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PRISMA—efficacy and safety of lixisenatide for type 2 diabetes mellitus
A meta-analysis of randomized controlled trials

Zhen-gang Wei, MD[a,b,c], Man-cai Wang, MD[a,b,c], Hui-han Zhang, MD[a,b,c], Zhe-yuan Wang, MD, PhD[a,b,c], Gen-nian Wang, MD[a,b,c], Feng-xian Wei, MD[a,b,c], Ya-wu Zhang, MD, PhD[a,b,c], Xiao-dong Xu, MD, PhD[a,b,c], You-cheng Zhang, MD, PhD[a,b,c],*

Abstract

Objective: We aimed to systematically evaluate the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus.

Methods: PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, Google, Web of Science and the Chinese Science Citation Database were searched up to March 2018. Randomized controlled trials determining the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus were eligible for inclusion. Two authors independently extracted the data in a prespecified Microsoft Excel spreadsheet. A meta-analysis was performed using Review Manager 5.3 software. Weighted mean difference (WMD) and relative risk (RR) together with their corresponding 95% confidence intervals (CIs) were estimated, and only the random effects model was used in order to achieve a more conservative estimate of the efficacy and safety.

Results: Fourteen multicenter randomized controlled trials involving 11,947 patients were eligible for inclusion. Compared to placebo, lixisenatide could more significantly reduce the level of HbA1c (WMD=-0.44; 95% confidence interval [CI] [-0.55,-0.33]), and a higher proportion of lixisenatide-treated patients achieved the HbA1c level of < 7.0% (RR = 1.89, 95% CI [1.75–2.03]) and < 6.5% (RR = 3.03, 95% CI [2.54–3.63]) than the placebo-treated patients. Lixisenatide was also associated with a significant reduction in fasting plasma glucose and 2-hour postprandial plasma glucose levels. The risks for any adverse events, gastrointestinal adverse events, and symptomatic hypoglycemia significantly increased in the lixisenatide-treatedment group compared to those in the placebo group. However, lixisenatideit did not increase the risks of serious adverse events, death, or severe hypoglycemia.

Conclusions: Lixisenatide was more effective than placebo in patients with type 2 diabetes mellitus, and the mild-to-moderate adverse events were found to be tolerated during the follow-up.

Abbreviations: AEs = adverse events, CIs = confidence intervals, DPP-4 = dipeptidyl peptidase-4, FPG = fasting plasma glucose, GLP-1 = glucagon-like peptide-1, IDF = International Diabetes Federation, OAD = oral antidiabetic agents, PPG = postprandial plasma glucose, RAs = receptor agonists, RCT = randomized controlled trial, RevMan = Review Manager, RR = relative risk, T2DM = type 2 diabetes mellitus, WMD = weighted mean difference.

Keywords: diabetes mellitus, lixisenatide, meta-analysis, review

1. Introduction

Diabetes mellitus is one of the leading causes of disability and death worldwide .[1] Currently, there are 425 million people living with diabetes, and the number will increase to 629 million in 2045 .[2] According to the International Diabetes Federation, 3 quarters of the people with diabetes live in low- and middle-income countries. It has the highest number of people with diabetes in the world, with a prevalence of 9.1%. Further, diabetes accounts for 2% of the global health expenditure.[2]

Although a variety of lifestyle and pathophysiological approaches are now available for the management of diabetes, because of the progressive nature of the disease, current management approaches often fail to achieve the glycemic targets (i.e, < 6.5% or < 7.0%) in the long term.[3,4,5] To maintain glycemic control in patients with type 2 diabetes mellitus (T2DM), multiple glucose-lowering agents and/or insulin are required. However, combination therapies are associated with significant adverse effects such as hypoglycemia, weight gain, gastrointestinal (GI) intolerance.[3,6] Therefore, there is an urgent need for developing more effective and better-tolerated glucose-lowering therapies.

The incretin system plays a significant role in the maintenance of glucose homeostasis. Some evidence suggests that glucagon-like peptide-1 (GLP-1) secretion is reduced in subjects with impaired glucose tolerance or T2DM, whereas the responsiveness to GLP-1 is preserved .[7] In recent years, GLP-1 receptor agonists (GLP-1 RAs) have shown promising effects and have become an important therapeutic option in the treatment of T2DM,[5,8] which is owing to the combination of both the promotion of insulin secretion and inhibition of glucagon secretion.[9,10] Studies in vitro and animal models suggested that GLP-1 RAs have the potential to preserve pancreatic islet β-cells by enhancing their proliferation and inhibiting apoptosis.[4,5] In addition, they can reduce the energy intake and therefore may result in weight loss.[4] The benefits of cardioprotection and neuroprotection have also been noted in some studies.[11,12,13]

Native GLP-1 is not suitable for the treatment of T2DM. It can be rapidly resolved by dipeptidyl peptidase-4 (DPP-4), and its half-life is less than 2 minutes .[5,13] Exenatide and liraglutide are 2 representatives of DDP-4-resistant GLP-1 RAs .[14] Their advantages included a low propensity to cause hypoglycemia, the ability to promote weight loss, and confer additional cardiovascular benefits.[6,15] Lixisenatide (AVE0010) is the 3rd synthetic GLP-1 RA; it is a 44-amino acid exendin-4-like GLP-1 RA, which is modified at the C-terminal by 6 Lys residues and deletion of one Pro residue.[5,7,16] Recent clinical studies have shown that lixisenatide is possibly highly effective in patients with T2DM. However, various GLP-1 RAs may have substantial differences in their duration of action and clinical profile. Moreover, the uncertainty associated with some adverse events (AEs) was highlighted in those studies. Thus, the objective of this meta-analysis was to systematically evaluate the efficacy and safety of lixisenatide in patients with T2DM.

2. Methods

The ethical approval was not necessary in this meta-analysis, all of the data were directly extracted from the published randomized controlled trials (RCTs) about lixisenatide for patients with T2DM.

2.1. Search strategy

The MEDLINE, EMBASE, Cochrane library, ClinicalTrials.gov, Google, Web of Science, and the Chinese Science Citation Database were searched up to March 2018. The search strategy was not limited by language or region. The search was performed using both free text and medical subject headlines, and search terms including lixisenatide, AVE0010, and diabetes mellitus.

