Lixisenatide for Type 2 Diabetes Mellitus Patients Inadequately Controlled on Oral Antidiabetic Drugs: A Mixed-Treatment Comparison Meta-analysis and Cost–Utility Analysis

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ABSTRACT

Introduction: The aim of this study was to compare the efficacy, safety and cost-utility (from the Chinese health insurance perspective) of lixisenatide and insulin regimens in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on oral antidiabetic drugs (OADs).

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Methods: A comprehensive literature search of English (PubMed and Cochrane Library) and Chinese (CNKI and WanFang) language databases was performed, and head-to-head relevant randomized controlled trials (RCTs) were retrieved and analyzed by performing a mixed-treatment comparison (MTC) meta-analysis for efficacy and safety endpoints. A cost–utility analysis was then conducted using the IQVIA CORE Diabetes Model to compare the lifetime pharmacoeconomic profiles among the treatment groups.

Results: Eleven RCTs were included in this MTC meta-analysis. Regarding glycated hemoglobin targets, lixisenatide was similar to both basal insulin (mean difference [MD] 0.27%; 95% credible interval [CrI] 0.02%, 0.57%) and premixed insulin (MD 0.32%; 95% CrI − 0.01%, 0.66%), respectively. Statistically significant differences were found for changes in body weight in favor of lixisenatide compared with basal insulin (MD − 3.22 kg; 95% CrI − 5.51 kg, − 0.94 kg) and premixed insulin (MD − 2.68 kg; 95% CrI − 5.16 kg, − 0.20 kg). The relative risk (RR) of symptomatic hypoglycemia associated with lixisenatide was also significantly lower than that associated with basal insulin (RR 0.22; 95% CrI 0.09, 0.52) and premixed insulin (RR 0.17; 95% CrI 0.07, 0.41). The cost–utility analysis yielded results of ¥61,072 ($8565, vs. basal insulin) and ¥127,169 ($17,836, vs. premixed insulin) per quality-adjusted life year gained, with both values falling

within the willingness-to-pay threshold in China.

Conclusions: For T2DM patients inadequately controlled on OADs, lixisenatide was shown to be comparable to basal insulin and premixed insulin in terms of HbA1c and better than both of the latter in terms of both body weight loss and hypoglycemia. Lixisenatide was also a cost-effective treatment option from the perspective of Chinese health insurance.

Key Summary Points

Why carry out this study?

The clinical effects and pharmacoeconomic profiles of lixisenatide versus both basal insulin and premixed insulin in type 2 diabetes mellitus (T2DM) patients inadequately controlled on oral antidiabetic drugs (OADs) have not yet been well reported.

The aim of the mixed-treatment comparison meta-analysis and cost-utility analysis reported here was to compare the efficacy, safety and cost-utility (from the Chinese health insurance perspective) of lixisenatide and insulin regimens in this population.

What was learned from the study?

The results showed that lixisenatide was comparable to basal insulin and premixed insulin in terms of HbA1c target and better than either of the latter medications in terms of both body weight loss and hypoglycemia in T2DM patients inadequately controlled on OADs.

Meanwhile, lixisenatide was shown to be a cost-effective treatment option from the perspective of Chinese health insurance in the above-mentioned patients.

INTRODUCTION

Diabetes is a global epidemic, with approximately 425 million adults aged 20–79 years (8.8% of the world's population) worldwide estimated to have this disease in 2017 [1]. Among countries, China has the highest number of patients with diabetes, and the number are expected to rise substantially to 129.7 million in 2030 [2]. Type 2 diabetes mellitus (T2DM) accounts for 95% of all diabetes cases.

T2DM is generally initially treated with one or two oral antidiabetic drugs (OADs), with most treatment regimens including metformin. However, the prevalence of uncontrolled blood sugar in persons with T2DM treated with OADs rises with increasing duration of diabetes, increasing from 23.7% in patients with a disease duration of < 5 years to 39.3, 57.1 and 75.9% among those with a disease duration of 5–9.9, 10–19.9 and $\geq$ 20 years, respectively [3]. Following the failure of treatments with OADs, other medications are recommended, with insulin therapies regarded as the mainstay of treatment for T2DM [4].

