Comparative efficacy and safety of glucagon-like peptide 1 receptor agonists for the treatment of type 2 diabetes
A network meta-analysis

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Abstract

Introduction: This study aimed to evaluate the clinical efficacy and safety of 4 weekly formulations of glucagon-like peptide 1 receptor agonists (GLP-1RAs) on glycemic control, including glycemic control, by using a network meta-analysis (NMA).

Methods: PubMed, EMBASE, and Cochrane Library Central Register of Controlled Trials were searched from inception until June 10, 2022. Randomized clinical trials (RCTs) enrolling participants with diabetes mellitus type 2 and a follow-up of at least 12 weeks were included, for which 4 eligible GLP-1RAs Exenatide, Dulaglutide, Semaglutide, Loxenatide were compared with either each other or placebo. The primary outcome is the change of hemoglobin A1c level. Secondary outcomes including additional glycemic control indicators and adverse events (AE). Frequentist random-effect NMA were conducted for effect comparison. This meta-analysis was registered on PROSPERO, CRD42022342241.

Results: The NMA synthesized evidence from 12 studies covering 6213 patients and 10 GLP-1RA regimens. A pairwise comparison of glycosylated hemoglobin type A1C (HbA1c) lowering effects showed that once-weekly GLP-1 receptor agonists were significantly better than placebo, and their glucose-lowering intensity was Semaglutide 2.0mg, Semaglutide 1.0mg, Dulaglutide 4.5mg, and Semaglutide 0.5mg, Dulaglutide 3.0mg, PEX168 200ug, Dulaglutide 1.5mg, PEX168 100ug and Dulaglutide 0.75mg. The GLP-1RA regimen has a comparable safety profile for hypoglycemia. And with the exception of PEX168, all other long-acting GLP-1RA drugs had lower rates of diarrhea, nausea and vomiting than placebo.

Conclusion: Regimens of GLP-1RAs had differential glycemic control. The efficacy and safety of Semaglutide 2.0mg in comprehensively lowering blood sugar showed the best performance.

Abbreviations: AE = adverse events, CI = confidence interval, GLP-1-RA = glucagon-like peptide 1 receptor agonists, HbA1c = glycosylated hemoglobin type A1C, NMA = network meta-analysis, ORs = odd ratios, RCTs = randomized clinical trials, SMD = standardized mean differences, T2DM = diabetes mellitus type 2.

Keywords: glucagon-like peptide 1, HbA1c, type 2 diabetes

1. Background

Diabetes mellitus type 2 (T2DM) is the most prevalent disease worldwide and is emerging as a serious public health threat.[1] At present, China has become the country with the largest number of diabetic patients in the world. In the past 10 years (2011–2021), the number of diabetic patients in China has increased from 90 million to 140 million, a growth rate of 56%. Therefore, the means to reduce blood sugar emerge in an endless stream. Among them, glucagon-like peptide 1 receptor agonists (GLP-1RAs), as an insulin secretagogue to lower blood sugar, have an increasingly important clinical status.

Since the first GLP-1RA was approved in 2005 (Exenatide twice daily) for T2DM, the class has developed with newer compounds having more pronounced effects on glycemic control and body weight.[2] Compared with other marketed hypoglycemic

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drugs, GLP-1RAs not only have oral dosage forms, but also injections. It also shows superiority in lowering blood sugar and reducing body weight. Comparing the evidence for the efficacy and safety of GLP-1RAs is therefore critical for choosing an appropriate clinical pathway.[3]

Previous meta-analysis have examined endpoints between 24 and 30 weeks. They did not include long-term outcomes that may be equally important. In addition, there was no correlation between dosage and adverse reactions in previous drug safety evaluation. To fufil this important evidentiary gap, the present analysis was conducted by focusing on GLP-1RAs approved.

2. Methods

The report of the present study is in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[4,5] This article is based on previously conducted studies which does not contain any new studies with human participants or animals. This systematic review and meta-analysis reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement and was registered at International Prospective Register of Systematic Reviews (CRD42022342241).

2.1. Study selection

We only included the randomized clinical trials (RCTs) published in English and completed, which compared various weekly preparations of GLP-RAs in subjects with T2DM. The main research focus of this study is the changes of glycosylated hemoglobin. Included studies had to report this primary endpoint in the adult population (age 18 years, male or female).

2.2. Study Identification

Search strategies for potentially eligible clinical trials were pre-specified for the PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception until April 30, 2022. The terms and rules used for the search strategy are summarized in Table S1, Supplemental Digital Content, http://links.lww.com/MD/J192, and the studies were filtered with all 4 levels of conditions in it. The type of included literature is research paper, and the corresponding trial registration is attached to the abstract. Repeat the search process using sentence-by-sentence and capitalization.

After removal of duplicates, the title and abstracts of search results were screened for relevance by a single author. The full texts of remaining results were independently assessed in duplicate by 2 authors for inclusion based on predetermined criteria. The final list of included studies was decided on discussion between authors with full agreement required prior to inclusion. No disagreements required resolution by a third reviewer (See Table S1, Supplemental Digital Content, http://links.lww.com/MD/J192, Supplemental Content, Strategy of literature retrieval).

The studies published in English were considered eligible for inclusion if they were RCTs conducted on individuals with T2DM mellitus and compared GLP-1RAs of interest with each other or with a control group, which contained results of at least one of the prespecified primary and secondary endpoint. Eligible patients should satisfy treated with metformin at least 90 days and had a follow-up of at least 12 weeks.

