Cardiovascular outcomes of liraglutide in patients with type 2 diabetes
A systematic review and meta-analysis
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Abstract

Background: Liraglutide is a novel, long-acting glucagon-like peptide-1 (GLP-1) analogue used to treat type 2 diabetes mellitus. However, the cardiovascular safety and benefits of liraglutide treatment on type 2 diabetes patients remain in debate. In this study, we aimed to examine the overall cardiovascular outcomes of liraglutide in patients with type 2 diabetes.

Methods: In this systematic review and meta-analysis, we searched the PubMed, Embase, and Web of Knowledge databases up to September 1st, 2017 for randomized trials in which type 2 diabetes patients were assigned to liraglutide and placebo or other comparators groups.

Results: Eight studies fulfilled the eligibility criteria for inclusion and 14,608 patients were analyzed in this systematic review and meta-analysis. We found patients in the liraglutide group had a lower risk of major cardiovascular events (MACE) (RR = 0.89, 95% CI: 0.82–0.96, \(P = .002\)), acute myocardial infarction (AMI) (RR = 0.85, 95% CI: 0.74–0.99, \(P = .036\)), all-cause death (RR = 0.84, 95% CI: 0.74–0.96, \(P = .009\)), and cardiovascular death (RR = 0.77, 95% CI: 0.65–0.91, \(P = .002\)) than all comparator groups. However, liraglutide treatment did not decrease incidence of stroke (RR = 0.86, 95% CI: 0.70–1.04, \(P = .124\)). But among the MACE subgroups analysis, a significant reduction of MACE with liraglutide was only observed in placebo-controlled trials (RR = 0.89, 95% CI: 0.83–0.96, \(P = .004\)) but not in studies concerning other comparators (RR = 0.58, 95% CI: 0.29–1.16, \(P = .122\)).

Conclusions: In conclusion, our results suggest that liraglutide treatment decreases the risk of MACE, AMI, all-cause death and cardiovascular death among patients with type 2 diabetes.

Abbreviations: AMI = acute myocardial infarction, CIs = confidence intervals, FDA = Food and Drug Administration, GLP-1 = Glucagon-like peptide-1, MACE = major cardiovascular events, MR-proADM = mid-regional pro-adrenomedullin, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = risk ratio, T2DM = type 2 diabetes mellitus, TNF-\(\alpha\) = tumor necrosis factor \(\alpha\).

Keywords: GLP-1, liraglutide, type 2 diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease which characterized by beta cell function decline and insulin resistance, which is often associated with both microvascular and macrovascular complications.\textsuperscript{[1]} As previously reported, patients with diabetes have a three-fold increase in cardiovascular mortality and a two-fold increase in all-cause mortality compared to those without diabetes.\textsuperscript{[2,3]} However, among the currently available glucose lowering agents’ therapies, parts of therapies were suspected of adverse cardiovascular effects, although it has not been confirmed yet.\textsuperscript{[4,5]} Thus, the US Food and Drug Administration (FDA) announced an updated Guidance for industry which requires any new diabetes drug must be proved that it shows no substantial increase in cardiovascular risk. For regulatory requirements from the FDA, a huge collection of data from randomized trials must be conducted to evaluate the effects of a diabetes drug on the cardiovascular risk of diabetes patients.

Glucagon-like peptide-1 (GLP-1) is an essential incretin hormone which shows trophic effects on the beta cells. GLP-1 could promote insulin biosynthesis and insulin gene expression which make GLP-1 as a potent blood-glucose-lowering agent, thus GLP-1 may modify the natural history of T2DM.\textsuperscript{[6]}
Liraglutide is a novel, long-acting GLP-1 analogue drug which is a recombinant once-daily human GLP-1 analog with 97% amino acid sequence identity to endogenous human GLP-1. The efficacy of liraglutide on lowering glucose levels was confirmed, and many previous clinical trials have demonstrated that liraglutide is associated with slight reductions in weight and blood pressure. Recently, a large number of studies were conducted to evaluate the cardiovascular safety and efficacy of liraglutide for patients with T2DM. Thus, we conducted a systematic review and meta-analysis of the cardiovascular safety and efficacy of liraglutide as stipulated by the FDA recommendations for the evaluation of new treatments for diabetes.