The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has provided a new treatment option. GLP-1 RAs are able to lower blood glucose levels by stimulating the incretin system, enhancing the secretion of insulin from pancreatic β-cells in response to ingested glucose, slowing gastric emptying, and augmenting satiety [5]. Lixisenatide, a once-daily GLP-1 RA, is effective in reducing the glycated hemoglobin (HbAc1) level in patients with T2DM by lowering both the fasting and the postprandial blood glucose levels [6].

To date, only one head-to-head randomized controlled trial (RCT) has been conducted on the efficacy and safety of lixisenatide versus basal insulin in T2DM patients inadequately controlled on OADs [2], and as yet there has been no direct comparison in RCTs of lixisenatide and premixed insulin in terms of efficacy and safety. Given this lack of data from RCTs, a mixed-treatment comparison (MTC) may provide useful insights to support clinical and policy decision-making. The aim of this study was to compare the efficacy, safety and

cost–utility of lixisenatide, basal insulin and premixed insulin in patients with T2DM inadequately controlled on one to two OADs from the Chinese health insurance perspective.

METHODS

Systematic Review and MTC

Identification of Eligible Trials and Data Extraction

A comprehensive literature search of head-to-head clinical RCTs involving T2DM patients inadequately controlled on one to two OADs was performed. Interventions were lixisenatide, basal insulin, premixed insulin and placebo. PubMed and Cochrane Library databases were searched for trials published in English, and the CNKI and WanFang databases were searched for studies published in Chinese, all up to July 2018. The inclusion criteria and full search strategies are presented in Electronic Supplementary Material (ESM) Appendices S1 and S2.

Identification of the trials to be included in the MTC and the extraction of data were performed independently by two authors. Any discrepancies were reconciled by a third author. The risk of bias for each RCT included in the study was assessed using the Cochrane Collaboration's Risk of Bias tool (ESM Appendices S1, S2) [7].

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

Analysis Methods

To conduct the MTC, we used the Bayesian framework with random-effects hierarchical models to perform network meta-analysis (NMA) according to the guidance from the UK National Institute for Health and Care Excellence (NICE) [8], using STATA® software (ver. 13.0; StataCorp, College Station, TX, USA). The relative effect sizes were estimated as mean differences (MDs) for continuous outcomes and relative risks (RRs) for dichotomous outcomes. Both types of effect sizes were reported with their 95% credible intervals (CrIs). A non-informative prior was chosen as prior distribution as there was a large difference in the outcome scale of the analysis. The posterior distribution was estimated using the Markov Chain Monte Carlo method. The loop-specific approach was used to evaluate the presence of inconsistency in each closed loop. The node-splitting method was used to assess the inconsistency of the model. The Z score and their associated p values for every closed-loop identified in the network were calculated under the assumption of the absence of inconsistency. The goodness of model fit was evaluated by comparing the deviance information criterion between the random-effect and fixed-effect model. The Grading of Recommendations and Assessment, Development, and Evaluation (GRADE) approach was applied to appraise the evidence of the results.

Cost–Utility Analysis

Model Overview

The cost–utility analysis (CUA) was conducted using the IQVIA CORE Diabetes Model (CORE model) to compare the lifetime pharmacoeconomic profiles among the lixisenatide, basal insulin, and premixed insulin treatment groups. The CORE model is a widely-used, web-based commercial health economic model that has been previously validated against 66 published studies, including second- (internal) and third- (external) order validation of simulations of T2DM [9]. The CORE model captures the long-term and progressive nature of diabetes and the interactivity of its complications through its combination of Monte Carlo simulation and Markov modeling. The simulations were performed over a lifetime horizon in order to fully capture the mortality rates and long-term complications of T2DM and associated medical costs.