2.3. Data extraction

Data were extracted using piloted forms, independently and in duplicate by 2 authors which were transcribed onto a dedicated database. Study characteristics including authors, year of publication, journal or conference name, trial name, trial registration, sponsorship, type of sponsor, RCT design (e.g., 2-arm vs 3-arm, double blind vs triple blind vs open label), follow-up duration, total sample size, and end point data were extracted. And patient characteristics including age, sex, diabetes duration, and baseline values of outcomes were also extracted. Moreover, treatment characteristics including preparation (drug, administration route, and dosage) and administration frequency, sample size of the arm, other medications and outcome data simultaneously extracted.

Two investigators independently assessed random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases to assess risk of bias according to the Cochrane Manual.

2.4. Outcomes

The pre-set primary outcome was change in hemoglobin A1c (HbA1c) from baseline to the endpoint of every study. Secondary outcomes included changes in fasting plasma glucose concentrations, body weight; and the proportion of patients reporting adverse events (AE) such as hypoglycemia, nausea, vomiting, diarrhea, and headache.

2.5. Data analysis

In this network meta-analysis (NMA), we estimated standardized mean differences (SMD) for continuous outcomes and summary odd ratios (ORs) for dichotomous outcomes. SMD or ORs and an associated 95% confidence interval (CI) were presented for the results. For the continuous outcomes HbA1c (%) fasting plasma glucose (mmol/L), and body weight (kg), a treatment associated with a greater mean reduction from baseline was favored. For dichotomous outcomes, a treatment associated with a decrease in the OR was favored, which meant the incidence of AE withdrawals and hypoglycemic episodes were low. To rank the treatments for each outcome, we used the surface under the cumulative ranking curve and the mean ranks.

The relative efficacy for each continuous outcome was represented by mean difference in the change of value from baseline to endpoint across treatment groups. The sample size and event count of each arm were used for comparison in the analyses of dichotomous outcomes, in which the relative efficacy was measured by OR. Frequentist NMA with random effects were performed for all outcomes. Along with that, I^2 was still computed and reported to quantify heterogeneity across studies but not used to choose random-effects model versus fixed-effects model.

The base-case analysis were based on consistency models. Inconsistency in the analysis was tested using the "design-by-treatment interaction" approach. In all analysis, placebo was used as the reference group. For the primary outcome, pairwise comparison was also conducted.

All analysis were conducted using Stata 16. Two-sided p values of 0.05 or less were considered statistically significant.

3. Results

Database searches yielded 4666 records (PubMed 1146; Embase 955; Cochrane Library 2565). The specific screening flow chart is shown in Figure 1.

3.1. Literature Identification

The RCTs were published from 2014 to 2020 and the characteristics of the twelve included studies are shown in Table 1[6–17] The mean age of all participants was 61 (range 50–59) and mean duration was 27.6 weeks (range 12–52 weeks). Patients
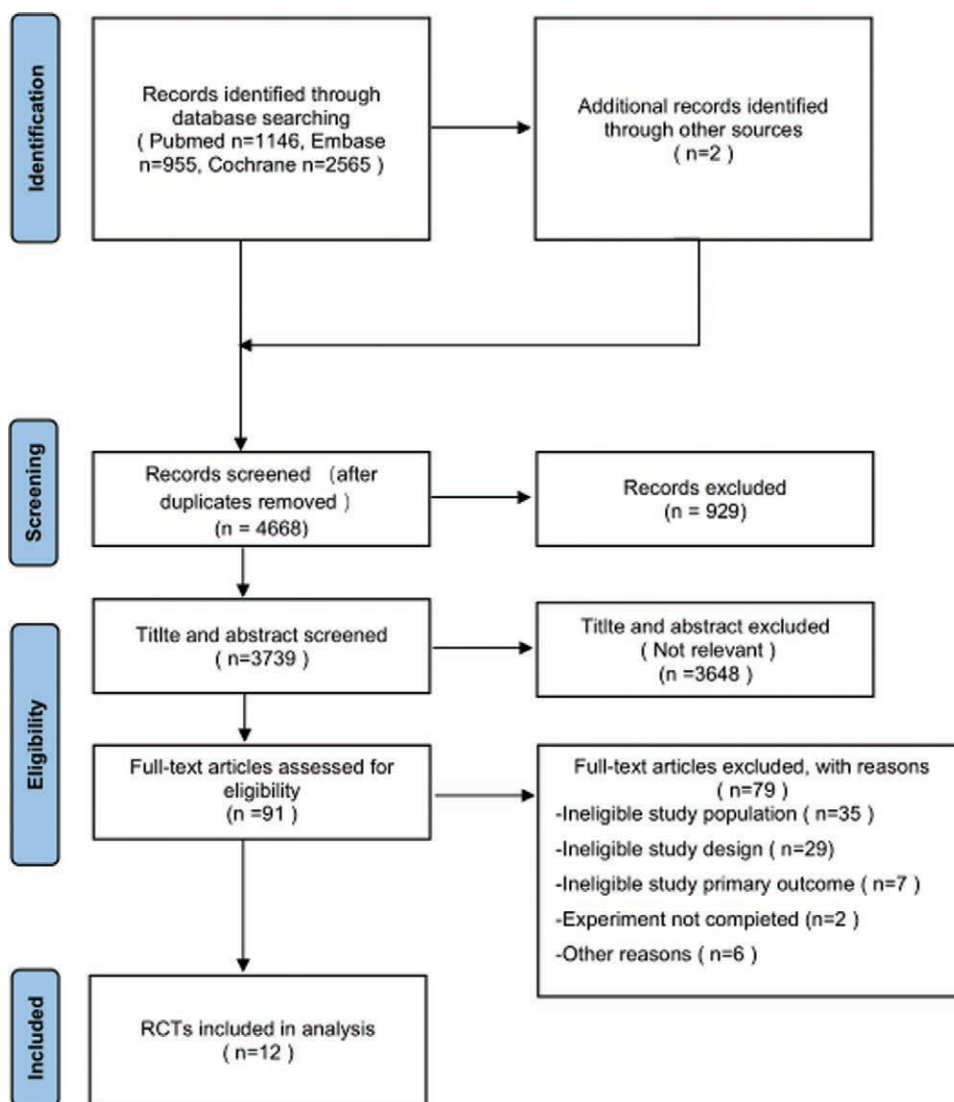
Figure 1. Flow diagram of the search results and study selection.