2.2. Inclusion criteria

The eligibility criteria were as follows. First, Study design: single- or double-blind RCTs, without a language limitation. Second, Population: patients ages > 18 years, with inadequately controlled type 2 diabetes and a glycated hemoglobin (HbA1c) level of 7–10%. Third, Intervention: lixisenatide or placebo was administered subcutaneously, with or without oral antidiabetic agents (OADs)/insulin; the dose of lixisenatide was not limited, and the follow-up period was not less than 12 weeks. Fourth, Outcomes: HbA1c level, HbA1c < 7.0% or < 6.5%, fasting plasma glucose (FPG), body weight, rescue therapy, and AEs.

2.3. Study selection and data extraction

Studies were assessed and data were extracted by 2 independent investigators according to the inclusion criteria in a prespecified

Microsoft Excel spreadsheet. Disagreements were resolved by discussion with a 3rd author. The following data were collected:

1. Study characteristics (e.g., author, year of publication, sample size, age, sex ratio, duration of diabetes, and baseline HbA1c level);
2. Intervention measures (e.g., does of lixisenatide, once-daily or twice-daily, 1-step or 2-step, morning or evening);
3. Efficacy (e.g., HbA1c level, HbA1c < 7.0% or < 6.5%, FPG, body weight, and rescue therapy);
4. Safety (e.g., serious AEs, death, gastrointestinal disorders, symptomatic hypoglycemia, and severe hypoglycemia); and
5. Risk of bias: (e.g., random sequence generation, allocation concealment, and blinding).

2.4. Risk of bias assessment

Two authors independently evaluated the methodological quality of the included studies according to the Cochrane Risk of Bias tool for RCTs,[17] and differences were resolved by discussion with a 3rd author.

2.5. Statistical analysis

Data were pooled using Review Manager 5.3 software (RevMan 5.3). Weighted mean difference (WMD) and relative risk (RR) together with their corresponding 95% confidence intervals (CIs) were determined. We analyzed all the outcomes with a random effects model in order to provide a more conservative estimate of the efficacy and safety. Statistical heterogeneity was estimated using the I^2 statistic with a cutoff of 50%, and the Chi-square test with a P value of < .10. If the $I^2 > 50\%$ and $P < .10$, we would remove the studies with obvious heterogeneity (according to the results of forest plot) and re-analyze the data. Finally, a fixed effects model was used to determine the stability of this meta-analysis, and publication bias was assessed using funnel plots.

3. Results

3.1. Study characteristics

Fourteen eligible multicenter RCTs[5,6,14,18–28] were included finally, with a total sample size of 11,947. The flow chart for trial selection is shown in Figure 1. Three RCTs [29–31] were finally excluded because of a short-term follow-up (<12 weeks); one open-label RCT [16] was also removed from this meta-analysis. The characteristics of included studies are listed in Table 1. The baseline HbA1c level was 7 to 10% in all studies, and the follow-up durations were 24 weeks,[6,18–24,26,28] 13 weeks,[5] 12 weeks,[14,27] and 25 months.[25] Lixisenatide 20 μg once daily was subcutaneously administered in most of the included studies. Metformin,[5,18–25,28] sulfonylurea,[6,18–21,25] thiazolidinedione,[24,25] pioglitazone,[22] and insulin[6,23–25,28] were used in different studies for glycemic control.

3.2. Risk of bias

Overall, the risk of bias was low (Fig. 2). Patients were randomly divided into 2 groups, and allocation concealment was performed using a centralized interactive voice response system or centralized assignment system in eight studies.[5,6,14,22–25] All of the eligible studies were double-blind trials.[5,6,14,18–28]

3.3. Efficacy of lixisenatide for T2DM
3.3.1. HbA1c level.
Seven RCTs [5,6,19–21,26,28] reported the HbA1c level at the end of the follow-up. High heterogeneity
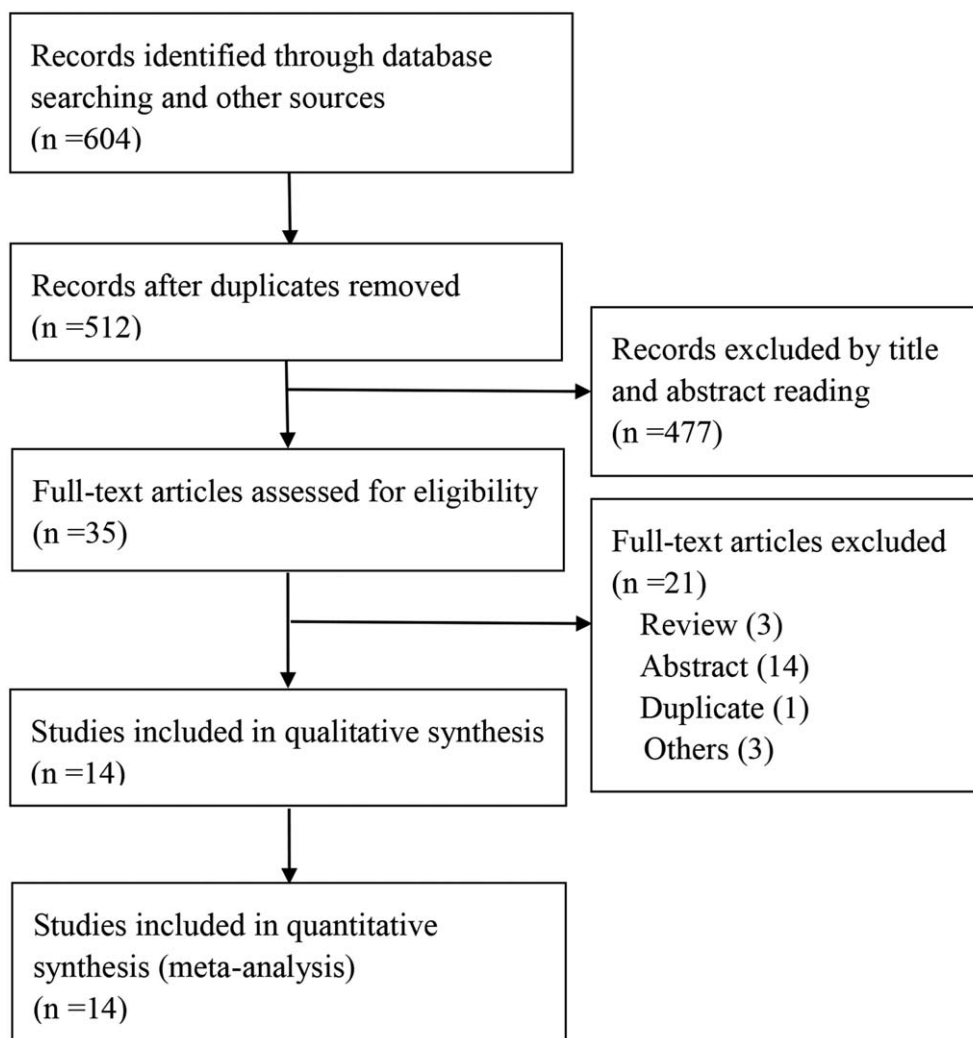
Figure 1. The flow chart of trial selection.