2. Methods

This meta-analysis and systematic review based on a predefined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. All analyses in this study were on the basis of previously reported studies, thus, ethical approval and patient consents were not required.

2.1. Search strategy and selection criteria

We searched Web of Knowledge, PubMed, and Embase databases through September 1st, 2017. Key words were identified as follows: "type 2 diabetes" AND "liraglutide" AND "cardiovascular". The literature search, data extraction, and quality assessments were conducted independently by 2 authors (T.-F.W., C.-M.D.). We also searched references cited in all included articles to avoid missing other relevant articles. If the effective data were not included in the original articles, we contacted the authors to get them. The studies were screened and evaluated by 2 authors (T.-F.W., C.-M.D.) independently for eligibility. The inclusion criteria are as follows:

1. all randomized clinical trials to assess the efficacy and safety of liraglutide in the treatment of T2DM were considered eligible for analysis;
2. adult T2DM patients with a duration of at least 12 weeks (with a glycated hemoglobin level of 7.0% or more);
3. comparing liraglutide with another anti-diabetic therapy or placebo, the cases with liraglutide treatment and controls with another anti-diabetic therapy or placebo;
4. reporting the available data on cardiovascular events. Studies with overlapping data or insufficient data to calculate or extract effect estimates were excluded.

Besides, the trials enrolling nondiabetic, or type 1 diabetic were also excluded.

2.2. Data extraction and outcomes

Two investigators (T.-F.W., C.-M.D.) managed data extraction independently to ensure the reliability of the results. Disagreement was resolved by consensus, and if necessary, consultation with a third reviewer (Y.W.). The information of studies meeting the inclusion criteria were extracted using a standardized tool. Relevant information included the first author’s name, publication year, study country, intervention, the numbers of cases and controls, baseline patient characteristics (age, sex, race, diabetes duration, HbA1c level, body weight index), cardiovascular events, and the Jadad Score.

The primary outcome of this analysis was the effect of liraglutide, compared with either another anti-diabetic therapy or placebo, on the incidence of major cardiovascular events (MACE), including cardiovascular death, nonfatal acute myocardial infarction (AMI) and stroke, and acute coronary syndromes and/or heart failure. Secondary outcomes included AMI, stroke, all-cause and cardiovascular mortality.

2.3. Assessment of study quality and statistical analysis

Two independent investigators (T.F.W., C.M.D.) evaluated the quality of the studies according to the Jadad Scale, which is used for assessing the quality of case-control studies and contains 3 parts: randomization (0–2 points), double-blind (0–2 points), and withdrawals (0–1 point). The Jadad Scale is a validated 5-point scale to assess the following 5 criteria:

1. whether the study was randomized (0–1 point);
2. whether randomization was described appropriately (0–1 point);
3. whether the study was double-blind (0–1 point);
4. whether the double-blinding was described appropriately (0–1 point); and
5. whether the dropouts and withdrawals were described (0–1 point). If the study meets a criterion, it would get 1 point.

The quality score ranges from 0 to 5 points. If a study got less than 3 points, it is defined as a low-quality report study. While a high quality study score is at least 3 points.

For each study, risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were derived from patient numbers with each outcome categorized by liraglutide treatment. All statistical analyses were conducted using STATA, Version 12.0 software (StataCorp, College Station, TX, USA). The statistical significance of pooled RRs and 95% CIs was performed by a Z test. The Chi-Squared-based Q-tests and I-squared ($I^2$) statistic were used to evaluate the heterogeneity across studies.