had mean baseline HbA1c of 8.17% (range 7.30–8.64), mean baseline body-mass index of 30.9 kg/m² (26.0–36.0), and mean duration of diabetes of 5.6 years (3.0–8.7). In the primary outcome analysis, a total of 10 regimens were used, including Exenatide 2.0mg, Loxenatide 100ug, Loxenatide 200ug, Dulaglutide 1.5mg, Semaglutide 0.5mg, Semaglutide 1.0mg, Dulaglutide 0.75mg, Dulaglutide 3.0mg, Dulaglutide 4.5mg, Semaglutide 2.0mg. All above are weekly preparations.

3.2. Quality assessment

We evaluated the risk of bias of the included studies using Cochrane Risk of Bias Tools. We found that 10 of these studies had a low risk of bias. The lack of participant blinding in the other 2 studies meant that they were open label RCTs. Participants dropped out in each study and were lost to follow-up in 8. None of these 8 studies reported resolution of missing data. Based on these limitations, the quality of evidence for our assessment of joint effects was reduced. For the remaining biases, most studies were moderate or low risk, and details are shown in (See Figure S1a, Supplemental Digital Content, http://links.lww.com/MD/J193, S1b, Supplemental Digital Content, http://links.lww.com/MD/J194, which illustrates the risk-of-bias graph/summary).

3.3. Efficacy outcomes

The network evidence of eligible comparisons for efficacy (ΔHbA1c, Δ FBG, Δ weight) were showed in Figure 2. All 12 trials considered in the NMA formed a connected network that compared placebo to 10 interventions. The agents were injected subcutaneously. All included studies used changes in HbA1c as the primary end point.

All GLP-1RAs significantly decreased HbA1c compared with placebo, and Semaglutide 2.0mg had the best hypoglycemic effect, with SMD between –0.74% (95% CI: –2.10%, –1.38%) with significant different. Followed by Semaglutide 1.0mg [–1.44% (95% CI: –1.69%, –1.19%)], Dulaglutide 4.5mg [–1.16% (95% CI: –1.42%, –0.90%)], Semaglutide 0.5mg [–1.11 (95% CI: –1.40, –0.82)], Dulaglutide 3.0mg [–1.02 (95% CI: –1.28, –0.76)], PEX168 200ug [–1.09 (95% CI: –1.45, –0.73)], Exenatide 2.0mg [–1.06 (95% CI: –1.48, –0.63)], Dulaglutide 1.5mg [–0.91 (95% CI: –1.13, –0.69)], PEX168 100ug [–0.94 (95% CI: –1.28, –0.59)] and Dulaglutide 0.75mg [–0.75 (95% CI: –1.01,–0.49)]. Significant different could also be found in Semaglutide 2.0mg versus all the other interventions, which all prove that Semaglutide 2.0mg get the best hypoglycemic effect (Fig. 3).

Different from HbA1c, in terms of weight loss, other GLP-1RAs had better weight loss effect except PEX168 100ug [0.49 kg

Table 1

Basic information included in the study.

