24–30 weeks when GLP-1RAs were combined with one antidiabetic drug or when other two-drug treatments were used.

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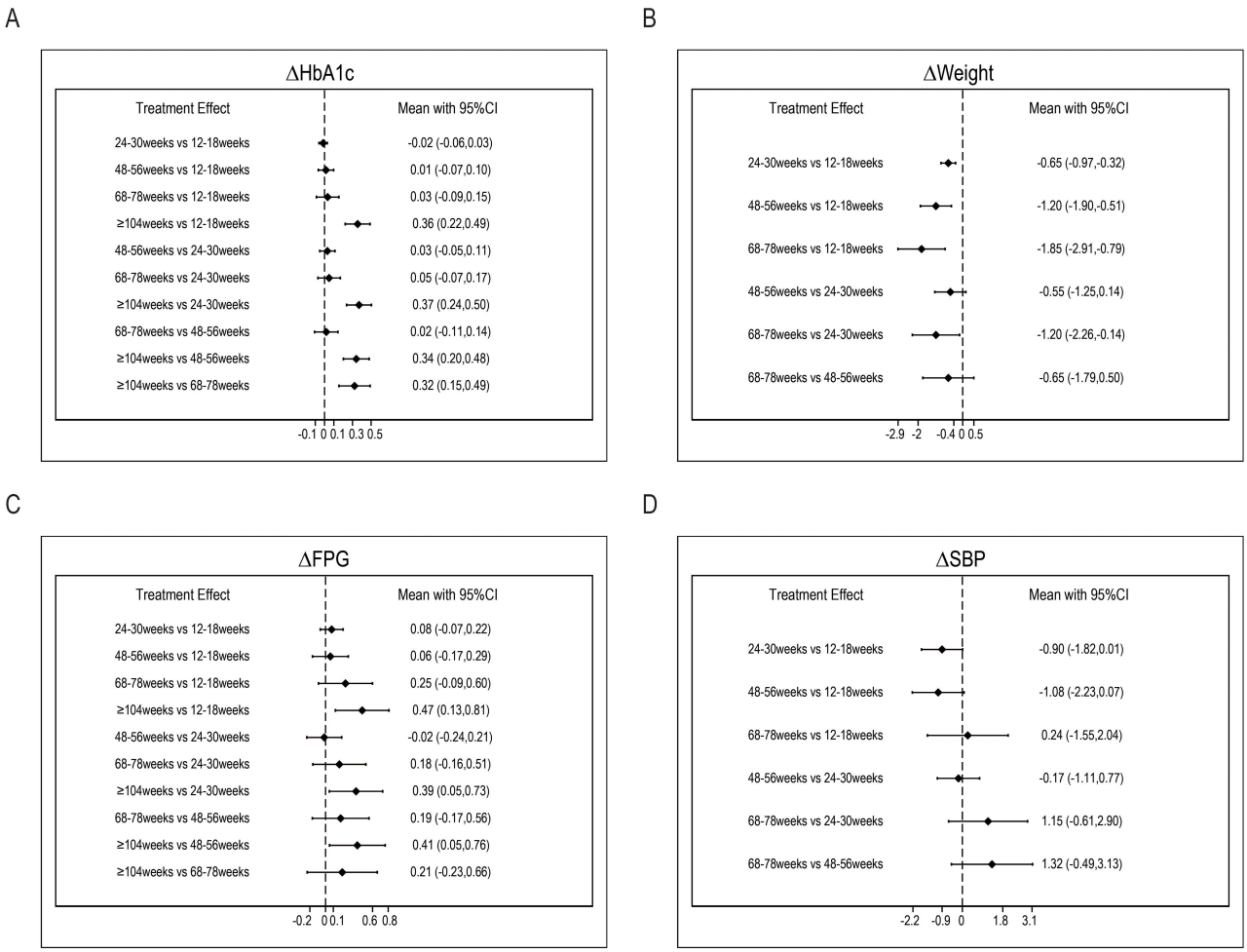

Figure 2 The interval plot of efficacy on placebo-subtracted comparison between different follow-ups. (**A**) ΔHbA1c; (**B**) ΔWeight; (**C**) ΔFPG; (**D**) ΔSBP.

Intragroup Differences

We also compared the intragroup differences via pairwise meta-analysis (Table S12). The results of the intragroup differences confirmed that GLP-1RAs led to the greatest reduction in HbA1c and FPG levels at 12–18 weeks, and such effects may weaken over time. Additionally, there were stable effects in terms of reducing body weight and SBP after 24–30 and 12–18 weeks, respectively.