Table 1

The characteristics of included studies in this meta-analysis.

Num.	Author	Sample size	Male (%)		Age		BMI		HbA1c (%)		Duration, years		follow up
			LIXI	Placebo	LIXI	Placebo	LIXI	Placebo	LIXI	Placebo	LIXI	Placebo	
1	Rosenstock	574/285	284 (49.5)	150 (52.6)	57.0±9.8	57.8±10.1	30.1±6.6	30.4±6.6	8.3±0.9	8.2±0.8	9.1±6.0	9.8±6.2	24w
2	Bolli (1-step)	161/81	44 (27.3)	45 (28.1)	55.4±8.9	58.2±9.8	33.0±5.8	32.4±5.5	8.0±0.9	8.0±0.8	5.8±3.9	6.2±4.7	24w
	Bolli (2-step)	161/81	45 (28.0)	45 (28.1)	54.6±8.9	58.2±9.8	32.1±4.8	32.4±5.5	8.1±0.9	8.0±0.8	6.0±4.6	6.2±4.7	24w
3	Pan	196/194	101 (51.5)	91 (46.9)	54.5±10.3	55.1±10.5	26.8±3.9	27.1±3.8	7.95±0.81	7.85±0.71	6.5±4.6	6.8±4.8	24w
4	Ahrén (morning)	255/170	98 (38.4)	81 (47.6)	54.5±9.2	55.0±9.4	33.2±6.9	33.1±6.5	8.0±0.9	8.1±0.9	6.2±5.3	5.9±4.7	24w
	Ahrén (evening)	255/170	114 (44.7)	81 (47.6)	54.8±10.4	55.0±9.4	32.5±5.8	33.1±6.5	8.1±0.9	8.1±0.9	6.2±5.4	5.9±4.7	24w
5	Pinget	323/161	171 (53)	82 (51)	56.0±9.5	55.3±9.5	33.7±6.7	34.4±7.0	8.1±0.9	8.1±0.8	8.1±5.4	8.1±5.6	24w
6	Riddle	328/167	146 (45)	82 (49)	57±10	57±10	31.9±6.2	32.6±6.3	8.4±0.9	8.4±0.8	12.5±7.0	12.4±6.3	24w
7	Riddle	223/223	109 (49)	113 (51)	56±10	56±10	32.0±6.6	31.7±6.0	7.6±0.5	7.6±0.5	9.6±6.0	8.7±5.8	24w
8	Seino	154/157	69 (44.8)	80 (51.0)	58.7±10.2	58.0±10.1	25.4±3.7	25.2±3.9	8.54±0.73	8.52±0.78	13.7±7.7	14.1±7.7	24w
9	Fonseca (1-step)	119/122	63 (52.9)	60 (49.2)	53.8±10.9	54.1±11.0	31.7±6.6	31.8±6.7	8.07±0.9	8.07±0.9	0.2–23.9*	0.2–12.5	12w
	Fonseca (2-step)	120/122	63 (52.5)	60 (49.2)	53.3±9.7	54.1±11.0	32.3±6.7	31.8±6.7	7.98±0.9	8.07±0.9	0.2–21.5*	0.2–12.5	12w
10	Ratner (5 μg QD)	55/109	26 (47.3)	61 (56.0)	56.8±7.8	56.3±9.2	30.7±4.6	31.7±4.2	7.58±0.7	7.53±0.6	7.2±4.9	7.1±5.4	13w
	Ratner (10 μg QD)	52/109	31 (59.6)	61 (56.0)	55.4±9.2	56.3±9.2	31.9±4.0	31.7±4.2	7.52±0.6	7.53±0.6	6.2±4.1	7.1±5.4	13w
	Ratner (20 μg QD)	55/109	28 (50.9)	61 (56.0)	55.4±9.9	56.3±9.2	32.0±4.3	31.7±4.2	7.58±0.7	7.53±0.6	6.4±6.8	7.1±5.4	13w
	Ratner (30 μg QD)	54/109	27 (50.0)	61 (56.0)	56.5±8.7	56.3±9.2	31.6±3.6	31.7±4.2	7.52±0.7	7.53±0.6	6.0±4.8	7.1±5.4	13w
	Ratner (5 μg BID)	53/109	25 (47.2)	61 (56.0)	57.1±8.2	56.3±9.2	31.6±4.2	31.7±4.2	7.60±0.6	7.53±0.6	6.2±6.0	7.1±5.4	13w
	Ratner (10 μg BID)	56/109	29 (51.8)	61 (56.0)	56.0±7.9	56.3±9.2	32.8±4.4	31.7±4.2	7.54±0.6	7.53±0.6	6.4±5.0	7.1±5.4	13w
	Ratner (20 μg BID)	54/109	20 (37.0)	61 (56.0)	56.7±8.3	56.3±9.2	32.7±4.4	31.7±4.2	7.61±0.7	7.53±0.6	6.6±5.1	7.1±5.4	13w
	Ratner (30 μg BID)	54/109	23 (42.6)	61 (56.0)	55.3±9.1	56.3±9.2	32.3±4.5	31.7±4.2	7.46±0.5	7.53±0.6	7.0±5.4	7.1±5.4	13m
11	Pfeffer	3034/3034	2111 (69.6)	2096 (69.1)	59.9±9.7	60.6±9.6	30.1±5.6	30.2±5.8	7.7±1.3	7.6±1.3	9.2±8.2	9.4±8.3	25m
12	Meneilly	176/174	92 (52.3)	90 (51.7)	74.0±4.0	74.4±3.8	29.9±3.7	30.1±4.5	8.1±0.7	8.1±0.7	13.6±7.3	14.6±7.9	24w
13	Miya	16/15	9 (56.2)	9 (60)	66.0±8.4	59.6±12.8	27.2±4.2	26.4±6.4	7.1±0.5	7.2±0.9	18.6±12.3	21.4±10.8	12w
14	Yang	224/224	105 (46.9)	98 (43.8)	53.9±9.9	56.2±9.1	27.5±4.39	27.9±4.48	7.9±0.66	7.9±0.70	10.3±6.1	10.2±6.2	24w