First author (yr)	Country	Study design	Study period	Intervention	Patients, n	Age (mean ± sd)	Weight (mean ± sd)	BMI (mean ± sd)	Baseline HbA1c (%)	Diabetes duration (yr)	SBP, mm Hg	DBP, mm Hg	Race, Asian/Others, n (%)	Male sex, n (%)	Primary outcome
								Population characteristics							
Gadde (2017)	USA	RCT	28-wk	Exenatide-QWS-AI	181	53.4 ± 9.8	89.2 ± 21.4	32.1 ± 5.4	8.4 ± 1.0	8.5 ± 6.3	127.6 ± 12.8	77.4 ± 8.9	9 (5.0)	89 (49.2)	HbA1c%
				Placebo	61	53.4 ± 9.5	89.0 ± 20.1	31.5 ± 5.1	8.5 ± 1.0	8.7 ± 5.8	127.7 ± 15.5	77.0 ± 8.1	3 (4.9)	37 (60.7)	
Chen (2016)	China	RCT	12 wk	PEX168100ug	41	52.6 ± 8.4	NA	27.2 ± 3.6	8.23 ± 0.88	4.12 ± 6.42	128 ± 11	78.1 ± 9.4	NA	22 (53.66%)	HbA1c%
				PEX168200ug	39	49.8 ± 10.9	NA	26.3 ± 3.3	8.34 ± 1.15	4 ± 5.67	126 ± 12	78.1 ± 8.0	NA	22 (56.41%)	
				Placebo	38	53.5 ± 10.2	NA	27.2 ± 4.5	8.28 ± 1.05	6.46 ± 7.92	130 ± 14	77.8 ± 9.0	NA	26 (68.42%)	
Gao (2020)	China	RCT	24 wk	PEX168100ug	179	53.6 ± 10.5	71.2 ± 12.8	26.0 ± 3.5	8.5 ± 0.9	4.3 ± 3.5	124.3 ± 11.9	77.1 ± 8.0	NA	102 (57.0)	HbA1c%
				PEX168200ug	175	52.8 ± 10.6	73.6 ± 14.6	26.6 ± 3.8	8.5 ± 0.9	4.8 ± 3.2	125.5 ± 12.1	78.5 ± 8.2	NA	106 (60.6)	
				Placebo	179	52.3 ± 10.7	73.8 ± 14.1	26.6 ± 3.8	8.6 ± 0.9	4.7 ± 3.4	126.8 ± 11.5	79.3 ± 8.0	NA	98 (54.7)	
Ji (2020)	China	RCT	30 wk	Sema0.5mg	288	53.0 ± 11.4	77.6 ± 16.4	28.2 ± 5.0	8.1 ± 0.9	6.3 ± 5.4	128.8 ± 14.6	80.3 ± 9.3	243 (84.4)	160 (55.6)	HbA1c%
				Sema1.0mg	290	53.0 ± 10.6	76.1 ± 16.3	27.9 ± 5.0	8.1 ± 0.9	6.7 ± 4.9	NA	NA	251 (86.6)	154 (53.1)	
Kim (2007)	USA	RCT	15 wk	Exe2.0mg	15	51 ± 11	110 ± 17	36 ± 6	8.3 ± 1.1	4 ± 5	NA	NA	NA	67%	HbA1c%
				Placebo	14	55 ± 9	101 ± 20	36 ± 6	8.6 ± 1.4	4 ± 4	NA	NA	NA	36%	
Pratley (2018)	USA	RCT	40 wk	Sema0.5mg	301	56 ± 10.9	96.4 ± 24.4	33.7 ± 7.1	8.3 ± 0.9	7.7 ± 5.9	134 ± 14.8	81 ± 9.0	50 (17)	169 (56%)	HbA1c%
				Dula0.75mg	299	55 ± 10.4	95.6 ± 23.0	33.6 ± 6.9	8.2 ± 0.9	7.0 ± 5.5	133 ± 14.0	81 ± 8.9	48 (16)	160 (54%)	
				Sema1.0mg	300	55 ± 10.6	95.5 ± 20.9	33.6 ± 6.5	8.2 ± 0.9	7.3 ± 5.7	133 ± 14.5	82 ± 9.1	38 (13)	162 (54%)	
				Dula1.5mg	299	56 ± 10.6	93.4 ± 21.8	33.1 ± 6.6	8.2 ± 0.9	7.6 ± 5.6	132 ± 13.6	80 ± 8.7	55 (18)	171 (57%)	
Grunberger (2012)	USA	RCT	12 wk	Dula 1.5mg	29	57.5 ± 7.9	85.8 ± 18.6	31.0 ± 4.3	7.3 ± 0.4	4.6 ± 4.1	127.3 ± 14.4	76.8 ± 9.2	14 (48.2)	13 (44.8)	HbA1c(%)
				Placebo	32	55.0 ± 9.3	90.9 ± 18.9	32.1 ± 5.2	7.4 ± 0.6	3.9 ± 4.7	128.5 ± 12.3	77.9 ± 10.5	16 (50.0)	18 (56.3)	
Umpierrez (2014)	USA	RCT	26 wk	Dula 0.75mg	270	56 ± 11	92 ± 19	33 ± 6	7.6 ± 0.9	3 ± 2	130 ± 16	80 ± 10	20 (7.4)	118 (44)	HbA1c(%)
				Dula 1.5mg	269	56 ± 10	93 ± 19	34 ± 6	7.6 ± 0.9	3 ± 2	130 ± 16	79 ± 9	21 (7.8)	114 (42)	
			52 wk	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Davies (2017)	UK	RCT	26 wk	Sema 1.0mg	69	56.8 ± 11.8	88.8 ± 15.4	30.7 ± 4.0	7.8 ± 0.7	5.6 ± 5.0	134.2 ± 14.5	80.9 ± 8.9	10 (14.5)	48 (69.6)	HbA1c(%)
				Placebo	71	58.9 ± 10.9	93.8 ± 18.1	32.6 ± 4.5	8.0 ± 0.8	6.7 ± 5.1	135.4 ± 15.5	80.6 ± 8.4	7 (9.9)	40 (56.3)	
Eli Lilly and Company (2019)	USA	RCT	18 wk	Dula 1.5mg	81	57.65 ± 9.79	NA	NA	8.02 ± 0.8	NA	NA	NA	0 (0.00)	39 (48.1)	HbA1c(%)
				Dula 3.0mg	79	55.90 ± 10.74	NA	NA	8.16 ± 0.92	NA	NA	NA	1 (1.3)	35 (44.3)	
				Dula 4.5mg	76	57.13 ± 9.63	NA	NA	8.12 ± 0.81	NA	NA	NA	3 (3.9)	36 (47.4)	
				Placebo	81	56.52 ± 8.93	NA	NA	8.08 ± 0.79	NA	NA	NA	0 (0.00)	48 (59.3)	
Eli Lilly and Company (2020)	USA	RCT	36 wk	Dula 1.5mg	612	57.8 ± 9.7	NA	NA	8.64 ± 0.94	NA	NA	NA	13 (2.1)	298 (48.7)	HbA1c(%)
				Dula 3.0mg	616	56.9 ± 10.2	NA	NA	8.63 ± 1.00	NA	NA	NA	18 (2.9)	328 (53.2)	
				Dula 4.5mg	614	56.6 ± 10.2	NA	NA	8.64 ± 0.91	NA	NA	NA	14 (2.3)	318 (51.8)	
Juan (2021)	USA	RCT	40 wk	Sema 1.0mg	481	58.2 ± 9.9	NA	NA	NA	NA	NA	NA	36 (7.5)	284 (59)	HbA1c(%)
				Sema 2.0mg	480	57.9 ± 10.0	NA	NA	NA	NA	NA	NA	33 (6.9)	279 (58.1)	