Model Inputs

Baseline Cohort Characteristics The baseline demographics and biochemical parameters of the modeled cohort were derived from the GetGoal-M-Asia trial [2], which included only Asian patients (Chinese patients > 90%) with

T2DM inadequately controlled on one to two OADs, and supplemented with data from the literature where necessary [10–13]. Detailed baseline cohort characteristics are listed in ESM Appendix S3.

Treatment Effects According to the setting of the CORE model, treatment effects incorporated in our analysis included the changes from baseline in HbA1c and body weight (body mass index [BMI]), as well as rates of hypoglycemia events. Since body weight change itself cannot be imputed in the CORE model directly, the BMI was applied instead. The treatment effects in the basal insulin and premixed insulin groups were calculated based on comparisons with the data in the lixisenatide group and the relative treatment effects from the results of the MTC. The treatment effects in the lixisenatide group were derived from the GetGoal-M-Asia clinical trial. The clinical input parameters of each treatment arm are listed in Table 1. The treatment effects applied in the first year of the analysis were based on the NMA using trial data over a period of 24–30 weeks. Patients were assumed to receive the intervention or comparator treatment before therapy was intensified. After intensification, HbA1c, BMI, hypoglycemic event rates, and annual costs of T2DM interventions were the same in all treatment arms, with immediate abolition of relative treatment effects representing a conservative modeling approach.

Utilities The utility and disutility values of various T2DM states and complications were derived from published studies [14–20]. Regarding the influence of excess BMI on the quality of life, we applied a disutility of 0.0061 for each unit of BMI over 25 kg/m^2, which is in line with the published time trade-off analysis from the CODE-2 study [21].

Costs This CUA was performed from the Chinese health insurance perspective; consequently, only direct medical costs were included in the analysis, including medication acquisition costs, management costs for diabetes-related complications and routine patient management costs. All cost data are reported in the 2017 Chinese yuan (¥). Costs were also converted into US dollars ($) for improving the international compatibility of the results ($1 = ¥7.13). The medication acquisition costs were obtained from the China Hospital Pharmaceutical Audit (CHPA) database. The daily costs of lixisenatide, premixed insulin and basal insulin were ¥30, ¥4, and ¥11 ($4, $1, and $2), respectively. Costs for the management of diabetes-related complications in the year of the event and the respective annual follow-up costs (each year of the simulation subsequent to the event) are listed in ESM Appendices S4–S6; these were mainly calculated from a study estimating the direct medical costs of diabetes-related complications using the sampling claims data collected by the China Health Insurance Research Association (CHIRA) [22].

Table 1 Treatment effects applied in the cost–utility analysis

Terms	HbA1c change from baseline (%)	BMI change from baseline (kg)	Symptomatic hypoglycemia (events per 100 patient-year)	Source
Lixisenatide	− 0.83	− 0.56	20.00	Pan et al. [2]
Premixed insulin	− 1.15	0.44	119.20	This MTC
Basal insulin	− 1.10	0.64	90.91	This MTC
Placebo	− 0.32	− 0.063	13.00	This MTC

BMI Body mass index, *HbA1c* hemoglobin A1c (glycated hemoglobin), *MTC* mixed-treatment comparison

Base-Case analysis

Direct medical costs, life-years and quality-adjusted life-years (QALYs) gained in the three different treatment groups were calculated. The results of the CUA were evaluated by calculating the incremental cost per QALY gained, i.e. the incremental cost–utility ratio (ICUR). Both costs and clinical outcomes were discounted at an annual rate of 3% per year [23]. A value of threefold the 2018 annual gross domestic product (GDP) per capita, as recommended by the Commission on Macroeconomics and Health of the World Health Organization [24], was regarded as the willingness-to-pay threshold (WTP; ¥193,562/$27,148 per QALY) [25] of the base-case analysis according to the local pharmacoeconomic guidelines [23].

Sensitivity Analysis

In order to assess the impact of variations in the key parameters on cost–utility results, we performed a series of one-way and probabilistic sensitivity analyses.

