

# Medicine

## PRISMA-Efficacy and Safety of Lixisenatide for Inadequately Controlled Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

--Manuscript Draft--

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Abstract:	<p>Objective: We aimed to systematically evaluate the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus.</p> <p>Methods: PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, and the Chinese Science Citation Database were searched up to May 2015. Randomized controlled trials estimating the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus were eligible for inclusion. Two authors independently extracted data in a prespecified Microsoft Excel spreadsheet. Review Manager 5.3 software was used to make meta-analysis. Weighted mean difference (WMD) and relative risk (RR) together with their corresponding 95% confidence intervals were estimated.</p> <p>Results: Ten multicenter randomized controlled trials involving 5,142 patients were eligible for inclusion finally. Lixisenatide could more significantly reduce the level of HbA1c (WMD=-0.38; 95% CI [-0.47, -0.28]), and had a higher proportion of patients who achieved the HbA1c targets of &lt;7.0% (RR=1.84, 95% CI [1.68, 2.02]) and &lt;6.5% (RR=3.00, 95% CI [2.49, 3.61]) compared with placebo. It was also associated with significant reduction in fasting plasma glucose and 2-hour postprandial plasma glucose versus placebo. The any adverse events, gastrointestinal adverse events and symptomatic hypoglycemia were significantly increased in lixisenatide-treatment group, but it did not increase the risks of serious adverse events, death, or severe hypoglycemia.</p> <p>Conclusions: Lixisenatide was more effective than placebo for patients with inadequately controlled type 2 diabetes mellitus, and the mild-to-moderate adverse events were tolerated in current short-term follow-up.</p>

## Response to Reviewers

1. Is the manuscript technically sound, and do the data support the conclusions?

Reviewer #1: Yes

Reviewer #2: Partly

Reviewer #3: Yes

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2. Has the statistical analysis been performed appropriately and rigorously?

Reviewer #1: Yes

Reviewer #2: No

Reviewer #3: Yes

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3. Does the manuscript adhere to standards in this field for data availability?

Reviewer #1: Yes

Reviewer #2: Yes

Reviewer #3: Yes

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4. Is the manuscript presented in an intelligible fashion and written in standard English?

Reviewer #1: Yes

Reviewer #2: No

Reviewer #3: Yes

### Response to Reviewers:

This manuscript has been respectively revised by two authors (You Cheng Zhang, Xiao Dong Xu), and disagreement was resolved by discussion. At the same time, we had consulted the professor Tian (Jin Hui Tian) of Evidence-based Medicine Center of Lanzhou University, he also gave us some valuable suggestions in the revision. Specific content as follows:

**Paper 3:** “Lixisenatide could more significantly reduce the level of HbA1c (WMD=-0.38; 95% **confidence interval** [-0.47, -0.28])” **change to** “Lixisenatide could more significantly reduce the level of HbA1c (WMD=-0.38; 95% **confidence interval [CI]** [-0.47, -0.28])”;

**Paper 7:** “**Studies were assessed independently by two authors according to the inclusion criteria above. Two authors independently extracted data in a prespecified Microsoft Excel spreadsheet.**” **change to** “**Studies were assessed and data were extracted by two independent investigators according to the inclusion criteria in a prespecified Microsoft Excel spreadsheet.**”

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5. Comments to Author (required)

**Reviewer #1:** This manuscript is well-written and the analysis is solid. I have only some minor suggestions

1. Abstract: it would be better to state the method of meta-analysis (inverse variance weighting ? random effect?) rather than the software used

## Response to Reviewers

### Response to Reviewers:

**Paper 3:** Add “and only the random effects model was used in order to give a more conservative estimate of the efficacy and safety.”

2. Introduction is too long. The second paragraph is not very necessary.

### Response to Reviewers:

**Paper 4:** Delete part of the second paragraph and reference 7 and 8. “Traditional Chinese Medicine (TCM) is a special treatment in China. It has a long history of more than 2,000 years for the treatment of diabetes mellitus (7). Unfortunately, the role of TCM and other herbal medicines in the management of type 2 diabetes is still not sufficiently established now (8).”

3. Methods: please list the initials of names of the two authors who assess and evaluate the data.

### Response to Reviewers:

**Paper 6 and 7:** Add the initials of names of the two authors (MCW, XWW; YJM, ZGW)

4. I personally prefer to move the figure for risk of bias (Figure 2) and Figure 5 to supplement and move some analysis for side effects to main tables.

**Response to Reviewers:** Keep the original state

### Reviewer #2:

1. Review was poorly written and incorrect statistical methods were applied (a fixed effects model should be applied in cases where  $I^2 < 50\%$ ).

### Response to Reviewers:

This manuscript has been respectively revised by two authors (You Cheng Zhang, Xiao Dong Xu), and only the random effects model was used in order to give a more conservative estimate than fixed effects model, Finally, a fixed effects model was used to estimate the stability of this meta-analysis.

## **Response to Reviewers**

2. Further the literature search protocol was not provided which is an important aspect for reproducibility.

### **Response to Reviewers:**

The search strategy was not limited by language and region. We performed this search using both free text and medical subject headline, search terms included lixisenatide, AVE0010, and diabetes mellitus.

3. By excluding studies of "obvious heterogeneity" appeared selective and is inappropriate. In the forest plots it is not clear if the data is independent when taken from multiple studies.

### **Response to Reviewers:**

**Pager 7:** The obvious heterogeneity could be found according to the forest plots.

Why were studies with a follow-up <12 weeks excluded? This was not explained and again appears selective and unsound. Overall a technically poor study.

### **Response to Reviewers:**

**Pager 7:** RCTs with short-term follow-up (<12 weeks) were excluded for decreasing the heterogeneity of characteristics.

**Reviewer #3:** No further comments.

## **Editorial Formatting Comments**

1. Title page: All author names, degrees, and affiliations are listed in the title page. (page 1)
2. Title: PRISMA-Efficacy and Safety of Lixisenatide for Inadequately Controlled Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials (page 1).
3. Abstract: bases on the PRISMA guidelines (including Objective, Methods, Results, Conclusions). (page 3)
4. List of abbreviations: (page 2)
5. Ethical approval: was not necessary for this meta-analysis.

## **Response to Reviewers**

6. Conflicts of Interest and Source of Funding: The work was supported by Gansu province Science and Technology Support Program (1204FKCA138). No potential conflict of interest relevant to this article was reported. (page 1)
7. Acknowledgments: Thanks for the support of Gansu Province Department of Science and Technology. The sponsors had no involvement in the study design, data collection and analysis, the writing or the decision to submit the manuscript for publication.( page 14)
8. License to Publish: We have completed and submitted a copy of the Open Access-License to Publish (LTP) as a submission item.

# **PRISMA-Efficacy and Safety of Lixisenatide for Inadequately Controlled Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**

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**Conflicts of Interest and Source of Funding:** The work was supported by Gansu province Science and Technology Support Program (1204FKCA138). No potential conflict of interest relevant to this article was reported.