HbA1c = glycosylated hemoglobin type A1C, RCTs = randomized clinical trials.
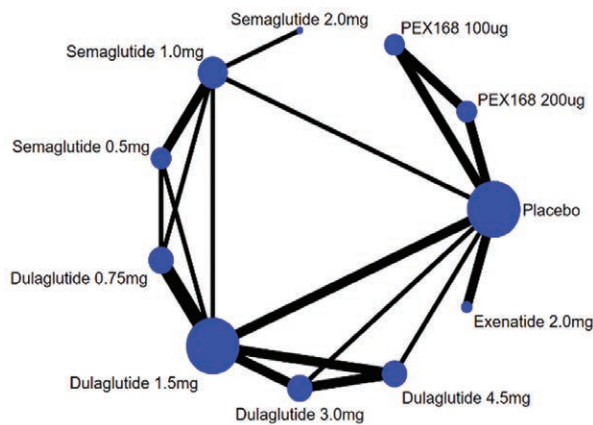
Figure 2. Network of treatment comparisons for network meta-analysis. Each circular node represents a type of treatment. The node size is proportional to the total number of patients receiving a treatment. Each line represents a type of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments.

(95% CI: −0.47, 1.46 kg)] was not as effective as placebo. Among them, Semaglutide 2.0mg had the best weight loss effect, with SMD between of −5.51 kg (95% CI: −6.64, −4.37kg). Followed by Dulaglutide 0.75mg [−4.51 kg (95% CI: −5.33, −3.68 kg)], Semaglutide 1.0mg [−2.84 kg (95% CI: −3.72, −1.97 kg)], Dulaglutide 4.5mg [−2.62 kg (95% CI: −3.31, −1.94 kg)], Dulaglutide 3.0mg [−1.92 kg (95% CI: −2.61, −1.24 kg)], Exenatide 2.0mg [−1.60 kg (95% CI: −2.67, −0.53 kg)], Semaglutide 0.5mg [−1.02 kg (95% CI: −1.71, −0.34 kg)], Dulaglutide 1.5mg [−0.36 kg (95% CI: −1.09, −0.37 kg)] and PEX168 200mg [−0.10 kg (95% CI: −1.30, 1.10 kg)]. There was also a significant difference with Semaglutide 2.0mg compared to all other interventions, all demonstrating that Semaglutide 2.0mg also had a favorable effect on weight loss (Fig. 3).

The results of lowering fasting blood glucose were about the same as the results of lowering HbA1c. All GLP-1RAs significantly reduced HbA1c, and Semaglutide 2.0 mg had the best hypoglycemic effect with SMD between −2.71% (95% CI: −3.46%, −1.96%). The main difference was that Exenatide 2.0mg [−2.07% (95% CI: −2.93%, −1.22%)] was more effective in lowering fasting blood glucose, followed by Semaglutide 2.0mg and Semaglutide 1.0mg [−2.51% (95%) CI: −3.00%, −2.02%)]; the efficacy of other GLP-1RAs in reducing fasting blood glucose was similar. Dulaglutide 4.5mg [−1.98% (95% CI: −2.58%, −1.38%)], Semaglutide 0.5mg [−1.87 (−2.43, −1.30)], Dulaglutide 3.0mg [−1.75 (−2.33, −1.16)], Dulaglutide 1.5mg [−1.71 (−2.18, −1.24)], Dulaglutide 0.75mg [−1.45 (−1.98, −0.91)], PEX168 200ug [−1.16 (−1.76, −0.56)] and PEX168 100ug [−1.07 (−1.67, −0.46)] (See Figure S2, Supplemental Digital Content, http://links.lww.com/MD/J195, Supplemental Content, which illustrates the results of NMA of the clinical efficacy of ten GLP-1RAs).

3.4. Safety outcomes

Results of safety and clinical efficacy were inconsistent, and serious AE, such as severe hypoglycemia, were rare among all GLP-1RAs. However, common adverse reactions such as gastrointestinal reactions and hypoglycemia often occur. Compared with placebo, the incidence of hypoglycemia was lower for all weekly formulations of GLP-1RAs except Exenatide 2.0 mg [0.70 (95% CI: 0.14–3.42)]. The lowest incidence was

Semaglutide 1.0mg, OR was 3.91 (95% CI: 0.53–29.03), followed by Dulaglutide 0.75mg [3.28 (95% CI: 0.46–23.39)], Dulaglutide 1.5mg [3.19 (95% CI: 0.47–21.68)], Dulaglutide 4.5mg [3.17 (95% CI: 0.16–61.67)], PEX168 100ug [3.02 (95% CI: 0.45–20.25)], Semaglutide 0.5mg [1.42 (95% CI: 0.16–12.92)], Semaglutide 2.0mg[1.33 (95% CI: 0.03–58.15)], Dulaglutide 3.0mg [1.06 (95% CI: 0.03–44.49)], PEX168 200ug [1.01 (95% CI: 0.10–9.77)] and Exenatide 2.0mg [0.70 (95% CI: 0.14–3.42)] (Fig. 4).