Besides, as previously reported, the effects model we used must refer to our heterogeneity test. The selection criteria were as follows: if the P value of the Q test was more than .1 and $I^2$ values was less than 50%, which may suggest no obvious heterogeneity across studies. Then Mantel-Haenszel fixed-effects model was applied; otherwise, DerSimonian-Laird random-effects model was used. In addition, to explore the source of between-study heterogeneity, the Galbraith plots were used. Further, we also conducted sensitivity analysis by removing each included study and then assess the stability of our results. Publication bias was quantified by the Egger regression and Begg methods, and showed by funnel plots. Statistical significance was defined as a P-value < .05.

3. Results

3.1. Characteristics of eligible studies

The search strategy identified 1909 records by different search strategies in PubMed, Web of Science, and Embase. After removing 463 duplications and 1420 unrelated records, 26 records were needed to further screen through full-text reading. Among the residual records, 17 records were excluded (6 records with insufficient data, 7 reviews, and 4 comments, Supplemental Table 1, http://links.lww.com/MD/D360). Besides, there was 1 record which was excluded for having overlapping data with...
other included records. Finally, 8 studies fulfilled the eligibility criteria for inclusion in the primary analysis. The study selection diagram is shown in Figure 1.

The characteristics of the included studies are listed in Table 1. All of the included studies were published during 2009 to 2016. Information on major cardiovascular events (MACE) and mortality were reported in all the trials. And only 8 studies were involved in the analysis of acute myocardial infarction (AMI) and stroke events.

### 3.2. Cardiovascular events and morbidity

Among all included studies, 14,608 patients in total were included. Of the 8 studies with available information on MACE and reporting at least 1 event were therefore included in the main analysis. The results of our meta-analysis suggested that the incidence of MACE differ significantly between the liraglutide group and the all-comparator groups (RR = 0.89, 95% CI: 0.82–0.96, P = .002) (Fig. 2A, Table 2). Moreover, we found few numerical differences for the other adjudicated endpoints with
Liraglutide versus all comparator, including AMI (RR = 0.85, 95% CI: 0.74–0.99, P = .036) (Fig. 2B, Table 2), all-cause death (RR = 0.84, 95% CI: 0.74–0.96, P = .009) (Fig. 2C, Table 2) and cardiovascular death (RR = 0.77, 95% CI: 0.65–0.91, P = .002) (Fig. 2D, Table 2). In contrast, among T2DM patients, liraglutide treatment did not decrease incidence of stroke (RR = 0.86, 95%
3.3. Heterogeneity analysis

To investigate the heterogeneity across studies, the I-squared (I²) statistic and Chi-Squared-based Q tests were performed. Importantly, all the I² values in this study was less than 50% and P > .10 for the Q test, which suggested that there is no obvious heterogeneity across studies, as shown in Table 2.

3.4. Sensitivity analysis and publication bias

Each study was removed sequentially to verify the effect of each individual study on our results. No obvious changes were found after excluding any study. Therefore, our results were reliable (data not shown). Both Egger and Begg methods were applied to explore the publication bias in our meta-analysis. There was no significant publication bias among the included studies (Begg’s test: P = .392). The funnel plots are shown in Supplemental Figure 1, http://links.lww.com/MD/D360.

4. Discussion

In the present meta-analysis including data from 14,608 patients, we found that patients in the liraglutide group had a lower risk of MACE, AMI, all-cause death and cardiovascular death than all-comparator groups. In contrast, for T2DM patients, liraglutide treatment did not decrease incidence of stroke. However, among the MACE subgroup analysis, a significant reduction of MACE with liraglutide treatment was only observed in placebo-controlled trials but not in studies versus other comparators. For the safety of drugs for type 2 diabetes, the FDA requires a formal demonstration of the absence of any risk or MACE, with an upper confidence limit of 1.30. This meta-analysis found the incidence ratio for MACE was < 1.0 compared with total comparator and the upper 95% CI (CI: confidence interval) was also < 1.0. Results from this study may provide reliable information on cardiovascular safety and efficacy of liraglutide for T2DM patients.

Liraglutide as a type of GLP-1 analogue drugs, was recommended once-daily injection for T2DM patients. Interestingly, liraglutide has been used in clinical practice before the FDA guidance was made. The major finding in our study was reporting CV outcomes in T2DM for liraglutide only (not as a class effect).