**List of abbreviations:**

T2DM=type 2 diabetes mellitus

IDF=International Diabetes Federation

TCM=Traditional Chinese Medicine

GLP-1=glucagon-like peptide-1

RAs=receptor agonists

DPP-4=dipeptidyl peptidase-4

CSCD=Chinese Science Citation Database

OAD=oral antidiabetic agents

FPG=fasting plasma glucose

RevMan=Review Manager

PPG=postprandial plasma glucose

AE=adverse events

RCT= randomized controlled trial

WMD=Weighted mean difference

RR=relative risk

CI= confidence intervals

## 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, and the Chinese Science Citation Database were searched up to May 2015. Randomized controlled trials estimating the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus were eligible for inclusion. Two authors independently extracted data in a prespecified Microsoft Excel spreadsheet. Review Manager 5.3 software was used to make meta-analysis. Weighted mean difference (WMD) and relative risk (RR) together with their corresponding 95% confidence intervals were estimated, and only the random effects model was used in order to give a more conservative estimate of the efficacy and safety.

**Results:** Ten multicenter randomized controlled trials involving 5,142 patients were eligible for inclusion finally. Lixisenatide could more significantly reduce the level of HbA1c (WMD=-0.38; 95% confidence interval [CI] [-0.47, -0.28]), and had a higher proportion of patients who achieved the HbA1c targets of <7.0% (RR=1.84, 95% CI [1.68, 2.02]) and <6.5% (RR=3.00, 95% CI [2.49, 3.61]) compared with placebo. It was also associated with significant reduction in fasting plasma glucose and 2-hour postprandial plasma glucose versus placebo. The any adverse events, gastrointestinal adverse events and symptomatic hypoglycemia were significantly increased in lixisenatide-treatment group, but it did not increase the risks of serious adverse events, death, or severe hypoglycemia.

**Conclusions:** Lixisenatide was more effective than placebo for patients with inadequately controlled type 2 diabetes mellitus, and the mild-to-moderate adverse events were tolerated in current short-term follow-up.

**Keywords:** Lixisenatide; diabetes mellitus; Meta-analysis; Review



## Introduction

Diabetes mellitus is one of the leading causes of death and disability all over the world (1). Today, there are 382 million people living with diabetes, and a further 316 million with impaired glucose tolerance are at high risk from it (2). According to the International Diabetes Federation (IDF), 80% of people with diabetes live in low- and middle-income countries, of which China is on the verge of being overwhelmed by diabetes. It has the highest number of people with diabetes in the world, with a prevalence of 8.3% (2).

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

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, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown the promise as an important therapeutic option in treatment of T2DM (5, 8), which are due to the combination of both the promotion of insulin secretion and inhibition of glucagon secretion (9, 10). Studies of in vitro and animal models suggested that GLP-1 RAs have the potential to preserve pancreatic islet  $\beta$ -cells by enhancing 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 are also noticed in some studies (11, 12, 13).

Native GLP-1 is not suitable for treatment of T2DM. It can be rapidly resolved by dipeptidyl peptidase-4 (DPP-4), its half-life is less than 2 minutes (5, 13). Exenatide and liraglutide are two representatives of the DPP-4-resistant GLP-1 receptor agonists (14). Their advantages included a low propensity to cause hypoglycaemia, the ability to promote weight loss and provide extra cardiovascular benefits (6, 15). Lixisenatide (AVE0010) is the third synthetic GLP-1 receptor agonists, it is a 44 amino acid exendin-4-like GLP-1 receptor agonist, which is modified at C-terminally with six Lys residues and one Pro deleted (5, 7, 16). Recent clinical studies have shown that lixisenatide was highly possibly effective in patients with T2DM. However, various GLP-1 receptor agonists may have substantial differences in their duration of action and clinical profile. What's more, the uncertainty of some adverse events was presented during those studies. Thus, the objective of the meta-analysis is to systematically evaluate the efficacy and safety of lixisenatide in patients with T2DM.

## Methods

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

### Search Strategy

MEDLINE, EMBASE, Cochrane library, ClinicalTrials.gov, and the Chinese Science Citation Database (CSCD) were searched up to May 2015. The search strategy was not limited by language and region. We performed this search using both free text and medical subject headline, search terms included lixisenatide, AVE0010, and diabetes mellitus.

### Inclusion Criteria

Eligibility criteria included: 1) Study design: randomized controlled trials (RCTs), single-blind or double-blind, without language limitation; 2) Population: patients aged >18 years, with inadequately controlled type 2 diabetes, with a glycated hemoglobin (HbA1c) level of 7-10%. 3) Intervention: lixisenatide or placebo was given subcutaneously, with or without oral antidiabetic agents (OADs)/insulin, the dose of lixisenatide was not limited. 4) Outcomes: reported at least one of the HbA1c, HbA1c < 7.0%, HbA1c < 6.5%, fasting plasma glucose (FPG), body weight, rescue therapy, and adverse events. Studies were excluded if the raw data could not be extracted.

### Study Selection and Data Extraction

Studies were assessed and data were extracted by two independent investigators (MCW, XWW) according to the inclusion criteria in a prespecified Microsoft Excel spreadsheet. Disagreement was resolved by discussion with a third author. The follow data were collected: 1) Study characteristics (e.g. author, year of publication, sample size, age, sex ratio, duration of diabetes, baseline HbA1c). 2) Intervention measures (e.g. does of lixisenatide, once-daily or twice-daily, one-step or two-step, morning or

evening). 3) Efficacy: (e.g. HbA1c, HbA1c < 7.0%, HbA1c < 6.5%, fasting plasma glucose (FPG), body weight, rescue therapy). 4) Safety: (e.g. serious adverse events, death, gastrointestinal disorders, symptomatic hypoglycemia, severe hypoglycemia). 5) Risk of bias: (e.g. random sequence generation, allocation concealment, blinding).

### **Risk of Bias Assessment**

Two authors (YJM, ZGW) independently evaluated the methodological quality of included studies according to the Cochrane Risk of Bias tool for RCTs (17), and differences were also resolved by discussion with a third author.

### **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 (CI) were estimated. We analyzed all of the outcomes with a random effects model in order to give a more conservative estimate of the efficacy and safety. The statistical heterogeneity was estimated using the  $I^2$  statistic with a cutoff of 50%, and the  $\chi^2$  test with a P value < 0.10. If the  $I^2 > 50\%$  and  $P < 0.10$ , we would remove the studies with obvious heterogeneity and re-analyze the data. Finally, a fixed effects model was used to estimate the stability of this meta-analysis, and publication bias was assessed by the funnel plot.

## **Results**

### **Study Characteristics**

Ten eligible multicenter RCTs (5, 6, 14, 18-24) were included finally, with a total sample size of 5,142. The flow chart of trial selection was shown in Figure 1. Three RCTs (25-27) were finally excluded because of a short-term follow-up (<12 weeks), one open-label RCT (16) was also removed in this meta-analysis. Table 1 represented the characteristics of included studies. The baseline HbA1c was 7-10% in all studies, duration of follow-up respectively were 24 weeks (6, 18-24), 13 weeks (5), and 12 weeks (14). Lixisenatide was subcutaneously given 20µg once daily in most of the

included studies (6, 14, 18-24), except for Ratner et al. (5). Metformin (5, 18-24), sulfonylurea (6, 18-21), thiazolidinedione (24), pioglitazone (22), or insulin (6, 23, 24) were used in different studies for the glycemic control.