One-Way Sensitivity Analysis The one-way sensitivity analysis (OWSA) involved the discounting rate of costs and clinical outcomes (0 or 5%), costs of all diabetes complications (± 25%), health state utility and event disutility values (± 25%), changes in HbA1c from baseline (the upper limit and lower limit of the 95% credible interval), changes in BMI from baseline (± 25%) and time horizon (20 years).

Probabilistic Sensitivity Analysis A Monte Carlo simulation with 1000 iterations was used to perform the probabilistic sensitivity analysis (PSA) with parameter inputs (utilities, complication costs, treatment effects, cohort characteristics, and clinical events) sampled from fixed distributions with the mean and standard deviation values. The results were then used to calculate the mean and 95% confidence intervals of QALYs, costs, and ICURs. Scatterplots and cost–utility acceptability curves were drawn to further illustrate the results.

RESULTS

Literature Review Results

The titles and abstracts of 2035 potentially eligible studies for inclusion in the MTC meta-analysis were screened. After removal of all duplicated studies and screebubg if abstracts, 283 potentially relevant citations were identified for full-text screening. Ultimately, 11 trials with 4511 patients were included (ESM Appendix S7) [2, 26–35].

The baseline characteristics of the included studies are given in ESM Appendix S8. The mean age, gender, BMI, HbA1c, fasting plasma glucose (FPG) and diabetes duration were similar across all studies. At baseline, patients in the included trials had a mean age of 55.9 years, mean BMI of 29.1 kg/m^2, mean HbA1c of 8.3%, mean FPG of 9.4 mmol/L and mean diabetes duration of 7.7 years. The trials were considered to have low/moderate-risk of bias based on assessment using the Cochrane Risk of Bias Assessment tool [7]. There was no study reporting items that were assessed to have a high risk of bias (ESM Appendix S9).

MTC Results

The network relationships of evidence included in the MTC are shown in Fig. 1. Results for pairwise comparisons are shown in ESM Appendix S10.
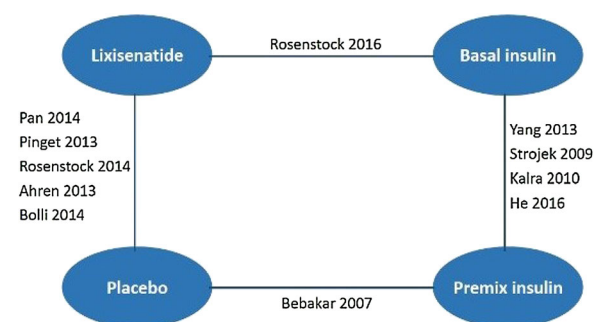

Fig. 1 Evidence network of the mixed-treatment comparison. First author and year of publication are shown

Mean Changes in the HbA1c and FPG Levels from Baseline

There was no statistically significant difference in HbA1c reduction from baseline between lixisenatide and basal insulin (MD 0.27%; 95% CrI − 0.02%, 0.57%) and lixisenatide and premixed insulin (MD 0.32%; 95% CrI − 0.01%, 0.66%). Basal insulin was associated with a statistically significant greater reduction in FPG from baseline compared with lixisenatide (MD 1.78 mmol/L; 95% CrI 1.51 mmol/L, 2.06 mmol/L). The difference in FPG reduction between lixisenatide and premixed insulin was not significant (MD − 0.03 mmol/L; 95% CrI − 0.71 mmol/L, 0.65 mmol/L) (Fig. 2).