* duration of diabetes mellitus was not all ≥1 year since diagnosis.
BMI = body mass index, LIXI = Lixisenatide.

Figure 2. The risk of bias in this meta-analysis.

existed among these studies ($I^2 = 66\%$, $P = .005$). The meta-analysis showed that there was a statistically significant difference between the lixisenatide and placebo groups (WMD = -0.48; 95% CI [-0.60, -0.36]) (Table 2). The forest plot showed obvious heterogeneity between the study by Rosenstock et al. [18] and the other studies. After removing it, a consistent result was obtained compared to that obtained previously (WMD = -0.44; 95% CI, [-0.55, -0.33]) (Fig. 3).

3.3.2. HbA1c<7.0%. Eleven RCTs [5,6,14,18–24,28] reported the number of patients with HbA1c < 7.0%. Moderate

heterogeneity existed among these studies ($I^2 = 58\%$, $P = .0005$). A comparison of the lixisenatide- and placebo-treated patients with T2DM showed statistically significant difference (RR = 1.94, 95% CI [1.73–2.16]) (Table 2). After the obviously heterogeneous study by Seino et al. [6] was removed, the result was similar to that achieved previously (RR = 1.89, 95% CI [1.75–2.03]) (Fig. 4).

3.3.3. HbA1c<6.5%. Eleven RCTs [5,6,14,18–24,28] reported the number of patients with HbA1c < 6.5%. No significant heterogeneity existed among these studies ($I^2 = 43\%$, $P = .02$). The meta-analysis showed statistically significant differences between lixisenatide- and placebo-treated patients (RR = 3.03, 95% CI [2.54–3.63]) (Fig. 5).

3.4. FPG

Seven RCTs [5,6,19–21,26,28] reported the FPG levels of their subjects. No significant heterogeneity existed among these studies ($I^2 = 28\%$, $P = .21$). There was a statistically significant difference between the lixisenatide and placebo groups (WMD = -0.43, 95% CI [-0.62, -0.25]) (Table 2).

3.4.1. Body weight. Body weight was reported in 6 [5,6,20,21,26,28] RCTs. No heterogeneity existed among these studies ($I^2 = 0\%$, $P = .78$). There was a statistically significant difference in body weight between the lixisenatide and placebo groups (WMD = -1.34, 95% CI [-2.67,-0.02]) (Table 2).

3.4.2. Rescue therapy. Nine RCTs [5,6,18,19,20,22,23,26,28] reported the proportion of patients who received rescue therapy during follow-up. No heterogeneity existed among these studies ($I^2 = 0\%$, $P = .66$). The meta-analysis showed that there was a statistically significant difference in the patients who received rescue therapy during follow-up between the lixisenatide and placebo groups (RR = 0.39, 95% CI [0.30–0.51]) (Table 2).

3.5. Others

Five RCTs [5,18,20,21,28] reported glucose excursion, and 5 RCTs [5,20,21,26,28] reported the 2-hour postprandial plasma glucose (PPG) levels after a standardized breakfast. The meta-analysis showed statistically significant differences for these factors between lixisenatide and placebo groups (WMD = -3.91, 95% CI [-4.72, -3.10]; WMD = -4.31, 95% CI [-5.50, -3.12], respectively) (Table 2).

3.6. Safety of lixisenatide for T2DMs
3.6.1. Any AEs and discontinuation. Twelve RCTs [5,6,14,18–24,26,28] and 14 RCTs (5, 6, 14, 18–28) respectively reported the outcomes of any AEs and discontinuation due to AEs. No significant heterogeneity existed among these studies ($I^2 = 46\%$, $P = .009$; $I^2 = 0\%$, $P = .52$, respectively). It was found that lixisenatide may increase the risk of any AEs and the rate of discontinuation due to AEs, and there were statistically significant differences with regard to these factors between the lixisenatide and placebo groups (RR = 1.14, 95% CI [1.08–1.19]; RR = 1.79, 95% CI [1.57–2.05], respectively) (Table 2).

3.6.2. Serious AEs and death. Thirteen RCTs [5,6,14,18–26,28] reported serious AEs, and drug-related deaths occurred in 6 included studies [5,6,20–22,26]. There was no heterogeneity among these studies ($I^2 = 0\%$, $P = .51$; $I^2 = 0\%$, $P = .82$). Lixisenatide was

Table 2

Outcomes of the meta-analysis and sensitivity analysis.