### **Risk of Bias**

Overall, the risk of bias was low (Figure 2), risk of bias of each outcome was presented in the forest plots below. Patients were randomly divided into two groups, and allocation concealment was performed by using a centralized interactive voice response system in 7 studies (5, 6, 14, 22-24). All of the eligible studies were double-blind trials (5, 6, 14, 18-24). No incomplete outcome data and selective reporting existed among them.

### **Efficacy of lixisenatide for T2DM**

#### **HbA1c level**

Five RCTs (18, 19, 22-24) reported the HbA1c level at the end of follow-up. Great heterogeneity existed among these studies ( $I^2=71\%$ ,  $p=0.004$ ). Meta-analysis shown that there was statistically significant difference between lixisenatide and placebo groups (WMD=-0.44; 95% CI [-0.59, -0.29]) (Table S1). Rosenstock et al. (18) had an obvious heterogeneity with others according to the forest plot. After removing it, we got a consistent result compared with that before (WMD=-0.38; 95% CI [-0.47, -0.28]) (Figure 3).

#### **HbA1c< 7.0%**

All of the included RCTs (5, 6, 14, 18-24) reported the patients number of HbA1c< 7.0%. Moderate heterogeneity existed among these studies ( $I^2=56\%$ ,  $p=0.001$ ). There was statistically significant difference compared lixisenatide with placebo for patients with T2DM (RR=1.90, 95% CI [1.70, 2.12]) (Table S1). After removing the obviously heterogeneous study Seino et al. (6), the result was similar with that before (RR=1.84, 95% CI [1.68, 2.02]) (Figure 4).

#### **HbA1c< 6.5%**

All of the included RCTs (5, 6, 14, 18-24) also reported the patients number of HbA1c < 6.5%. No significant heterogeneity existed among them ( $I^2=43\%$ ,  $p=0.02$ ). Meta-analysis shown that there was statistically significant difference compared lixisenatide with placebo (RR=3.00, 95% CI [2.49, 3.61]) (Figure 5).

### **Fasting plasma glucose**

Six RCTs (18-20, 22-24) reported the level of fasting plasma glucose (FPG), the raw data of one study could not be obtained (20). No significant heterogeneity existed among these studies ( $I^2=45\%$ ,  $p=0.10$ ). It was shown that there was statistically significant difference between lixisenatide and placebo groups (WMD=-0.47, 95% CI [-0.71, -0.23]) (Table S1).

### **Body weight**

Body weight was reported in four (18, 19, 23, 24) RCTs. No heterogeneity existed among these studies ( $I^2=0\%$ ,  $p=0.53$ ). There was no statistical difference for body weight when compared lixisenatide with placebo groups (WMD=-1.04, 95% CI [-3.17, 0.37]) (Table S1).

### **Rescue therapy**

Seven RCTs (6, 14, 18, 19, 21-23) reported the proportion of rescue therapy during follow-up. No heterogeneity existed among these studies ( $I^2=0\%$ ,  $p=0.63$ ). Our meta-analysis shown that there was statistically significant difference between lixisenatide and placebo groups (RR=0.40, 95% CI [0.31, 0.53]) (Table S1).

### **Others**

Three RCTs (18, 23, 24) reported the glucose excursion and 2-hour postprandial plasma glucose (PPG) after a standardized breakfast. Meta-analysis shown that there was statistically significant differences between lixisenatide and placebo groups (WMD=-3.31, 95% CI [-3.90, -2.72]; WMD=-3.41, 95% CI [-4.00, -2.82]).

### **Safety of lixisenatide for T2DM**

#### **Any adverse events and discontinuation**

All of the included RCTs (5, 6, 14, 18-24) reported the outcomes of any adverse events (AE) and discontinuation due to AE. No significant heterogeneity existed among these studies ( $I^2=27\%$ ,  $p=0.13$ ;  $I^2=0\%$ ,  $p=0.78$ ). It was shown that lixisenatide may increase the risk of any adverse events and the rate of discontinuation due to AE, there were statistically significant differences versus placebo (RR=1.13, 95% CI [1.08, 1.18]; RR=2.42, 95% CI [1.87, 3.14]) (Table S1).

### **Serious adverse events and death**

Ten RCTs (5, 6, 14, 18-24) reported the serious adverse events, death occurred in five included studies (6, 18, 19, 23, 24). Both of them had no heterogeneity ( $I^2=0\%$ ,  $p=0.69$ ;  $I^2=0\%$ ,  $p=0.82$ ). Lixisenatide was not associated with serious adverse events or death for patients with T2DM, no statistically significant difference existed when compared with placebo (RR=1.00, 95% CI [0.75, 1.34]; RR=0.73, 95% CI [0.18, 2.98]) (Table S1).

### **Gastrointestinal adverse events**

Gastrointestinal adverse events included gastrointestinal disorders, nausea, vomiting, and diarrhea. They were respectively reported in nine (6, 14, 18-24), ten (5, 6, 14, 18-24), ten (5, 6, 14, 18-24), and nine (5, 6, 18-24) RCTs. Meta-analysis shown that, compared with placebo in patients with T2DM, lixisenatide could increase the risks of gastrointestinal disorders ( $I^2=69\%$ ,  $p=0.0002$ ; RR=2.06, 95% CI [1.72, 2.47]), nausea ( $I^2=36\%$ ,  $p=0.06$ ; RR=4.17, 95% CI [3.36, 5.17]), vomiting ( $I^2=18\%$ ,  $p=0.23$ ; RR=5.23, 95% CI [3.59, 7.62]), and diarrhea ( $I^2=11\%$ ,  $p=0.32$ ; RR=1.27, 95% CI [1.03, 1.56]), there were statistically significant differences in these events (Table S1).

### **Hypoglycemia**

Ten RCTs (5, 6, 14, 18-24) reported the patients of symptomatic hypoglycemia, of which severe hypoglycemia occurred in three studies (18, 23, 24). No significant heterogeneity existed among them ( $I^2=0\%$ ,  $p=0.77$ ;  $I^2=0\%$ ,  $p=0.88$ ). Meta-analysis shown that, compared with placebo in patients with T2DM, lixisenatide was associated with the risk of symptomatic hypoglycemia (RR=1.59, 95% CI [1.35,

1.89]), but there was no statistically significant difference in severe hypoglycemia (RR=2.83, 95% CI [0.47, 16.90]) (Table S1).

### **Skin reaction**

Injection-site reactions and allergic reaction were respectively reported in nine (6, 14, 18-24) and five (6, 14, 22-24) RCTs. Our meta-analysis shown that lixisenatide could increase the risk of injection-site reactions ( $I^2=0\%$ ,  $p=0.74$ ; RR=2.05, 95% CI [1.43, 2.95]), but no statistical difference in allergic reaction between lixisenatide and placebo groups ( $I^2=0\%$ ,  $p=0.97$ ; RR=2.11, 95% CI [0.68, 6.54]) (Table S1).

### **Publication Bias**

Publication bias was estimated by funnel plots of HbA1c < 7.0% and HbA1c < 6.5%. They were relatively symmetrical, suggesting that there is no publication bias in this meta-analysis (Figure S1-2).

### **Sensitivity analysis**

Sensitivity analysis was performed by using a fixed effects model to estimate the stability of this meta-analysis. All of the results were consistent with these above (Table S1).