Table 3 League Tables of Placebo-Subtracted Differences for GLP-1RAs in Efficacy by Follow-Up

(A)ΔHbA1c and ΔWeight				
12-18 weeks	**−0.65 (−0.97, −0.32)**	**−1.20 (−1.90, −0.51)**	**−1.85 (−2.91, −0.79)**	–
0.02 (−0.03, 0.06)	**24-30 weeks**	−0.55 (−1.25, 0.14)	**−1.20 (−2.26, −0.14)**	–
−0.01 (−0.10, 0.07)	−0.03 (−0.11, 0.05)	**48-56 weeks**	−0.65 (−1.79, 0.50)	–
−0.03 (−0.15, 0.09)	−0.05 (−0.17, 0.07)	−0.02 (−0.14, 0.11)	**68-78 weeks**	–
−0.36 (−0.49, −0.22)	**−0.37 (−0.50, −0.24)**	**−0.34 (−0.48, −0.20)**	**−0.32 (−0.49, −0.15)**	**≥ 104 weeks**

(*Continued*)

Table 3 (Continued).

(B)ΔFPG and ΔSBP				
12-18 weeks	−0.90 (−1.82, 0.01)	−1.08 (−2.23, 0.07)	0.24 (−1.55, 2.04)	–
−0.08 (−0.22, 0.07)	**24-30 weeks**	−0.17 (−1.11, 0.77)	1.15 (−0.61, 2.90)	–
−0.06 (−0.29, 0.17)	0.02 (−0.21, 0.24)	**48-56 weeks**	1.32 (−0.49, 3.13)	–
−0.25 (−0.60, 0.09)	−0.18 (−0.51, 0.16)	−0.19 (−0.56, 0.17)	**68-78 weeks**	–
−0.47 (−0.81, −0.13)	**−0.39 (−0.73, −0.05)**	**−0.41 (−0.76, −0.05)**	−0.21 (−0.66, 0.23)	**≥ 104 weeks**

Notes: Results of ΔHbA1c and ΔFPG were presented in the bottom left corner, and results of Δweight and ΔSBP were in the upper right corner. The columns represent the comparison of the row follow-up to the column follow-up. The rows represent the comparison of the row follow-up to the column follow-up. Data are WMD (95% CI) in the column-defining treatment compared with the row-defining treatment. WMD < 0 favors the follow-up in the column, and WMD > 0 favors the follow-up in the row. Statistically significant differences are in bold.

Abbreviations: HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; SBP, systolic blood pressure; GLP-1RAs, glucagon-like peptide 1 receptor agonists.

Safety Outcomes

A summary of the overall safety and selected adverse events (AEs) is shown in Table 4. Compared with placebo, GLP-1RAs were associated with a significant increase in AEs at 24–30 weeks (RR 1.14, 95% CI 1.09 to 1.18, P < 0.001, I^2 =