Outcomes	Study	I²%	Random effects model		Fixed effects model	
			WMD/RR (95% CI)	P	WMD/RR (95% CI)	P
Efficacy						
HbA1c	7	66	−0.48 (−0.60, −0.36)	<.00001	−0.49 (−0.56, −0.42)	<.00001
HbA1c<7.0%	11	58	1.94 (1.73–2.16)	<.00001	1.94 (1.81–2.09)	<.00001
HbA1c<6.5%	10	43	3.03 (2.54–3.63)	<.00001	2.92 (2.57–3.33)	<.00001
Fasting plasma glucose	7	28	−0.43 (−0.62, −0.25)	<.00001	−0.43 (−0.58, −0.28)	<.00001
Body weight	6	0	−1.34 (−2.67,−0.02)	0.05	−1.34 (−2.67,−0.02)	.05
Rescue therapy	9	0	0.39 (0.30–0.51)	<.00001	0.39 (0.30–0.50)	<.00001
Glucose excursion	5	93#	−3.91 (−4.72, −3.10)	<.00001	−3.83 (−3.91, −3.75)	<.00001
2-hour PPG	5	92&	−4.31 (−5.50, −3.12)	<.00001	−4.49 (−4.82, −4.16)	<.00001
Safety						
Any adverse events (AE)	12	46	1.14 (1.08–1.19)	<.00001	1.14 (1.09–1.19)	<0.00001
Discontinuation due to AE	14	0	1.79 (1.57–2.05)	<0.00001	1.84 (1.61–2.10)	<.00001
Serious adverse events	13	0	0.94 (0.86–1.04)	.49	0.60 (0.18–1.96)	.40
Death*	6	0	0.64 (0.18, 2.32)	.49	0.60 (0.18–1.96)	.40
Gastrointestinal disorders	13	74	2.23 (1.86–2.68)	<.00001	2.20 (2.01–2.40)	<.00001
Nausea	12	30	4.09 (3.38–4.95)	<.00001	4.09 (3.52–4.76)	<.00001
Vomiting	12	18	5.57 (3.88–7.98)	<.00001	5.99 (4.48–8.01)	<.00001
Diarrhea	10	7	1.28 (1.05–1.55)	.01	1.28 (1.07–1.53)	.007
Symptomatic hypoglycemia	14	0	1.59 (1.35–1.89)	<.0001	1.64 (1.39–1.94)	<.00001
Severe hypoglycemia	5	0	0.74 (0.40–1.36)	.33	0.80 (0.45–1.42)	.44
Injection-site reactions	9	0	2.05 (1.43–2.95)	.0001	2.19 (1.54–3.13)	<.0001
Allergic reaction	6	0	2.11 (0.68–6.54)	.20	2.19 (0.72–6.69)	.17

AE = adverse events, PPG = postprandial plasma glucose.

Significant heterogeneity existed among these studies, while after removing the obviously heterogeneous study Ahrén et al[21] and Rosenstock et al[18], the result (I² = 0%, P = .50; WMD = −3.32, 95% CI [−3.73,−2.91]) was similar with that before.

& Significant heterogeneity existed among these studies, while after removing the obviously heterogeneous study Meneilly et al[26] and Rosenstock et al[18], the result (I² = 0%, P = .49; WMD = −3.47, 95% CI [−3.91,−3.03]) was similar with that before.

* Eleven of the 14 studies reported drug-related deaths, of which 6 of the studies confirmed the death event.

not associated with serious AEs or death in patients with T2DM; no statistically significant difference with regard to these factors between the lixisenatide and placebo groups (RR = 0.94, 95% CI [0.86–1.04]; RR = 0.73, 95% CI [0.18–2.98], respectively) (Table 2).

3.7. Gastrointestinal AEs

Gastrointestinal AEs included gastrointestinal disorders, nausea, vomiting, and diarrhea. They were respectively reported in 13,[5,6,14,18–23,25–28] 12,[5,6,14,18–24,26,28] 12,[5,6,14,18–24,26,28] and 10[5,6,18–24,26] RCTs. The meta-analysis showed that compared to the placebo in patients with T2DM, lixisenatide could increase

the risks of gastrointestinal disorders (I² = 74%, P < .00001; RR = 2.23, 95% CI [1.86–2.68]), nausea (I² = 30%, P = .09; RR = 4.09, 95% CI [3.38–4.95]), vomiting (I² = 18%, P = .23; RR = 5.57, 95% CI [3.88–7.98]), and diarrhea (I² = 7%, P = .38; RR = 1.28, 95% CI [1.05–1.55]); there were statistically significant differences in these events between the 2 groups (Table 2).

3.8. Hypoglycemia

All RCTs [5,6,14,18–28] reported patients with symptomatic hypoglycemia and severe hypoglycemia; severe hypoglycemia was reported in 5 studies [5,20,21,25,26]. No significant heterogeneity existed among these studies (I² = 0%, P = .61; I² = 0%,
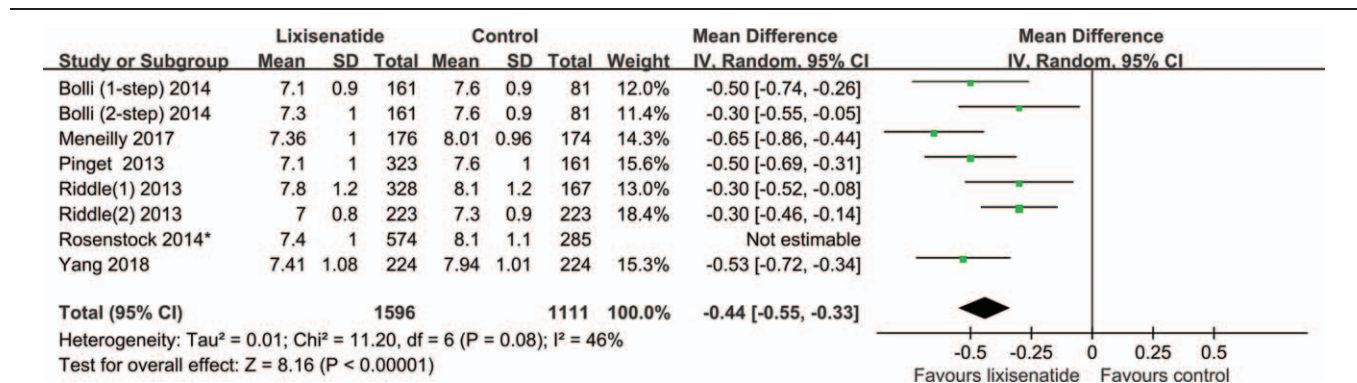

Figure 3. The meta-analysis of HbA1c levels at the end of the follow-up *The study by Rosenstock et al showed obvious heterogeneity with others, according to the forest plot. After the study was removed, we obtained results consistent with those obtained before.