However, previous meta-analysis mainly focused on evaluating the cardiovascular safety of all the GLP-1 receptor agonists (GLP-1 RA) class drugs. A meta-analysis found the difference in the incidence of MACE between GLP-1 RA and comparators did not reach statistical significance and the incidence ratio was 0.78 (95% CI 0.54–1.13). This study only confirmed the cardiovascular safety of all the GLP-1 RA class drugs, but did not find any beneficial effect on the incidence of MACE and mortality compared with all comparators. This disparity may be resulted from which in some of the trials included, cardiovascular events were reported only as adverse events, without being prospectively adjudicated. Another study also only found no detrimental effect of GLP-1 RA on cardiovascular events, but did not find any significant benefits in regard to rates of cardiovascular events or death. Compared to those studies, our meta-analysis mainly focuses on the liraglutide but not all GLP-1 RA drugs. Importantly, we revealed liraglutide treatment can reduce the cardiovascular events and death, but previous meta-analysis just found the cardiovascular safety of liraglutide. Therefore, the meta-analysis of clinical trials at different endpoints not only provides reliable safety information, but also provides information on efficacy.

In fact, our study found that the treatment of liraglutide was associated with a reduction of MACE risk. However, this effect disappeared when the placebo-comparator trials were excluded. This may attribute to the sample size of all included trials which compared the MACE risk between liraglutide and other comparative drugs were too small. In addition, as far as the existing knowledge is concerned, MACE risk was correlated with the morbidity and mortality. As previously reported, GLP-1 receptor agonists (GLP-1 RA) class drugs. A meta-analysis found the difference in the incidence of MACE between GLP-1 RA and comparators did not reach statistical significance and the incidence ratio was 0.78 (95% CI 0.54–1.13). This study only confirmed the cardiovascular safety of all the GLP-1 RA class drugs, but did not find any significant benefits in regard to rates of cardiovascular events or death. Compared to those studies, our meta-analysis mainly focuses on the liraglutide but not all GLP-1 RA drugs. Importantly, we revealed liraglutide treatment can reduce the cardiovascular events and death, but previous meta-analysis just found the cardiovascular safety of liraglutide. Therefore, the meta-analysis of clinical trials at different endpoints not only provides reliable safety information, but also provides information on efficacy.

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has found liraglutide treatment could decrease the cardiovascular risk biomarkers significantly, including TNF-α (tumor necrosis factor α) and MR-proADM (mid-regional pro-adrenomedullin), while the decrease in MR-proANP levels effectively show a clinically related benefit for heart failure. In contrast, recent study found albiglutide, a type of GLP-1 RA, shows no decrease effects on the MACE risk for T2DM patients. This conflict may attribute to the greater statistical power in our study than previous. Moreover, other factors may also have been involved. For example, the different effects of glucagon-like peptide-1 receptor agonists on heart rate, as an increase in heart rate is considered to be associated with higher cardiovascular risk.
Thus, the details of factors which contributed to those differences among albiglutide and liraglutide should be explored in the future studies.

To our knowledge, we must admit there were several limitations in our study. Firstly, the diagnosis standard for incident cardiovascular disease were not normalized among the studies included. This would cause misdiagnosis and underdiagnosis. Secondly, some of included studies were intended to evaluate the effects of liraglutide on glycaemic control and the safety of liraglutide treatment for T2DM patients, but not designed for the assessment of cardiovascular outcomes. Thus, more large-scale, well-conducted RCTs are required.

In conclusion, available data from clinical trials confirm that liraglutide treatment could decrease the risk of MACE, AMI, all-cause death and cardiovascular death among patients with type 2 diabetes. However, the mechanisms of action of liraglutide on the cardiovascular outcomes in patients with T2DM are needed to confirm in the future studies.

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Author contributions
Q.W.Y. conceived the study. T.F.W. and C.M.D. collected the data and drafted the manuscript. Y.W. revised the manuscript and language.

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