### **Discussion**

Incretin based therapies, such as the glucagon-like peptide-1 (GLP-1) receptor agonists, represent a major advance in T2DM treatment (27, 28). Several GLP-1 receptor agonists are available and are increasingly used as monotherapy or as “add-on” to OADs/insulin (16, 29). As a novel agent in this class, lixisenatide is one of the centers of attention for T2DM now. Our meta-analysis shown that, compared with placebo group, lixisenatide could significantly reduce the level of HbA1c, and a significantly higher proportion of patients achieved HbA1c targets of <7.0% and <6.5%. Meanwhile, lixisenatide was associated with a significant reduction in fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (PPG) after a



standardized breakfast versus placebo. All these conclusions above are consistent with those current studies (6, 14, 18-24). Horowitz et al. (28) hold the view that GLP-1 participates in the regulation of appetite and energy intake. However, compared lixisenatide with placebo in this meta-analysis, there was no statistically significant difference in body weight at the end of follow-up. It is inconsistent with the dominant idea in some studies (18, 19, 23, 24, 28, 30).

The mechanisms of lixisenatide glucose-lowering effect have been investigated in several studies (28). It was shown that lixisenatide could restore the first and second-phase insulin responses and accelerate glucose disposition (28, 31). At the same time, lixisenatide could reduce the postprandial glycemic excursions by producing sustained slowing of gastric emptying, which is of fundamental significance for patients with T2DM (32). In addition, it is thought that GLP-1 could reduce appetite and energy intake (33), although no statistically significant difference was found in body weight in this meta-analysis. The most noteworthy is that various GLP-1 receptor agonists may exhibit different effects on pre and postprandial glucose. Buse et al. (34) performed a direct comparison between liraglutide and exenatide, two different kinds of GLP-1 receptor agonists, in patients with inadequately controlled T2DM. Results shown that liraglutide more significantly reduced the FPG, while exenatide had a greater effect on PPG excursions. Similar results were demonstrated between lixisenatide and liraglutide in diabetics (35).

The safety profile of lixisenatide is another focus in this meta-analysis. The adverse events were experienced by 69% (2289/3302) of participants administered lixisenatide compared with 62% (1086/1748) receiving placebo. Lixisenatide was associated with the potential risk of any adverse events ( $p < 0.01$ ), and more large proportion of patients with lixisenatide discontinued treatment due to the adverse events as well ( $p < 0.01$ ). Even so, there were no statistical differences in both serious adverse events and death compared lixisenatide with placebo ( $p > 0.05$ , both).

The incidence of gastrointestinal adverse events was higher in lixisenatide group than placebo group. The most common gastrointestinal adverse events included gastrointestinal disorders, nausea, vomiting, and diarrhea. Most of them were mild to moderate in intensity, dissipated with ongoing use and resolved within 6-8 weeks (21, 28, 34). In our meta-analysis, the percentage of symptomatic hypoglycemia was 10.9% (360/3302) for lixisenatide and 8.60% (151/1748) for placebo ( $p<0.01$ ). However, the incidence of severe hypoglycemia was comparable between lixisenatide and placebo ( $p=0.25$ ). In addition, lixisenatide could significantly reduce the frequency of rescue therapy ( $p<0.01$ ). What's more, lixisenatide provided lower incidence of hypoglycemia and better gastrointestinal tolerability compared with other GLP-1 receptor agonists, such as exenatide and liraglutide (16, 35).

There were several strengths in our meta-analysis. First, all of the eligible studies were randomized controlled trials, with a larger sample size of 5,142. Meanwhile, double-blind was performed in both patients and investigators. Second, an interactive voice response or web-based system was used in most of these studies to ensure the sufficiently concealment of random allocation. Third, all of the patients aged  $>18$  years, with HbA1c 7-10%. However, one limitation that could not be ignored was the short-term follow up ( $\leq 24$  weeks). As a new drug, longer-term studies are required to estimate the efficacy and safety of lixisenatide in patients with T2DM.

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

**Acknowledgements:**

Thanks for the support of Gansu province Science and Technology Support Program.

The sponsors had no involvement in the study design, data collection and analysis, the writing or the decision to submit the manuscript for publication.