Study or Subgroup	Lixisenatide Events	Total	Control Events	Total	Weight	Risk Ratio M-H. Random. 95% CI	Risk Ratio M-H. Random. 95% CI
Ahrén (evening) 2013	104	255	37	170	5.1%	1.87 [1.36, 2.58]	
Ahrén (morning) 2013	110	255	37	170	5.1%	1.98 [1.44, 2.72]	
Bolli (1-step) 2014	74	156	38	158	5.1%	1.97 [1.43, 2.72]	
Bolli (2-step) 2014	64	152	38	158	4.9%	1.75 [1.25, 2.44]	
Fonseca (1-step) 2012	53	114	32	112	4.5%	1.63 [1.14, 2.32]	
Fonseca (2-step) 2012	59	113	32	112	4.7%	1.83 [1.30, 2.57]	
Pan 2014	103	195	75	193	7.3%	1.36 [1.09, 1.70]	
Pinget 2013	169	323	43	161	6.0%	1.96 [1.49, 2.58]	
Ratner (10µg BID) 2010	36	56	35	109	4.8%	2.00 [1.43, 2.80]	
Ratner (10µg QD) 2010	27	52	35	109	4.2%	1.62 [1.11, 2.36]	
Ratner (20µg BID) 2010	33	54	35	109	4.7%	1.90 [1.35, 2.69]	
Ratner (20µg QD) 2010	37	55	35	109	4.9%	2.10 [1.51, 2.91]	
Ratner (30µg BID) 2010	42	54	35	109	5.3%	2.42 [1.78, 3.30]	
Ratner (30µg QD) 2010	37	54	35	109	5.0%	2.13 [1.54, 2.96]	
Ratner (5µg BID) 2010	27	53	35	109	4.1%	1.59 [1.09, 2.32]	
Ratner (5µg QD) 2010	26	55	35	109	4.0%	1.47 [1.00, 2.18]	
Riddle(1) 2013	86	328	19	167	3.2%	2.30 [1.45, 3.65]	
Riddle(2) 2013	121	223	85	223	7.7%	1.42 [1.16, 1.75]	
Rosenstock 2014	209	574	38	285	5.2%	2.73 [1.99, 3.74]	
Seino 2012*	55	154	8	157	0.0%	7.01 [3.45, 14.22]	
Yang 2018	83	224	30	224	4.2%	2.77 [1.90, 4.02]	
Total (95% CI)		**3345**		**3005**	**100.0%**	**1.88 [1.71, 2.07]**	
Total events	1500		784				

Heterogeneity: Tau² = 0.02; Chi² = 33.36, df = 19 (P = 0.02); I² = 43%
Test for overall effect: Z = 12.93 (P < 0.00001)

0.5 0.7 1 1.5 2
Favours control Favours lixisenatide

Figure 4. The meta-analysis of HbA1c < 7% * The study by Seino et al showed obvious heterogeneity with others, according to the forest plot. After the study was removed, we obtained results consistent with those obtained before.
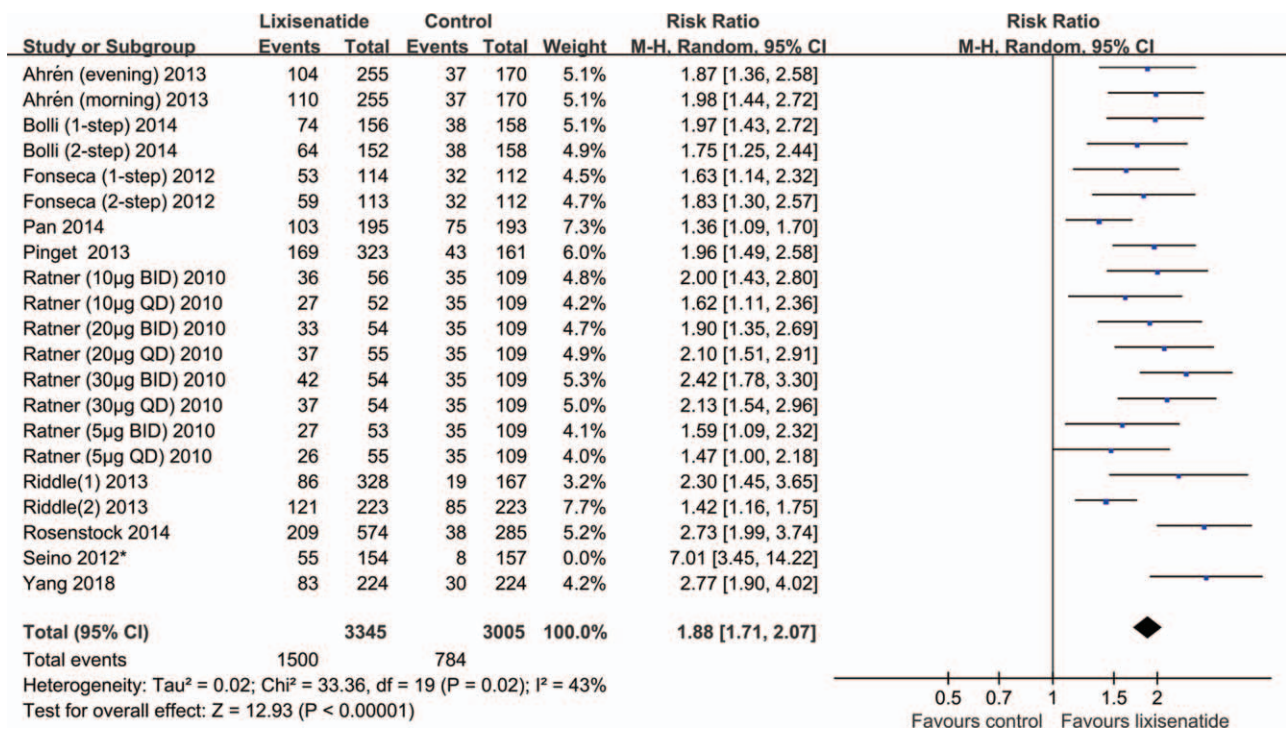
$P = .45$). The meta-analysis showed that compared to the placebo, lixisenatide was associated with the risk of symptomatic hypoglycemia (RR = 1.36, 95% CI [1.24–1.50]). However, there was no statistically significant difference in severe hypoglycemia between the 2 groups (RR = 0.74, 95% CI [0.40–1.36]) (Table 2).