Incidence of Gastrointestinal Reactions such as Nausea: The incidence of all GLP-1RAs was lower than placebo. The least nausea occurred was PEX168 200ug, with OR value of 14.01 (95% CI: 3.62–54.21), followed by Dulaglutide 4.5mg [7.88 (95% CI: 2.52–24.69)], Semaglutide 2.0mg [6.63 (95% CI: 1.32–33.32)]. Dulaglutide 3.0mg [6.28 (95% CI: 2.02–19.45)]. Semaglutide 1.0mg [5.99 (95% CI: 2.05–17.50)]. Semaglutide 0.5mg [5.58 (95% CI: 1.61–19.36)]. Exenatide 2.0mg [4.51 (95% CI: 0.90–22.54)]. Dulaglutide 1.5mg [3.77 (95% CI: 1.36–10.46)]. Dulaglutide 0.75mg [3.36 (95% CI: 0.98–11.53)] and PEX168 100ug [2.51 (95% CI: 0.57–11.15)] (Fig. 4).

Overall, semaglutide 2.0 mg has good efficacy and a favorable safety profile, and we recommend semaglutide as a treatment for patients with T2DM.

4. Discussion

This NMA included 12 studies covering 6213 individuals and primarily compared the HbA1c lowering effects of 4 GLP-1RA regimens with placebo and with each other. As expected, most GLP-1RA regimens significantly reduced HbA1c in the base case. However, the HbA1c-lowering effects of different regimens varied, with Semaglutide 2.0mg QW, Semaglutide 1.0mg QW, Dulaglutide 4.5mg QW, Semaglutide 0.5mg QW, Dulaglutide 3.0mg QW, 200ug QW relatively superior in the spectrum one end. The effects on fasting blood sugar and weight loss varied, for example, PEX168 100ug was less effective than placebo in weight loss. The other GLP-1RAs had better effects on fasting blood glucose and body weight than placebo. In terms of safety, the frequency of hypoglycemia in the 5 regimens of Semaglutide 1.0mg, Dulaglutide 0.75mg, Dulaglutide 1.5mg, PEX168 100ug, and Dulaglutide 4.5mg was significantly lower than the other 5 regimens and placebo. Therefore, it can be seen that although Semaglutide 2.0mg has the best efficacy, the incidence of AE of hypoglycemia is relatively higher than that of the above 5 regimens. Therefore, we need to strike a balance between efficacy and safety in clinical drug use, because no drug can guarantee absolute safety while having the best efficacy. To develop an individualized dosing regimen for patients can improve clinical efficacy and ensure drug safety.

GLP-1RAs as an emerging drug developed for the treatment of T2DM, not only achieves remarkable results in hypoglycemic therapy, but also helps diabetic patients lose weight. GLP-1RA works by reducing appetite and hunger, slowing the release of food from the stomach, increasing the feeling of fullness after eating. Since many people face difficulties maintaining weight loss, lifelong treatment may be required. In clinical trials, GLP-1RA was well tolerated and effective in helping people prevent weight regain, which may be a good option for long-term weight control and reducing the chance of serious health problems in patients.[18]

The "younger" trend of diabetes is becoming more and more obvious. The launch of GLP-1 weekly preparation brings convenience to patients.[3] The most common adverse reactions are hypoglycemia and gastrointestinal reactions such as nausea, vomiting and diarrhea, which are mostly transient and mainly occur at the beginning of treatment for a few weeks, and then gradually weakens or stabilizes over time. Based on this NMA, with the exception of an increased incidence of hypoglycemia