Mean Change in Body Weight from Baseline

The change in body weight from baseline was significantly greater in patients receiving lixisenatide than in those on basal insulin (MD
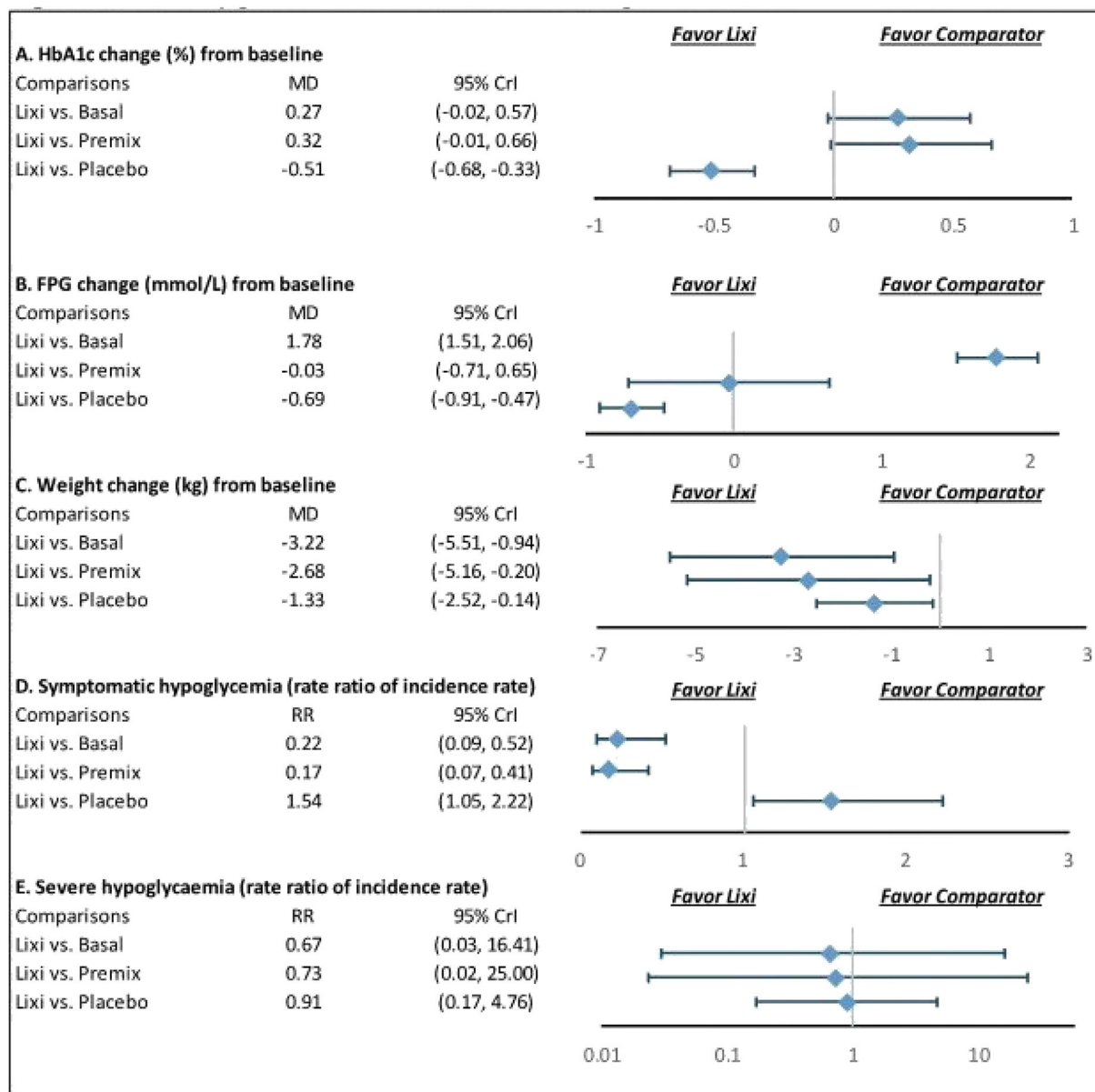

Fig. 2 Summary plots of the mixed-treatment comparison results. *CrI* Credible interval, *FPG* Fasting plasma glucose, *HbA1c* hemoglobin A1c (glycated hemoglobin), *Lixi* lixisenatide, *MD* mean difference, *RR* risk ratio

Table 2 Summary of the base–case analysis results of the cost-utility analysis

Items targeted in base–case analysis	Lixisenatide	vs. Comparators					
		Basal insulin	Δ Mean	Premixed insulin	Δ Mean	Placebo	Δ Mean
Life expectancy (years)	16.84 (0.21)	16.88 (0.20)	− 0.04	16.88 (0.21)	− 0.037	16.75 (0.2)	0.084
QALY	11.13 (0.14)	11.04 (0.13)	0.092	11.06 (0.14)	0.073	11.00 (0.14)	0.134
Direct costs (¥)	391,685 (10,217)	386,090 (9916)	5594	382,414 (10,529)	9271	387,941 (11,333)	3744
ICUR (QALY, ¥)			61,072		127,169		27,978