Table 4 Safety of GLP-1RAs Compared with Placebo in T2DM Patients by Follow-Up

Comparison		**No. of Comparisons**	**Participants (GLP-1RAs/ Placebo)**	**Overall Effect**		**Heterogeneity**		
Outcomes	**Subgroups**			**Pooled Results RR (95% CI)**	**P**	**Tau²**	**I², %**	**P**
Adverse events (AEs)	Overall	50	9666/6954	1.11 [1.08, 1.15]	<0.001	0.01	50	<0.001
(N)	24-30 weeks	36	6720/5002	1.14 [1.09, 1.18]	<0.001	0.01	44	0.003
	48-56 weeks	9	1690/1173	1.08 [1.02, 1.15]	0.009	0.00	52	0.030
	68-78 weeks	4	1358/1038	1.02 [0.97, 1.08]	0.450	0.00	42	0.160
	≥ 104 weeks	1	302/101	1.34 [0.52, 3.47]	0.550	NA	NA	NA
Serious adverse	Overall	57	10,720/7876	0.95 [0.84, 1.08]	0.460	0.00	0	0.470
Events (SAEs) (N)	24-30 weeks	43	7774/5933	0.96 [0.81, 1.14]	0.650	0.02	7	0.350
	48-56 weeks	9	1690/1173	0.90 [0.65, 1.24]	0.520	0.05	23	0.240
	68-78 weeks	4	1047/723	0.91 [0.70, 1.17]	0.460	0.00	0	0.730
	≥ 104 weeks	1	302/101	0.93 [0.51, 1.68]	0.800	NA	NA	NA
Withdrawal due to	Overall	58	10,962/8280	2.11 [1.74, 2.56]	<0.001	0.18	36	0.004
AEs (N)	24-30 weeks	44	7909/5952	2.23 [1.76, 2.83]	<0.001	0.22	40	0.005
	48-56 weeks	9	1690/1173	1.97 [1.21, 3.20]	0.006	0.23	43	0.080
	68-78 weeks	4	1358/1038	1.41 [0.98, 2.05]	0.070	0.00	0	0.820
	≥ 104 weeks	1	302/101	1.34 [0.52, 3.47]	0.550	NA	NA	NA
Total hypoglycemia	Overall	54	10,436/7966	1.51 [1.31, 1.73]	<0.001	0.11	63	<0.001
(N)	24-30 weeks	41	7650/5817	1.61 [1.36, 1.91]	<0.001	0.14	68	<0.001
	48-56 weeks	8	1530/1096	1.27 [0.97, 1.67]	0.080	0.04	27	0.210
	68-78 weeks	4	1358/1038	1.58 [0.86, 2.94]	0.140	0.22	57	0.070
	≥ 104 weeks	1	302/101	0.87 [0.32, 2.38]	0.790	NA	NA	NA
Severe hypoglycemia	Overall	51	10,026/7330	1.87 [0.89, 3.91]	0.100	0.00	0	0.960
(N)	24-30 weeks	40	7405/5379	1.87 [0.73, 4.77]	0.190	0.00	0	0.910
	48-56 weeks	6	961/812	2.77 [0.67, 11.56]	0.160	0.00	0	0.900
	68-78 weeks	4	1358/1038	NA	NA	NA	NA	NA
	≥ 104 weeks	1	302/101	NA	NA	NA	NA	NA

(*Continued*)

Table 4 (Continued).

Comparison		No. of Comparisons	Participants (GLP-1RAs/ Placebo)	Overall Effect		Heterogeneity		
Outcomes	**Subgroups**			**Pooled Results RR (95% CI)**	**P**	**Tau²**	**I², %**	**P**
Gastrointestinal	Overall	33	6980/5029	2.06 [1.82, 2.33]	<0.001	0.09	72	<0.001
Adverse events (N)	24-30 weeks	27	5466/4022	2.17 [1.92, 2.45]	<0.001	0.06	60	<0.001
	48-56 weeks	3	582/428	1.47 [1.18, 1.82]	<0.001	0.01	22	0.280
	68-78 weeks	3	1047/723	2.07 [1.44, 3.00]	0.008	0.09	84	0.002
	≥ 104 weeks	1	302/101	0.97 [0.72, 1.30]	0.830	NA	NA	NA
Nausea	Overall	54	10,355/7593	3.40 [2.93, 3.94]	<0.001	0.14	55	<0.001
(N)	24-30 weeks	41	7569/5727	3.73 [3.17, 4.38]	<0.001	0.12	50	<0.001
	48-56 weeks	8	1530/1096	2.51 [1.61, 3.90]	<0.001	0.22	62	0.010
	68-78 weeks	4	1358/1038	3.09 [2.22, 4.29]	<0.001	0.06	56	0.080
	≥ 104 weeks	1	302/101	0.94 [0.49, 1.81]	0.860	NA	NA	NA
Diarrhea	Overall	51	10,007/7254	1.77 [1.58, 1.99]	<0.001	0.02	9	0.280
(N)	24-30 weeks	38	7221/5388	1.81 [1.55, 2.12]	<0.001	0.03	15	0.210
	48-56 weeks	8	1530/1096	1.58 [1.22, 2.04]	<0.001	0.01	6	0.380
	68-78 weeks	4	1358/1038	1.37 [0.82, 2.28]	0.230	0.22	83	<0.001
	≥ 104 weeks	1	302/101	1.16 [0.61, 2.17]	0.650	NA	NA	NA
Vomiting	Overall	49	9713/7134	3.95 [3.33, 4.69]	<0.001	0.00	0	0.510
(N)	24-30 weeks	38	7125/5468	4.50 [3.61, 5.61]	<0.001	0.04	9	0.320
	48-56 weeks	6	1332/896	2.35 [1.52, 3.62]	<0.001	0.00	0	0.880
	68-78 weeks	4	1358/1038	4.07 [1.91, 8.07]	<0.001	0.38	69	0.020
	≥ 104 weeks	1	302/101	5.69 [0.77, 42.19]	0.090	NA	NA	NA
Pancreatitis	Overall	34	6710/5232	0.83 [0.29, 2.37]	0.720	0.00	0	0.870
(N)	24-30 weeks	22	3843/3158	0.99 [0.14, 7.01]	0.990	0.91	0	0.340
	48-56 weeks	8	1530/1096	0.47 [0.09, 2.37]	0.360	0.78	0	0.680
	68-78 weeks	3	1035/877	1.01 [0.18, 5.79]	0.990	0.79	0	0.380
	≥ 104 weeks	1	302/101	1.68 [0.08, 34.77]	0.740	NA	NA	NA

Abbreviations: GLP-1RAs, glucagon-like peptide 1 receptor agonists; T2DM, type 2 diabetes mellitus; RR, risk ratio; CI, confidence internal; NA, mot available.