3.9. Skin reaction

Injection-site reactions and allergic reactions were respectively reported in 9[5,6,18–23] and 6[19–23,28] RCTs. Our meta-analysis showed that lixisenatide could increase the risk of injection-site reactions ($I^2 = 0\%$, $P = .61$; RR = 2.05, 95% CI [1.43–2.95]).

Study or Subgroup	Lixisenatide Events	Total	Control Events	Total	Weight	Risk Ratio M-H. Random. 95% CI	Risk Ratio M-H. Random. 95% CI
Ahrén (evening) 2013	49	225	18	170	6.2%	2.06 [1.24, 3.40]	
Ahrén (morning) 2013	61	225	18	170	6.4%	2.56 [1.57, 4.17]	
Bolli (1-step) 2014	40	156	12	158	5.0%	3.38 [1.84, 6.19]	
Bolli (2-step) 2014	31	152	12	158	4.8%	2.69 [1.43, 5.03]	
Fonseca (1-step) 2012	29	114	14	112	5.3%	2.04 [1.14, 3.64]	
Fonseca (2-step) 2012	36	113	14	112	5.5%	2.55 [1.46, 4.46]	
Pan 2014	63	195	35	193	8.1%	1.78 [1.24, 2.56]	
Pinget 2013	93	323	16	161	6.2%	2.90 [1.76, 4.76]	
Ratner (10µg BID) 2010	20	56	8	109	3.8%	4.87 [2.29, 10.34]	
Ratner (10µg QD) 2010	9	52	8	109	3.0%	2.36 [0.97, 5.76]	
Ratner (20µg BID) 2010	18	54	8	109	3.7%	4.54 [2.11, 9.77]	
Ratner (20µg QD) 2010	19	55	8	109	3.8%	4.71 [2.20, 10.06]	
Ratner (30µg BID) 2010	23	54	8	109	4.0%	5.80 [2.78, 12.11]	
Ratner (30µg QD) 2010	18	54	8	109	3.7%	4.54 [2.11, 9.77]	
Ratner (5µg BID) 2010	17	53	8	109	3.7%	4.37 [2.02, 9.47]	
Ratner (5µg QD) 2010	10	55	8	109	3.1%	2.48 [1.04, 5.92]	
Riddle(1) 2013	44	328	6	167	3.3%	3.73 [1.62, 8.58]	
Riddle(2) 2013	69	223	36	223	8.1%	1.92 [1.34, 2.74]	
Rosenstock 2014	111	574	13	285	5.5%	4.24 [2.43, 7.40]	
Seino 2012	27	154	2	157	1.4%	13.76 [3.33, 56.88]	
Yang 2018	50	224	13	224	5.3%	3.85 [2.15, 6.88]	
Total (95% CI)		**3439**		**3162**	**100.0%**	**3.03 [2.54, 3.63]**	
Total events	837		273				

Heterogeneity: Tau² = 0.07; Chi² = 34.74, df = 20 (P = 0.02); I² = 42%
Test for overall effect: Z = 12.21 (P < 0.00001)

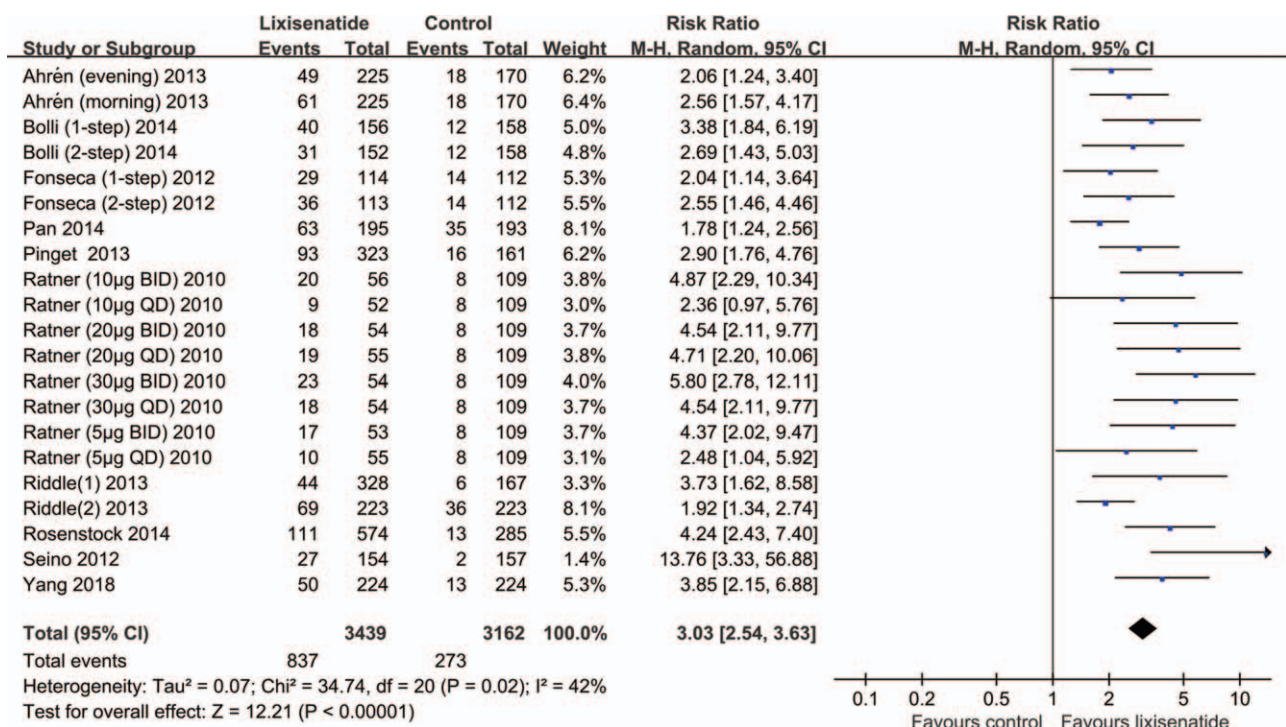0.1 0.2 0.5 1 2 5 10
Favours control Favours lixisenatide

Figure 5. The meta-analysis of HbA1c < 6.5%.