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**Figures legends:**

Figure 1. The flow chart of trial selection

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

Figure 3. The meta-analysis of HbA1c level at the end of follow-up

Figure 4. The meta-analysis of HbA1c < 7%

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

Figure S1. Funnel plot of HbA1c <7.0%

Figure S2. Funnel plot of HbA1c < 6.5%

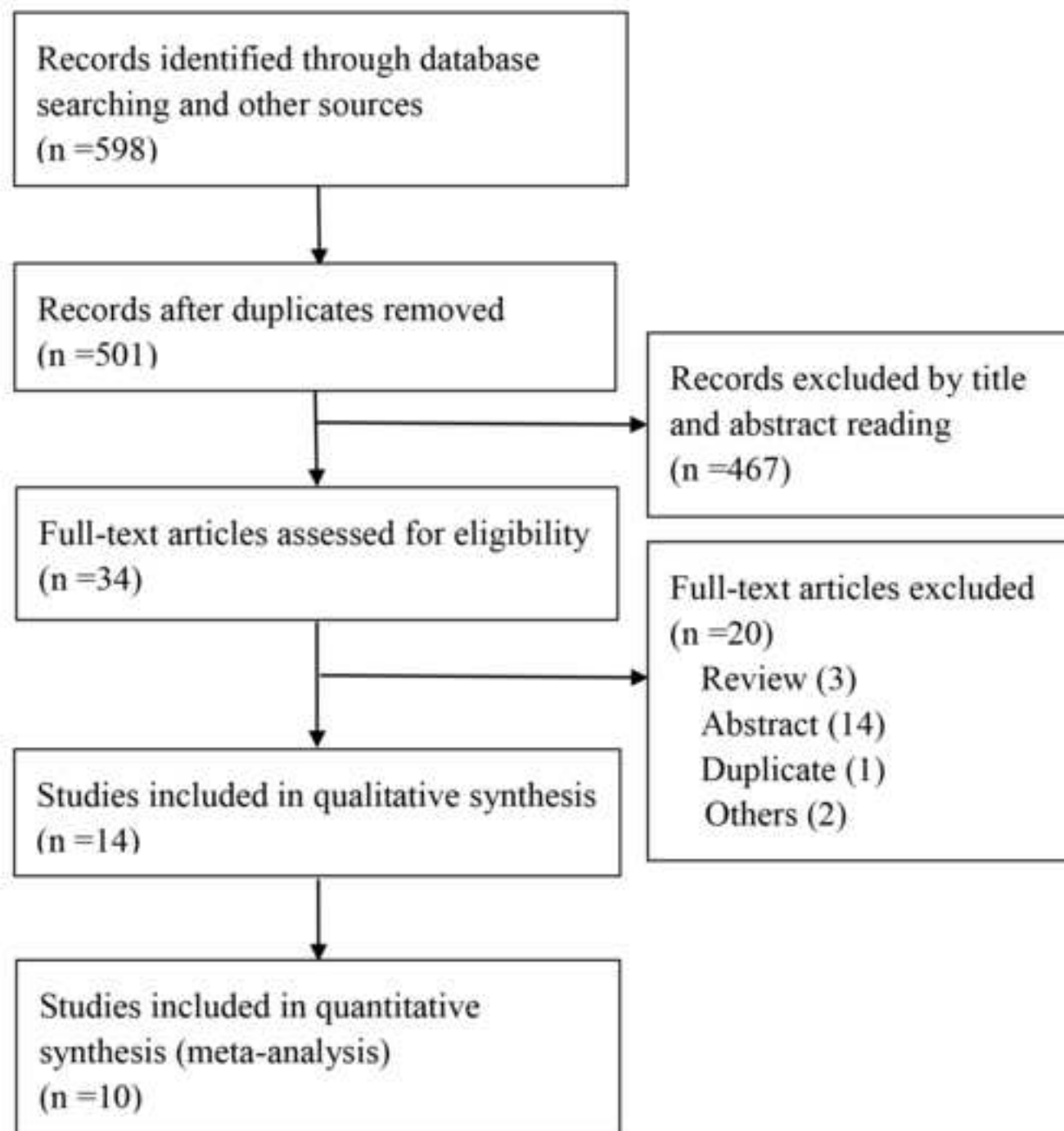


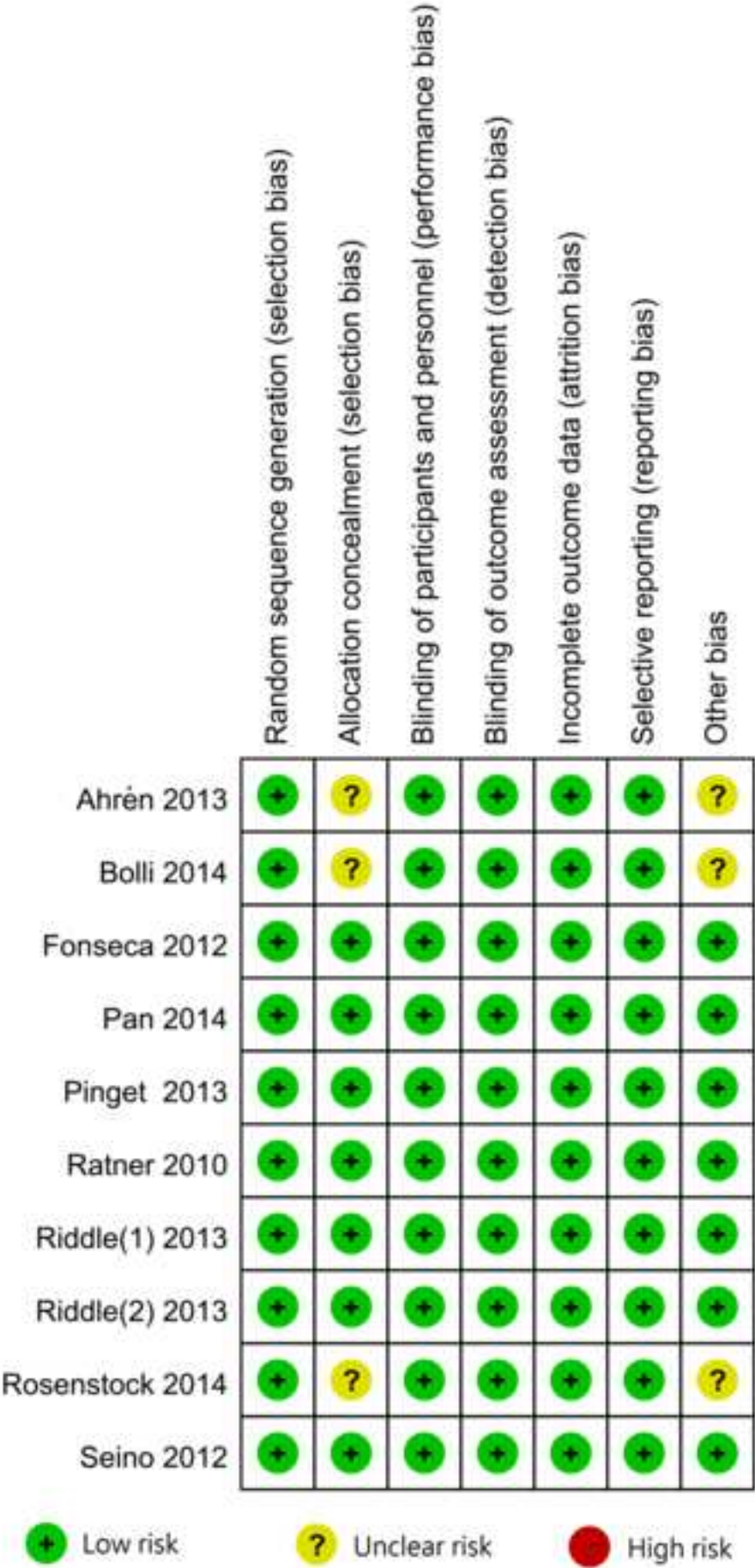
Table 1. The characteristics of included studies in this meta-analysis

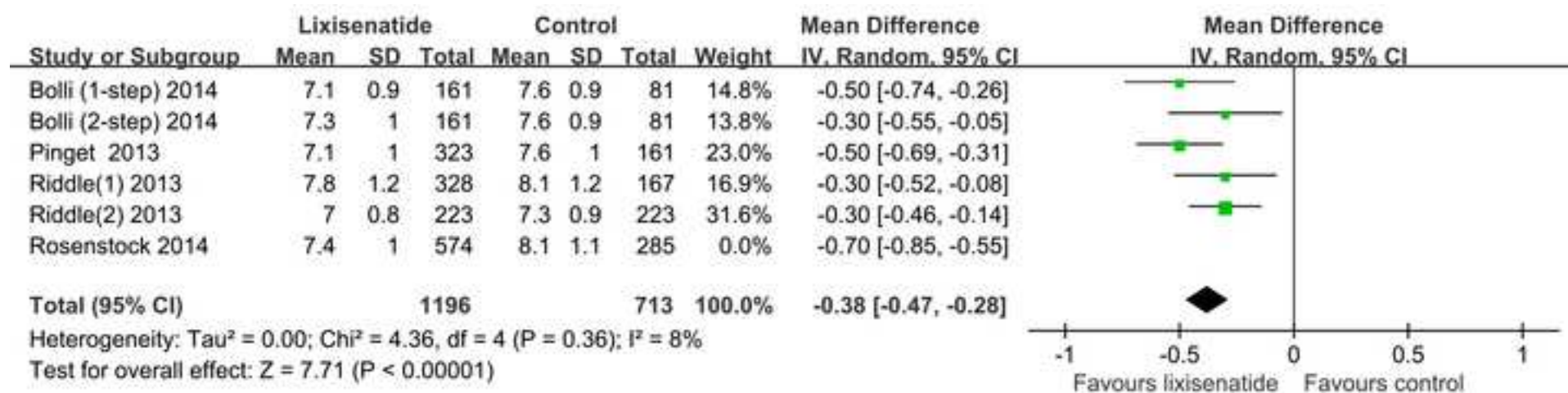
Num.	Author, et al.	Sample	Sex (Male, %)		Age		BMI		HbA1c (%)		Duration (years)		follow up
			LIXI	Placebo	LIXI	Placebo	LIXI	Placebo	LIXI	Placebo	LIXI	Placebo	
1	Rosenstock	574/285	284(49.5)	150(52.6)	57.0±9.8	57.8±10.1	30.1±6.6	30.4±6.6	8.3±0.9	8.2±0.8	9.1±6.0	9.8±6.2	24w
2	Bolli (1-step)	161/81	44(27.3)	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 (5µg 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 (10µg 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 (20µg 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 (30µg 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 (5µg 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 (10µg 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 (20µg 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 (30µg 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	13w