44%) and 48–56 weeks (RR 1.08 [1.02, 1.15], P = 0.009], I^2 = 52%), but not at 68–78 weeks and ≥ 104 weeks, with RRs of 1.02 ([0.97, 1.08], P = 0.450) and 1.34 ([0.52, 3.47], P = 0.550), respectively. In addition, there was a higher incidence of withdrawal due to AEs at 24–30 and 48–56 weeks, with RRs of 2.23 and 1.97, respectively (P < 0.01, respectively). However, the frequency of serious adverse effects (SAEs) did not increase at each follow-up (P > 0.05). The incidence of hypoglycemic episodes (plasma glucose ≤ 70 mg/dL) was significantly greater than that associated with the placebo at 24–30 weeks (RR 1.61, 95% CI 1.36 to 1.91; P < 0.001, I^2 = 68). No significant differences were found at 48–56, 68–78 or ≥ 104 weeks (P > 0.05). Gastrointestinal adverse events associated with GLP-1RAs occurred more frequently than those associated with placebos, especially nausea, diarrhea and vomiting (RR 3.40, 95% CI [2.93, 3.94], 1.77 [1,58, 1.99], 3.95 [3.33, 4.69]; P < 0.001, respectively). Eight trials (7 patients treated with GLP-1RAs) reported cases of pancreatitis, but no significant difference in the incidence of this AE was detected between the GLP-1RA and placebo groups (RR 0.83, 95% CI [0.29, 2.37], P=0.720, I^2 = 0%). One patient treated with albiglutide reported the occurrence of thyroid cancer, but this disease was considered to be unrelated to albiglutide.[29]

Certainty of Evidence and Network Inconsistency

After applying the CINeMA framework to evaluate certainty, we found low confidence in short-to-medium term outcomes due to imprecision and inconsistency (Table S13). This primarily stemmed from the limited number of studies and wide confidence intervals. However, high confidence was demonstrated for the long-term (≥ 104 weeks) HbA1c reduction effects.

The global inconsistency (chi^2) for placebo-subtracted differences in changes in HbA1c levels, body weight, FPG levels and SBP was 11.98, 5.48, 13.33 and 8.10, respectively, and there were no significant differences ($P > 0.05$) (Table S14). The local inconsistency revealed no placebo-subtracted differences between the direct and indirect comparisons of lowering HbA1c, body weight and SBP ($P > 0.05$) (Table S15). Significant placebo-subtracted differences were observed between the 12–18 weeks and ≥ 104 weeks follow-up durations ($P = 0.046$) (Table S15).

Discussion

In summary, similar to previous studies, our network meta-analysis demonstrated that GLP-1RAs had positive effects on improving blood glucose, body weight, systolic blood pressure, and serum lipid levels in T2DM patients. However, this is the first study to present the long-term efficacy trajectory of GLP-1RAs by comparing the placebo-subtracted between different follow-ups. We found that the optimal effects on lowering HbA1c and FPG levels were observed at 12–18 weeks, with a significant deterioration starting at 104 weeks. These trajectories were hook-shaped. In addition, the greatest reductions in body weight and SBP were observed at 24–30 and 12–18 weeks, respectively, after which both parameters reached a plateau.