Values in table are presented as the mean, with the standard deviation given in parenthesis as appropriate

BI Basal insulin, *¥* Chinese Yuan, *ICUR* incremental cost–utility ratio, *QALY* quality-adjusted life-year

− 3.22 kg; 95% CrI − 5.51 kg, − 0.94 kg) and premixed insulin (MD − 2.68 kg; 95% CrI − 5.16 kg, − 0.20 kg) (Fig. 2).

Incidence Rate of Symptomatic and Severe Hypoglycemia

Symptomatic hypoglycemia and severe hypoglycemia refer to clinical symptoms when the plasma glucose level is < 3.1 and 2.0 mmol/L, respectively, with prompt recovery after oral carbohydrate administration. In this MTC, the incidence of symptomatic hypoglycemia was significantly lower in patients on lixisenatide than in those on basal insulin (RR 0.22; 95% CrI 0.09, 0.52) and premixed insulin (MD 0.17; 95% CrI 0.07, 0.41), respectively. The difference in the incidence of severe hypoglycemia was not significant between the lixisenatide and basal insulin treatment arms (RR 0.67; 95% CrI 0.03, 16.41) and between the lixisenatide and premixed insulin treatment arms (RR 0.73; 95% CrI 0.02, 25.00) (Fig. 2).

Inconsistency, Model Fitness, Heterogeneity, and Evidence Appraisal

We did not note significant inconsistencies between evidence derived from direct and indirect comparisons in any analyses, irrespective of the method of inconsistency assessment (ESM Appendix S11). A small I^2 statistic indicated a low heterogeneity (ESM Appendix S12). The results of the GRADE appraisal were shown in ESM Appendix S13.

CUA Results

Base-Case Analysis

Lixisenatide was associated with an incremental benefit of 0.073 QALYs and an increased cost of ¥9271 ($1300) compared with the premixed insulin. According to the WTP threshold, lixisenatide was a cost-effective option, with an ICUR of ¥127,169 ($17,836) per QALY gained. Lixisenatide was also cost-effective compared with basal insulin (ICUR ¥61,072/$8,565 per QALY gained). The detailed results of this analysis are shown in Table 2.

Sensitivity Analyses

The OWSA showed that the results were robust to parameter changes. Lixisenatide remained cost-effective compared with the other three interventions in the majority of scenarios investigated (Table 3).

The PSA showed that the likelihoods of lixisenatide being considered cost-effective at a WTP threshold of ¥193,562 ($27,148) per QALY gained were 63.2% and 54.7% for basal insulin and premixed insulin as comparators, respectively (ESM Appendices S14, S15).

DISCUSSION

To our knowledge, this is the first study to evaluate the comparative efficacy, safety and long-term cost-utility of lixisenatide versus

Table 3 One-way sensitivity analysis of the cost–utility analysis

Sensitivity analysis	vs. Basal insulin (ICUR)	vs. Premixed insulin (ICUR)	vs. Placebo (ICUR)
Base case	61,072	127,169	27,978
0% discount rates for costs and clinical outcomes	33,441	90,470	5985
5% discount rates for costs and clinical outcomes	76,175	146,776	48,867
Complication costs increased by 25%	60,685	131,393	15,540
Complication costs decreased by 25%	61,147	122,567	40,673
Utility increased by 25%	68,389	146,919	24,120
Utility decreased by 25%	55,170	112,099	33,276
Upper limit of 95% CrI for the change in HbA1c from baseline	63,988	93,968	42,733
Lower limit of 95% CrI for the change in HbA1c from baseline	61,428	167,236	33,329
BMI change from baseline increased by 25%	70,664	132,661	33,047
BMI change from baseline decreased by 25%	70,072	111,543	26,787
20-year time horizon	80,420	145,848	63,511

CrI Credible interval

basal insulin and premixed insulin, respectively, for patients with T2DM inadequately controlled on one to two OADs.