Sema2.0mg	1.00 (0.22, 1.78)	2.88 (1.91, 3.86)	2.66 (1.71, 3.62)	3.58 (2.61, 4.56)	5.40 (3.75, 7.05)	3.90 (2.34, 5.46)	4.48 (3.51, 5.46)	5.99 (4.50, 7.48)	5.15 (4.17, 6.13)	5.50 (4.37, 6.63)
-0.30 (-0.55, -0.05)*	Sema1.0mg	1.88 (1.29, 2.47)	1.66 (1.11, 2.22)	2.58 (1.99, 3.17)	4.40 (2.95, 5.86)	2.90 (1.55, 4.25)	3.48 (2.89, 4.07)	4.99 (3.72, 6.26)	4.15 (3.55, 4.74)	4.50 (3.68, 5.32)
-0.58 (-0.96, -0.20)*	-0.28 (-0.56, 0.01)	Dula4.5mg	0.22 (-0.39, 0.83)	0.70 (0.68, 0.72)	2.52 (1.14, 3.90)	1.02 (-0.25, 2.28)	1.60 (1.58, 1.62)	3.11 (1.93, 4.29)	2.27 (1.98, 2.55)	2.62 (1.94, 3.30)
-0.63 (-0.96, -0.30)*	-0.33 (-0.54, -0.12)*	-0.05 (-0.36, 0.25)	Sema0.5mg	0.92 (0.31, 1.53)	2.74 (1.26, 4.23)	1.24 (-0.15, 2.62)	1.82 (1.21, 2.43)	3.33 (2.03, 4.63)	2.49 (1.87, 3.10)	2.84 (1.96, 3.71)
-0.72 (-1.09, -0.34)*	-0.42 (-0.70, -0.14)*	-0.14 (-0.34, 0.06)	-0.09 (-0.38, 0.21)	Du1a3.0mg	1.82 (0.44, 3.20)	0.32 (-0.95, 1.59)	0.90 (0.88, 0.92)	2.41 (1.23, 3.59)	1.57 (1.28, 1.85)	1.92 (1.24, 2.60)
-0.65 (-1.15, -0.14)*	-0.35 (-0.78, 0.09)	-0.07 (-0.51, 0.37)	-0.02 (-0.48, 0.44)	0.07 (-0.37, 0.51)	PEX168200ug	0.92 (-0.10, 3.11)	0.59 (-0.46, 2.30)	0.59 (-0.48, 1.66)	0.26 (-1.15, 1.66)	0.10 (-1.10, 1.30)
-0.68 (-1.23, -0.13)*	-0.38 (-0.87, 0.11)	-0.10 (-0.61, 0.40)	-0.05 (-0.56, 0.46)	0.03 (-0.47, 0.54)	-0.03 (-0.59, 0.52)	Exe2.0mg	0.58 (-0.68, 1.85)	2.09 (0.65, 3.54)	1.25 (-0.05, 2.55)	1.60 (0.53, 2.67)
-0.83 (-1.15, -0.50)*	-0.53 (-0.73, -0.32)*	-0.25 (-0.45, -0.05)*	-0.20 (-0.42, 0.03)	-0.11 (-0.31, 0.09)	-0.18 (-0.60, 0.24)	-0.14 (-0.62, 0.33)	Dula1.5mg	1.51 (0.33, 2.69)	0.67 (0.38, 0.95)	1.02 (0.34, 1.70)
-0.80 (-1.29, -0.30)*	-0.50 (-0.93, -0.07)*	-0.22 (-0.66, 0.21)	-0.17 (-0.62, 0.28)	-0.08 (-0.52, 0.35)	-0.15 (-0.48, 0.18)	-0.12 (-0.67, 0.43)	0.03 (-0.38, 0.44)	PEX168100ug	0.85 (-0.37, 2.06)	0.49 (-0.47, 1.46)
-0.99 (-1.32, -0.65)*	-0.69 (-0.91, -0.47)*	-0.41 (-0.67, -0.15)*	-0.36 (-0.59, -0.13)*	-0.27 (-0.52, -0.02)*	-0.34 (-0.78, 0.10)	-0.31 (-0.80, 0.19)	-0.16 (-0.32, -0.01)*	-0.19 (-0.62, 0.24)	Dula0.75mg	0.35 (-0.38, 1.08)
-1.74 (-2.10, -1.38)*	-1.44 (-1.69, -1.19)*	-1.16 (-1.42, -0.90)*	-1.11 (-1.40, -0.82)*	-1.02 (-1.28, -0.76)*	-1.09 (-1.45, -0.73)*	-1.06 (-1.48, -0.63)*	-0.91 (-1.13, -0.69)*	-0.94 (-1.28, -0.59)*	-0.75 (-1.01, -0.49)*	Placebo

Interventions   Change of HBA1C   Change of weight

Figure 3. Lague of inclined interventions in evaluating change of HBA1C (A) and weight (B). Data in each cell are hazard or odds ratios (95% credible intervals) for the comparison of row-defining treatment versus column-defining treatment. Significant results are marked*. Dula = dulaglutide, Exe = exenatide, HbA1c = glycosylated hemoglobin type A1C, Sema = Semaglutide.