However, there were statistically significant differences in allergic reactions between the lixisenatide and placebo groups ($I^2 = 0\%$, $P = .97$; RR = 2.11, 95% CI [0.68–6.54]) (Table 2).

3.10. Publication bias

A publication bias was shown by funnel plots for HbA1c < 7.0% and HbA1c < 6.5%. The funnel plots were relatively symmetrical, suggesting that there was no publication bias in this meta-analysis (Figure S1–2, http://links.lww.com/MD/C712).

3.11. Sensitivity analysis

A sensitivity analysis was performed using a fixed-effects model to determine the stability of this meta-analysis. All of the results were consistent with that obtained using random-effects model (Table 2).

4. Discussion

Incretin based therapies, such as the GLP-1RAs, represent a major advancement in T2DM treatment.[28,32] Several GLP-1 RAs are available and are increasingly been used as mono-therapies or "add-on" therapies to OADs/insulin.[16,33] As a novel agent in this class, lixisenatide is receiving attention as a T2DM treatment. Our meta-analysis showed that, compared with placebo, lixisenatide could significantly reduce the level of HbA1c, and a significantly higher proportion of lixisenatide-treated patients achieved the HbA1c targets of < 7.0% and < 6.5%. Further, compared to placebo, lixisenatide was associated with a significant reduction in FPG and 2-hour PPG levels after a standardized breakfast. These findings are consistent with those of recent studies.[6,14,18–25] Horowitz et al[34] hold the view that GLP-1 participates in the regulation of appetite and energy intake. However, in this meta-analysis, there was no statistically significant difference in body weight at the end of follow-up between the 2 groups. This finding is inconsistent with the dominant idea in some studies.[18,19,23,24,32,35]

The mechanisms of lixisenatide's glucose-lowering effect have been investigated in several studies .[32] It was shown that lixisenatide could restore the 1st and 2nd-phase insulin responses and accelerate glucose disposition .[32,34] At the same time, lixisenatide could reduce the postprandial glycemic excursions by sustained slowing of gastric emptying, which is of fundamental significance for patients with T2DM.[36] In addition, it is thought that GLP-1 could reduce appetite and energy intake,[37] although no statistically significant difference was found in body weight between the 2 groups in this meta-analysis. It is most noteworthy that various GLP-1 RAs may exhibit different effects on pre- and postprandial glucose levels. Buse et al[38] performed a direct comparison between liraglutide and exenatide, 2 different kinds of GLP-1 RAs, in patients with inadequately controlled T2DM. Results showed that liraglutide more significantly reduced the FPG level while exenatide had a greater effect on PPG excursions. Similar results were found for lixisenatide and liraglutide in type 2 diabetic patients .[30] Some small open-label trials shown that short-acting GLP-1 RAs seem to have a preserved and sustained effect on glucagon secretion and gastric emptying in patients with type 1 diabetes, which could translate into effective lowering of postprandial glucose excursions .[39] However, there is no direct evidence of how lixisenatide works in patients with type 1 diabetes.

The safety profile of lixisenatide was another focus in this meta-analysis. Lixisenatide is associated with the potential risk of any AEs, and a larger proportion of patients with lixisenatide discontinued treatment due to the AE as well. Even so, there were no statistical differences in serious AEs and death between the lixisenatide and placebo groups. The incidence of gastrointestinal AEs was higher in the lixisenatide group than in the placebo group. The most common gastrointestinal AEs included gastrointestinal disorders, nausea, vomiting, and diarrhea. Most of them were mild to moderate in intensity, reduced with ongoing treatment, and resolved within 6 to 8 weeks.[21,32] In our meta-analysis, the percentage of patients with symptomatic hypoglycemia was 13.5% in the lixisenatide group and 9.4% in the placebo group ($P < .01$). However, the incidence of severe hypoglycemia was comparable between the lixisenatide and placebo ($P = .25$). In addition, lixisenatide could significantly reduce the frequency of rescue therapy ($P < .01$). Moreover, it resulted in a lower incidence of hypoglycemia and better gastrointestinal tolerability than those associated with other GLP-1 RAs such as exenatide and liraglutide.[16,30]

There are several strengths of our meta-analysis. First, all of the eligible studies were RCTs, sample size (11,947) was large. Furthermore, the studies were double-blind. Second, an interactive voice response or web-based system was used in most of these studies to ensure sufficient concealment of random allocation. Third, all of the patients were ages > 18 years and had an HbA1c level of 7 to 10%. However, 1 limitation that could not be ignored was the short-term follow-up ($\geq$ 12 weeks, $\leq$ 24 weeks). Because lixisenatide is a new drug, longer-term studies are required to determine the efficacy and safety of lixisenatide in patients with T2DM.

Compared to placebo, lixisenatide could significantly reduce the levels of HbA1c, FPG, and PPG, and higher proportion of lixisenatide-treated patients achieved the HbA1c targets of < 7.0% and < 6.5% in lixisenatide-treatment group. It increased the incidence of mild-to-moderate gastrointestinal AEs and symptomatic hypoglycemia, but it was not associated with serious AEs, death, or severe hypoglycemia. In conclusion, lixisenatide was effective and relatively well tolerated in patients with inadequately controlled T2DM.

Author contributions

Data curation: Hui-han Zhang, Zhe-yuan Wang.
Formal analysis: Zhe-yuan Wang, Gen-nian Wang.
Investigation: Xiao-dong Xu.
Methodology: Gen-nian Wang, Feng-xian Wei, Xiao-dong Xu.
Resources: Ya-wu Zhang.
Software: Man-cai Wang, Feng-xian Wei.
Visualization: Zhen-gang Wei.
Writing – original draft: Zhen-gang Wei, Man-cai Wang, Ya-wu Zhang.
Writing – review & editing: You-cheng Zhang.

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