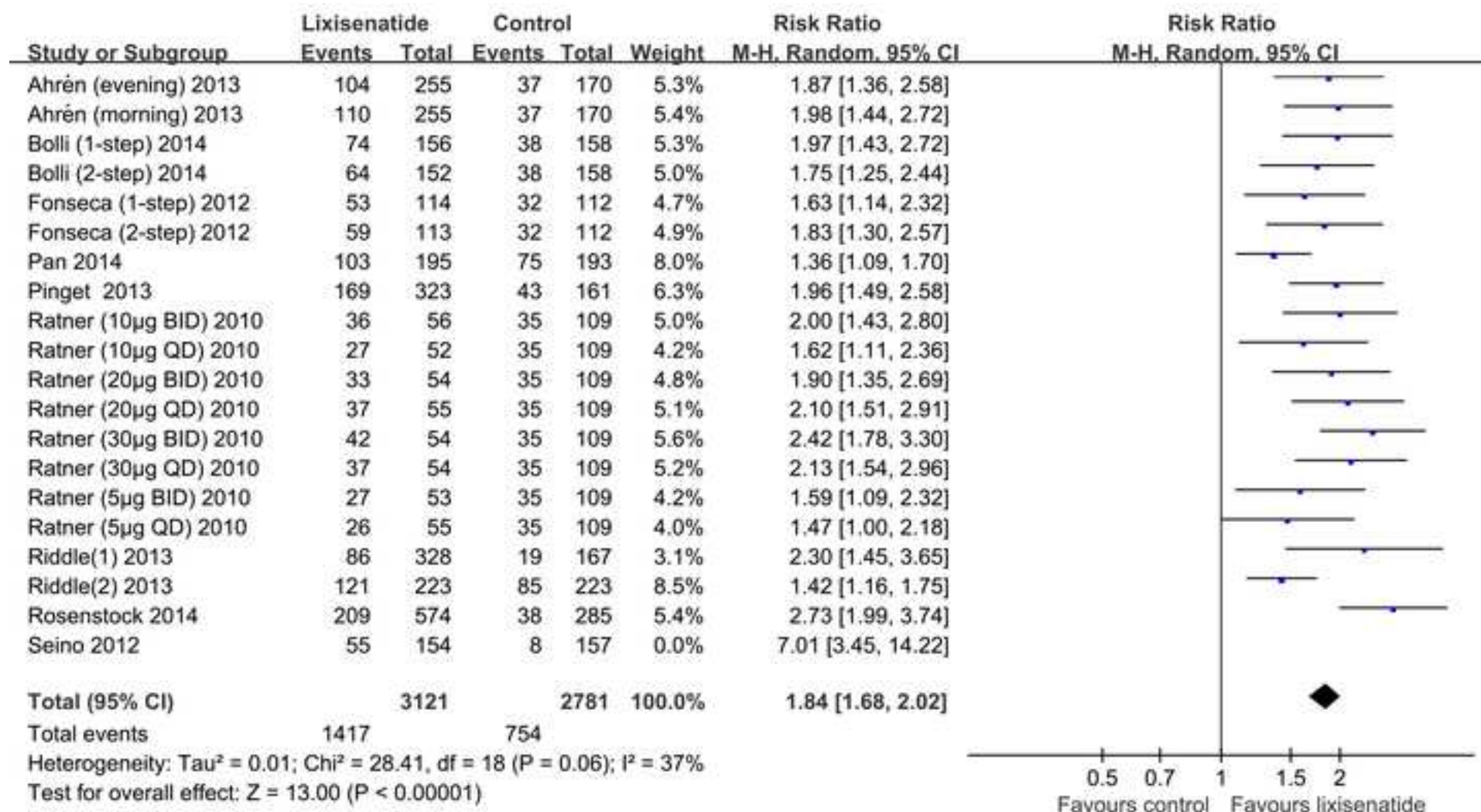
\*duration of diabetes mellitus was not all ≥1 year since diagnosis.

LIXI, Lixisenatide; BMI, body mass index.