Exe2.0mg	4.51 (0.90, 22.54)	3.11 (0.38, 25.45)	1.39 (0.19, 9.96)	1.24 (0.16, 9.47)	1.47 (0.15, 14.38)	1.75 (0.24, 12.58)	1.79 (0.20, 16.12)	1.20 (0.18, 8.04)	1.34 (0.18, 10.19)	1.33 (0.19, 9.19)
0.70 (0.14, 3.42)	Placebo	14.01 (3.62, 54.21)*	6.28 (2.02, 19.45)*	5.58 (1.61, 19.36)*	6.63 (1.32, 33.32)*	7.88 (2.52, 24.69)*	2.51 (0.57, 11.15)	3.77 (1.36, 10.46)*	3.36 (0.98, 11.53)	5.99 (2.05, 17.50)*
0.70 (0.04, 11.13)	0.99 (0.10, 9.64)	PEX168200ug	2.23 (0.38, 13.03)	2.51 (0.40, 15.77)	2.11 (0.26, 17.39)	1.78 (0.30, 10.44)	5.58 (1.73, 17.97)*	3.72 (0.68, 20.25)	4.17 (0.67, 26.01)	2.34 (0.42, 13.16)
0.66 (0.01, 38.07)	0.94 (0.02, 39.27)	0.95 (0.01, 74.77)	Dula3.0mg	1.12 (0.31, 4.05)	1.06 (0.19, 5.78)	1.26 (0.51, 3.11)	2.50 (0.38, 16.23)	1.66 (0.69, 4.01)	1.87 (0.56, 6.19)	1.05 (0.32, 3.47)
0.50 (0.03, 7.48)	0.70 (0.08, 6.40)	0.71 (0.03, 16.84)	0.75 (0.02, 23.84)	Sema0.5mg	1.19 (0.27, 5.19)	1.41 (0.39, 5.13)	2.22 (0.32, 15.49)	1.48 (0.54, 4.02)	1.66 (0.58, 4.73)	1.07 (0.46, 2.50)
0.53 (0.01, 31.86)	0.75 (0.02, 32.98)	0.76 (0.01, 62.37)	0.80 (0.01, 83.84)	1.07 (0.04, 32.13)	Sema2.0mg	1.19 (0.22, 6.55)	2.64 (0.29, 23.78)	1.76 (0.38, 8.04)	1.97 (0.41, 9.48)	1.11 (0.33, 3.70)
0.22 (0.01, 6.41)	0.32 (0.02, 6.14)	0.32 (0.01, 13.35)	0.34 (0.01, 8.26)	0.45 (0.03, 6.14)	0.42 (0.01, 24.35)	Dula4.5mg	3.14 (0.48, 20.56)	2.09 (0.86, 5.08)	2.35 (0.70, 7.83)	1.32 (0.39, 4.39)
0.23 (0.02, 2.77)	0.33 (0.05, 2.22)	0.33 (0.05, 2.24)	0.35 (0.01, 23.28)	0.47 (0.03, 8.68)	0.44 (0.01, 30.28)	1.05 (0.03, 35.69)	PEX168100ug	1.50 (0.25, 9.13)	1.34 (0.19, 9.26)	2.38 (0.38, 14.97)
0.22 (0.02, 2.65)	0.31 (0.05, 2.13)	0.32 (0.02, 6.18)	0.33 (0.01, 8.22)	0.45 (0.12, 1.65)	0.42 (0.01, 12.13)	0.99 (0.10, 9.59)	0.95 (0.06, 14.11)	Dula1.5mg	1.12 (0.48, 2.63)	1.59 (0.63, 4.00)
0.21 (0.02, 2.67)	0.30 (0.04, 2.18)	0.31 (0.02, 6.19)	0.32 (0.01, 8.29)	0.43 (0.11, 1.64)	0.40 (0.01, 11.92)	0.97 (0.09, 9.83)	0.92 (0.06, 14.19)	0.97 (0.59, 1.59)	Dula0.75mg	1.78 (0.65, 4.86)
0.18 (0.01, 2.32)	0.26 (0.03, 1.90)	0.26 (0.01, 5.34)	0.27 (0.01, 7.93)	0.36 (0.12, 1.15)	0.34 (0.01, 8.37)	0.81 (0.07, 9.86)	0.77 (0.05, 12.27)	0.82 (0.29, 2.33)	0.84 (0.28, 2.48)	Sema1.0mg

interventions   hypoglycemia   Gastrointestinal reactions

Figure 4. Comparisons for the safety of the 10 interventions. Data in each cell are hazard or odds ratios (95% credible intervals) for the comparison of row-defining treatment versus column-defining treatment. Significant results are marked*. Dula = dulaglutide, Exe = exenatide, Sema = Semaglutide.

in the Exenatide 2.0 mg group compared with placebo, other GLP-1RAs had lower incidences of both hypoglycemia and gastrointestinal reactions than placebo. It can be seen that most of the GLP-1RAs are relatively safe.

Semaglutide is approved in China in 2021. Previously, there was no specific analysis of GLP-1RA, which is approved weekly in China. Therefore, the indirect comparative evidence established through this study provides important clinical evidence for Chinese physicians who treat more than a quarter of the world diabetic patients.[19] In addition, the 2 regimens in this analysis, Semaglutide and Loxenatide, were not previously indirectly compared in the NMA of any GLP-1RAs, which may be related to the unique combination of GLP-1RAs in China.

As a newly marketed weekly preparation of GLP-1RAs, Semaglutide can significantly reduce the glycated hemoglobin of patients with T2DM regardless of the original treatment measures and the duration of the disease.[20,21] The greater the drop after the peptide, and the "smart" weight loss can be achieved while reducing blood sugar. In general, long-acting formulations reduced HbA1c more than short-acting formulations, with Semaglutide having the greatest HbA1c reduction.[22] And for Semaglutide, the 2.0 mg weekly preparation has a more obvious

hypoglycemic effect than the 1.0 mg weekly preparation, but there is a lack of high-quality research evidence, and further research is needed. Although Semaglutide is the best among GLP-1RAs in terms of clinical efficacy, it is not very stable in terms of safety and still has a high incidence of gastrointestinal reactions.[23–25]

This meta-analysis is more comprehensive than previous studies and includes all marketed weekly GLP-1RAs formulations and different doses commonly used in clinical practice. We put more emphasis on the efficacy and differences between the 2 in clinical treatment, as well as the efficacy and adverse reactions of different doses. Global inconsistency is not evident in inconsistent model analysis. At the same time, the research bias was tested. As shown in the figure, the funnel plot is roughly symmetrical, indicating that the article has no obvious bias (See Figure S3, Supplemental Digital Content, http://links.lww.com/MD/J196, which illustrates Funnel plots).

This study has several potential limitations. First, basic information such as race and ethnicity were not extracted, and differences in the prevalence and etiology of T2DM between races and ethnicities may influence treatment response. Secondly, the treatment duration of the included studies varies greatly, ranging from 12 weeks to 52 weeks, and no in-depth research has

been carried out on this, so the clinical efficacy of the specific treatment course of GLP-1RA needs to be further explored.

5. Conclusion

The 4 GLP-1RAs had better hypoglycemic and weight loss effects on T2D adults. Among them, Semaglutide 2.0mg has the best efficacy, including relatively low incidence of AE. Therefore, in terms of clinical medication, while ensuring the clinical efficacy of patients, we also need to pay more attention to the adverse reactions of drugs and monitor blood sugar at all times.

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