The risk of diabetes-related complications in T2DM patients is reported to be dependent on blood glucose levels and, consequently, glycemic control is fundamental to the management of diabetes. The results of our MTC, based on 11 studies involving 4511 adult T2DM patients inadequately controlled on OADs, suggest that the ability of lixisenatide to control glycemic level is similar to that of basal insulin and premixed insulin. In addition to the efficacy of the medication, adverse effects commonly associated with insulin therapies, such as weight gain and hypoglycemia events, also have a significant impact on the patient's (quality of) life and pose a substantial cost burden through increased treatment costs and reduced productivity. GLP-1 RAs, such as lixisenatide, can promote satiety and suppress energy intake and thus have a significant beneficial value in terms of weight control compared with insulins [36]. In addition, lixisenatide was associated with a significantly lower hypoglycemia risk in our NMA, indicating that it should be a more tolerable treatment option. It should be noted that although there were no statistical differences between the lixisenatide treatment arm and basal/premixed insulin treatment arms in terms of HbA1c level, the reduction in HbA1c was numerically greater in the basal or premixed insulin arms than in the lixisenatide arm.

Given the limited healthcare resources in China, the pharmacoeconomic profiles of therapies are regarded as important reference factors affecting healthcare decision-making. In our study, after extrapolating the short-term treatment effects to predict the long-term effects and corresponding costs, we found that lixisenatide, in comparison with basal insulin and premixed insulin, achieved a higher gain in QALYs and was associated with higher direct medical costs over a lifetime horizon. Assuming the WTP threshold was set at three times the GDP per capita in China, lixisenatide is a cost-effective option compared with premixed insulin and basal insulin. A series of one-way and probabilistic sensitivity analyses confirmed the robustness of our outcomes. Moreover, recent analyses have focused on the cost-effectiveness of combination therapy with lixisenatide + basal insulin versus other insulin regimens in

T2DM patients inadequately controlled on basal insulin alone, with the results showing that combination therapy with lixisenatide + basal insulin is a cost-effective option in China [37] and the Republic of Korea [38].

There are a number of limitations to our study. First, although the population criterion was T2DM patients whose blood sugar level was inadequately controlled on one to two OADs, some trials included patients previously treated with one OAD (metformin) while others included patients treated with two OADs (metformin plus another drug, mostly a sulphonylurea). This variability may have affected the homogeneity of the population. However, the pooling of such populations was required to ensure network connectivity. Secondly, no RCT included in this MTC had a duration of > 30 weeks. Thus, more data are needed to clarify the long-term sustained efficacy and ability to differentiate lixisenatide from basal/premixed insulin. Thirdly, there was a lack of direct comparisons between lixisenatide and premixed insulin, which may have resulted in a greater emphasis on the consistency between direct and indirect evidence. However, in the analysis there was no hint of any evidence of inconsistency. Also, only one study that directly compared lixisenatide to basal insulin was found and included in the MTC. Finally, the transition probabilities and disease progressions used in the CORE Model are based on the UK Prospective Diabetes Study (UKPDS) survey rather than on the Chinese population. Since there are as yet no long-term follow-up data available on Chinese diabetes patients, studies on Western populations are the best source of relevant data. The CUA was based on the assumption that the reduction of symptomatic hypoglycemia and prevention of weight gain that was demonstrated in the MTC can be extrapolated to the lifetime case, which may increase the uncertainty. Caution should be taken in interpreting and utilizing these results.

CONCLUSION

In summary, lixisenatide showed a similar capacity to basal insulin and premixed insulin to reduce HbA1c, but showed a significantly lower risk of hypoglycemia and a greater body weight loss. Based on this MTC, lixisenatide is a cost-effective treatment alternative for patients with T2DM inadequately controlled on OADs in China, compared with basal insulin and premixed insulin.

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