Our study revealed that GLP-1RAs significantly improved glycemic control within 104 weeks. Consistent with our results, a real-world study conducted in Belgium revealed that the efficacy of lowering HbA1c levels persisted for four years,[20] and in another Spanish study, this effect lasted until 39 months.[25] However, in our study, the optimal effect of GLP-1RAs on reduced HbA1c levels was observed at 12–18 weeks, whereas the optimal effects were observed at 1 year and 6 months in the other two abovementioned studies, respectively.[20,25] One reason for the inconsistency in the overall trajectory may be that the longest follow-up duration for most RCTs was 104 weeks, which was far shorter than that of real-world studies. Another possible reason for the difference may be the greater number of kinds of GLP-1RA, such as semaglutide, used in our meta-analysis. In a previous network meta-analysis, a subgroup analysis based on different follow-up durations confirmed that semaglutide had stable effects on reducing HbA1c levels after 3 months.[22]

For long-term glycemic control, maintaining weight loss has also emerged as a key factor,[30] as a retrospective study suggested that modest and sustained weight loss could meaningfully improve glycemic control.[31] In the present study, weight loss was maintained for nearly 68–78 weeks. The significant long-term improvements in body weight have also been supported by evidence from a network meta-analysis that demonstrated sustained effects on body weight for more than 12 months.[22] So GLP-1RAs could be considered the optimal choice for long-term glucose and body weight management.

However, there was a trend of these effects to weaken over time. In our study, the effect of reducing HbA1c levels at ≥ 104 weeks was 0.36% smaller than than that at 12–18 weeks. A similar trend was observed for FPG, which was 0.47 mmol/L higher at ≥ 104 weeks than at 12–18 weeks. This aligns with a 3-year pooled analysis of exenatide QW, which reported diminished HbA1c reduction between weeks 52 and 156.[32] The nonlinear trajectories of HbA1c and FPG underscore the importance of both regular glycemic monitoring beyond two years and timely initiation of adjunct therapies when glycemic control plateaus or rebounds. For daily GLP-1RAs, we should pay attention to these changes earlier. Additionally, a post hoc analysis of the GRADE study demonstrated that β-cell function declined over time as glycemia deteriorated.[33] Several researches also reported the chronic agonism of GLP-1RAs that led to β-cell failure.[34] We inferred that this trend may indicate disease progression and the diminishing effects of GLP-1RAs on β-cell function.[32–35] However, this mechanistic explanation remains hypothetical, and further RCTs with longer follow-up durations are needed to confirm our findings.

Another important factor in the long-term management of T2DM is blood pressure, which is related to the risk of long-term cardiovascular complications. The present study revealed that GLP-1RAs had a positive effect on systolic blood pressure but not diastolic blood pressure at 68–78 weeks. The exact mechanism responsible for the blood pressure-lowering effects of GLP-1RAs has not been fully elucidated, but it has been suggested that the blood pressure reduction caused by GLP-1RA treatment might be in part due to weight loss.[36,37]

With respect to safety outcomes, we found that GLP-1 receptor agonists were associated with an increased risk of gastrointestinal adverse events for at least 68–78 weeks. However, there was no increase in the incidence of withdrawal from 68–78 weeks. The increased risk of hypoglycemia occurred mainly at 24–30 weeks. It seemed that long-term use of

GLP-1RAs did not increase the risk of side effects, indicating possible tolerance development over time. Similar trends in safety outcomes over time were also described in a review.[12] Nevertheless, as the trend at ≥104 weeks remains inconclusive due to insufficient data, larger longitudinal studies are needed to evaluate the risk of delayed adverse effects.

This study also has potential limitations. First, we chose only GLP-1RAs approved by the FDA, with only one dose selected for each drug, resulting in narrow coverage. Second, we included trials with primary outcomes restricted to changes in HbA1c levels or body weight, which led to missing data from some large sample trials. Third, as differences in baseline characteristics of participants and follow-up duration among included studies were varied, the accuracy of the findings could be influenced. Fourth, our exclusion of non-English language studies may limit the comprehensiveness of our search. Fifth, we combined all the included GLP-1RAs to analyze the overall trajectory; however, the effects of different GLP-1RAs varied greatly. For example, albiglutide had no effect on weight loss, whereas tirzepatide markedly reduced body weight (−8.80 [−9.62, −7.99], $P < 0.001$). This difference may have led to some bias. Finally, meta-regression failed to identify significant sources of heterogeneity for HbA1c and weight changes. This indicates that some potential confounders were either not consistently reported across studies or could not be adequately adjusted for in this meta-analysis.

Conclusion

In summary, GLP-1RAs demonstrate sustained long-term efficacy for glycemic control and weight management, with optimal effects observed at 12–18 weeks and 24–30 weeks. While the effects of lowering HbA1c and FPG attenuated after 104 weeks, the trend of weight loss plateaued until 68–78 weeks. Therefore, GLP-1RAs are recommended for long-term treatment for patients with type 2 diabetes, but clinicians should monitor for potential efficacy changes beyond 2 years.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and as supplementary information files.

Ethics Approval and Informed Consent

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Consent for Publication

All authors confirm that they have read the paper and consent to its submission.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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