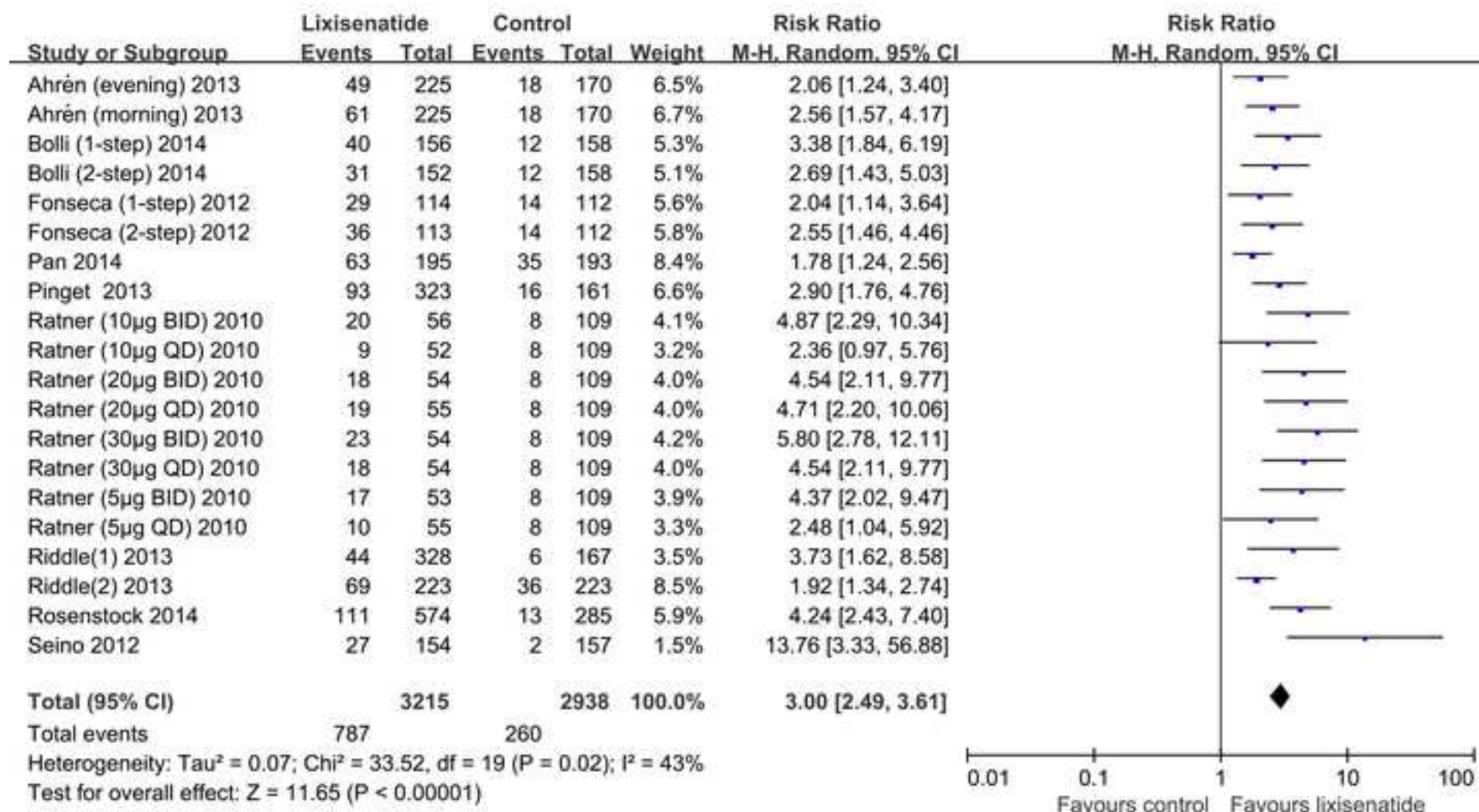














# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Efficacy and Safety of Lixisenatide for Inadequately Controlled Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	1
<b>ABSTRACT</b>			
Structured summary	2	<p><b>Objective:</b> We aimed to systematically evaluate the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus. <b>Methods:</b> PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, and the Chinese Science Citation Database were searched up to May 2015. Randomized controlled trials estimating the efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus were eligible for inclusion. Two authors independently extracted data in a prespecified Microsoft Excel spreadsheet. Review Manager 5.3 software was used to make meta-analysis. Weighted mean difference (WMD) and relative risk (RR) together with their corresponding 95% confidence intervals were estimated. <b>Results:</b> Ten multicenter randomized controlled trials involving 5,142 patients were eligible for inclusion finally. Lixisenatide could more significantly reduce the level of HbA1c (WMD=-0.38; 95% CI [-0.47, -0.28]), and had a higher proportion of patients who achieved the HbA1c targets of &lt;7% (RR=1.84, 95% CI [1.68, 2.02]) and &lt;6.5% (RR=3.00, 95% CI [2.49, 3.61]) compared with placebo. It was also associated with significant reduction in fasting plasma glucose and 2-hour postprandial plasma glucose versus placebo. The any adverse events, gastrointestinal adverse events and symptomatic hypoglycemia were significantly increased in lixisenatide-treatment group, but it did not increase the risks of serious adverse events, death, or severe hypoglycemia. <b>Conclusions:</b> Lixisenatide was more effective than placebo for patients with inadequately controlled type 2 diabetes mellitus, and the mild-to-moderate adverse events were tolerated in current short-term follow-up.</p>	3
<b>INTRODUCTION</b>			
Rationale	3	<p>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. In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown the promise as an important therapeutic option in treatment of T2DM, which are due to the combination of both the promotion of insulin secretion and inhibition of glucagon secretion. Studies of in vitro and animal models suggested that GLP-1 RAs have the potential to preserve pancreatic islet <math>\beta</math>-cells by enhancing proliferation and</p>	4-5



## PRISMA 2009 Checklist

		<p>inhibiting apoptosis. In addition, they can reduce the energy intake and therefore may result in weight loss. The benefits of cardioprotection and neuroprotection are also noticed in some studies.</p> <p>Native GLP-1 is not suitable for treatment of T2DM. It can be rapidly resolved by dipeptidyl peptidase-4 (DPP-4), its half-life is less than 2 minutes. Exenatide and liraglutide are two representatives of the DPP-4-resistant GLP-1 receptor agonists. Their advantages included a low propensity to cause hypoglycaemia, the ability to promote weight loss and provide extra cardiovascular benefits. Lixisenatide (AVE0010) is the third synthetic GLP-1 receptor agonists, it is a 44 amino acid exendin-4-like GLP-1 receptor agonist, which is modified at C-terminally with six Lys residues and one Pro deleted. Recent clinical studies have shown that lixisenatide was highly possibly effective in patients with T2DM. However, various GLP-1 receptor agonists may have substantial differences in their duration of action and clinical profile.</p>	
Objectives	4	<p>1) Study design: randomized controlled trials (RCTs), single-blind or double-blind, without language limitation; 2) Population: patients aged &gt;18 years, with inadequately controlled type 2 diabetes, with a glycated hemoglobin (HbA1c) level of 7-10%. 3) Intervention: lixisenatide or placebo was given subcutaneously, with or without oral antidiabetic agents (OADs)/insulin, the dose of lixisenatide was not limited. 4) Outcomes: reported at least one of the HbA1c, HbA1c &lt; 7.0%, HbA1c &lt; 6.5%, fasting plasma glucose (FPG), body weight, rescue therapy, and adverse events.</p>	6
<b>METHODS</b>			
Protocol and registration	5	No	
Eligibility criteria	6	<p>1) Study design: randomized controlled trials (RCTs), single-blind or double-blind, without language limitation; 2) Population: patients aged &gt;18 years, with inadequately controlled type 2 diabetes, with a glycated hemoglobin (HbA1c) level of 7-10%. 3) Intervention: lixisenatide or placebo was given subcutaneously, with or without oral antidiabetic agents (OADs)/insulin, the dose of lixisenatide was not limited. 4) Outcomes: reported at least one of the HbA1c, HbA1c &lt; 7.0%, HbA1c &lt; 6.5%, fasting plasma glucose (FPG), body weight, rescue therapy, and adverse events.</p>	6
Information sources	7	PubMed, EMBASE, the Cochrane Library, etc.	6





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Search	8	MEDLINE, EMBASE, Cochrane library, ClinicalTrials.gov, and the Chinese Science Citation Database (CSCD) were searched up to May 2015. The search strategy was not limited by language and region. We performed this search using both free text and medical subject headline, search terms included lixisenatide, AVE0010, and diabetes mellitus.	6
Study selection	9	Studies were assessed independently by two investigators, disagreement was resolved by discussion with a third reviewer.	6
Data collection process	10	Two authors independently extracted data in a prespecified Microsoft Excel spreadsheet. Disagreement was resolved by discussion with a third author.	6
Data items	11	The follow data were collected: 1) Study characteristics (e.g. author, year of publication, sample size, age, sex ratio, duration of diabetes, baseline HbA1c). 2) Intervention measures (e.g. does of lixisenatide, once-daily or twice-daily, one-step or two-step, morning or evening). 3) Efficacy: (e.g. HbA1c, HbA1c< 7.0%, HbA1c< 6.5%, fasting plasma glucose (FPG), body weight, rescue therapy). 4) Safety: (e.g. serious adverse events, death, gastrointestinal disorders, symptomatic hypoglycemia, severe hypoglycemia). 5) Risk of bias: (e.g. random sequence generation, allocation concealment, blinding).	6-7
Risk of bias in individual studies	12	Two authors independently evaluated the methodological quality of included studies according to the Cochrane Risk of Bias tool for RCTs , and differences were also resolved by discussion with a third author.	7
Summary measures	13	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 (CI) were estimated.	7
Synthesis of results	14	We analyzed all of the outcomes with a random effects model in order to give a more conservative estimate of the efficacy and safety. The statistical heterogeneity was estimated using the I <sup>2</sup> statistic with a cutoff of 50%, and the $\chi^2$ test with a P value <0.10. If the I <sup>2</sup> >50% and P <0.10, we would remove the studies with obvious heterogeneity and re-analysis the data.	7



## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Overall, the risk of bias was low (Figure 2), risk of bias of each outcome was presented in the forest plots below. Patients were randomly divided into two groups, and allocation concealment was performed by using a centralized interactive voice response system in 7 studies. All of the eligible studies were double-blind trials. No incomplete outcome data and selective reporting existed among them.	8
Additional analyses	16	A fixed effects model was used to estimate the stability of this meta-analysis, and publication bias was assessed by the funnel plot.	7
<b>RESULTS</b>			
Study selection	17	Ten eligible multicenter RCTs (5, 6, 16, 20-26) were included finally, with a total sample size of 5,142.	7
Study characteristics	18	Three RCTs were finally excluded because of a short-term follow-up (<12 weeks), one open-label RCT was also removed in this meta-analysis. Table 1 represented the characteristics of included studies. The baseline HbA1c was 7-10% in all studies, duration of follow-up respectively were 24 weeks, 13 weeks, and 12 weeks. Lixisenatide was subcutaneously given 20µg once daily in most of the included studies, except for Ratner et al. Metformin, sulfonylurea, thiazolidinedione, pioglitazone, or insulin were used in different studies for the glycemic control.	7-8
Risk of bias within studies	19	Overall, the risk of bias was low, risk of bias of each outcome was presented in the forest plots below. Patients were randomly divided into two groups, and allocation concealment was performed by using a centralized interactive voice response system in 7 studies. All of the eligible studies were double-blind trials. No incomplete outcome data and selective reporting existed among them. Figure 2.	8
Results of individual studies	20	Figure 3, 4, Table S1.	8-11
Synthesis of results	21	Figure 3, 4, Table S1.	8-11
Risk of bias across studies	22	Figure 2.	7
Additional analysis	23	Publication bias was estimated by funnel plots of HbA1c< 7.0% and HbA1c< 6.5%. They were relatively symmetrical,	11



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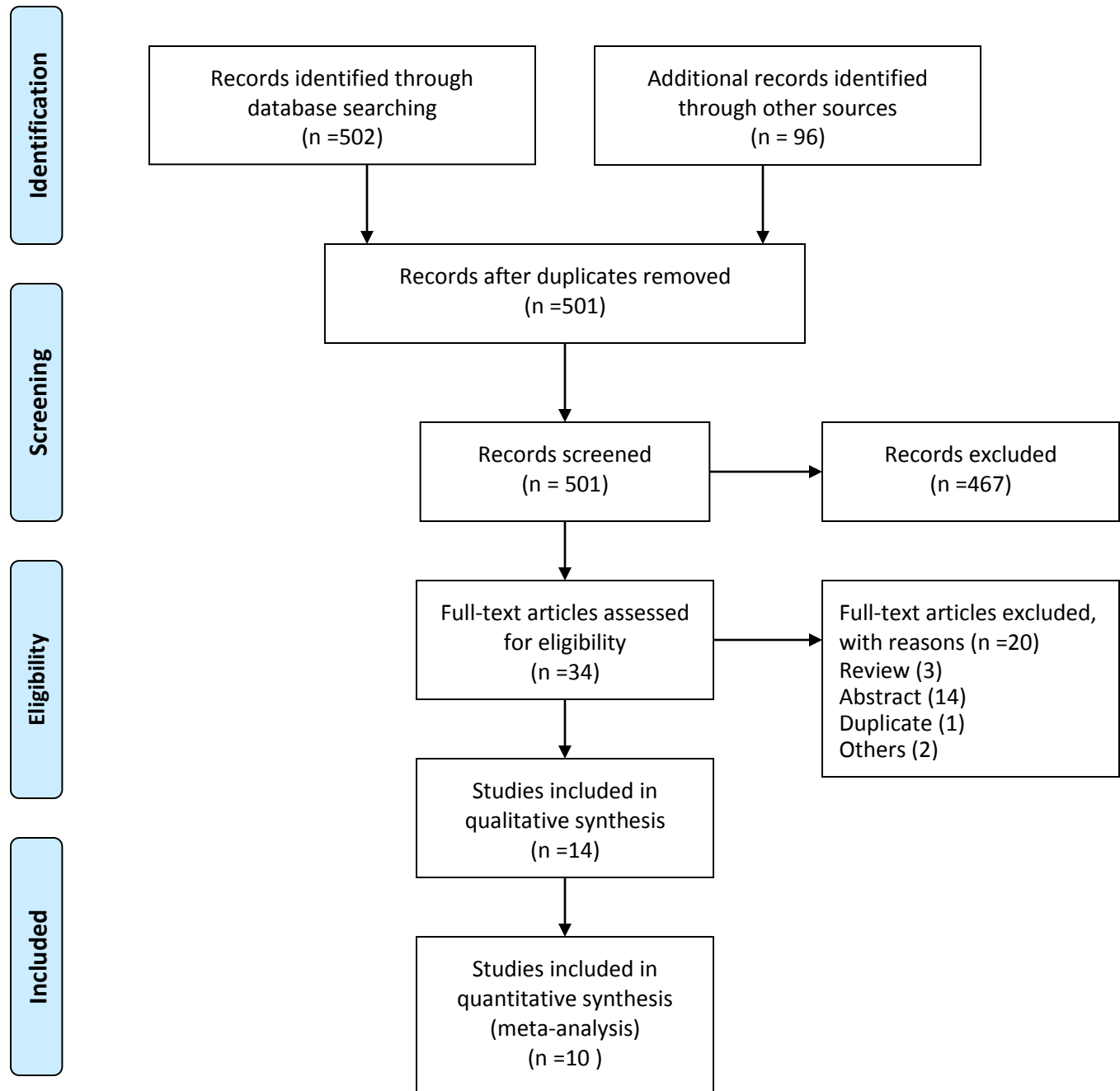
		suggesting that there is no publication bias in this meta-analysis (Figure S1-2). Sensitivity analysis was performed by using a fixed effects model to estimate the stability of this meta-analysis. All of the results were consistent with these above (Table S1).	
<b>DISCUSSION</b>			
Summary of evidence	24	Compared with placebo, lixisenatide could significantly reduce the levels of HbA1c, FPG and PPG, and higher proportion of patients achieved the HbA1c targets of <7.0% and <6.5% in lixisenatide-treatment group. It increased the incidence of mild-to-moderate gastrointestinal adverse events and symptomatic hypoglycemia, but it was not associated with serious adverse events, death, or severe hypoglycemia.	13
Limitations	25	One limitation that could not be ignored was the short-term follow up ( $\leq 24$ weeks). As a new drug, longer-term studies are required to estimate the efficacy and safety of lixisenatide in patients with T2DM.	13
Conclusions	26	Lixisenatide was effective and relatively tolerated in patients with inadequately controlled T2DM.	13
<b>FUNDING</b>			
Funding	27	The work was supported by Gansu province Science and Technology Support Program (1204FKCA138).	1,14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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## PRISMA 2009 Flow Diagram



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Table S1. Outcomes of the meta analysis and sensitivity analysis.docx





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