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Effects of glucagon-like peptide-1 receptor agonists on mortality and cardiovascular events: A comprehensive meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: The publication of the results of LEADER and SUSTAIN-6 trials suggested a possible beneficial effect of the class of GLP-1 receptor agonists on cardiovascular morbidity and mortality. The aim of the present meta-analysis is to collect and synthetize all available evidence on the effect of GLP-1 receptor agonists on cardiovascular events and mortality.

Methods: A Medline search for GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, or semaglutide) was performed, collecting all randomized clinical trials with a duration >11 weeks, enrolling patients with type 2 diabetes, and comparing a GLP-1 receptor agonist with placebo or any other non-GLP-1 receptor agonist drug. The principal outcome of this analysis was the effect of GLP-1 receptor agonists on all-cause and cardiovascular mortality, overall (fatal plus nonfatal) myocardial infarction, stroke, and heart failure.

Results: Out of 113 trials fulfilling inclusion criteria (mean duration 41.7 ± 38.2 weeks), 32, 25, 48, 43 and 32 reported at least one event for all-cause and cardiovascular mortality, overall (fatal plus nonfatal) myocardial infarction, stroke, and heart failure, respectively. In GLP-1 receptor agonist-treated patients, all-cause mortality, cardiovascular mortality, and myocardial infarction were significantly lower than in comparators (MH-OR [95% CI] 0.88 [0.79–0.97], $p = 0.015$, 0.84 [0.74–0.96], $p = 0.009$, and 0.90 [0.80–1.00], $p = 0.050$, respectively), whereas no beneficial effect was observed for stroke and heart failure (MH-OR [95% CI] 0.90 [0.81–1.00]. $p = 0.059$. 0.89 [0.76–1.04]. $p = 0.15$. and 0.92 [0.81–1.06]. $p = 0.25$. respectively).

Conclusions: Overall, the agents of this class appear to reduce all-cause mortality, cardiovascular mortality, and the incidence of myocardial infarction at mid-term follow up.

1. Introduction

Three cardiovascular outcome studies with different Glucagon-Like Peptide-1 (GLP-1) receptor agonists were recently published [1–3]. All the three trials reached their principal endpoint, i.e. the demonstration of non-inferiority versus placebo with respect to major cardiovascular events, thus confirming the safety of the experimental drugs. However, in one [1] of the trials (with lixisenatide), no difference across treatment groups was observed for the principal endpoint or any pre-defined secondary endpoint, whereas in the other two studies the incidence of major cardiovascular events was significantly reduced in the active treatment group. In addition, the trial with liraglutide showed a significant reduction in all-cause and cardiovascular mortality, whereas that with semaglutide reported a significant reduction in the incidence of stroke [1–3].

These results raised important questions about the possibility of a class effect of GLP-1 receptor agonists on cardiovascular risk. In fact, the populations enrolled in the three trials were notably different, with trials with liraglutide and semaglutide including a majority of subjects with established (non-recent) cardiovascular disease, and the study with lixisenatide enrolling patients with a recent coronary event [1–3]. On the other hand, the three molecules differ for kinetic and chemical structure: lixisenatide is a short-acting analogue of exenatide, with a low homology to human GLP-1 [4], whereas both liraglutide and semaglutide are long-acting GLP-1 receptor agonists, with an amino acid sequence almost identical to that of human GLP-1 [4].

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The aim of the present meta-analysis is to collect and synthetize all available evidence on the effect of GLP-1 receptor agonists on cardiovascular events and mortality, including data from randomized trials with non-cardiovascular endpoints, in order to improve our insight on the cardiovascular effects of these molecules.

2. Materials and methods

This analysis is part of a larger systematic review, the protocol of which (CRD42015020245) was published on the University of York (Centre for Reviews and Dissemination) website [5].

2.1. Data sources and searches

A Medline/Embase search for GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, or semaglutide) was performed, collecting all randomized clinical trials on humans published in English up to September 15th. 2016. The identification of relevant abstracts, the selection of studies based on the criteria described below, and the subsequent data extraction were performed independently by two of the authors (S.Z., M.M.), and conflicts resolved by the third investigator (E.M.). Completed but still unpublished trials were identified through a search of www.clinicaltrials.gov website, using the same keywords. In addition, for approved drugs, Medical Reviews were retrieved from the Food and Drug Administration (FDA) website [6], and the Summary of Product Characteristics from the European Medicines Agency (EMA) website [7], for the identification of further unpublished and otherwise undisclosed trials.

2.2. Study selection

A meta-analysis was performed including all randomized clinical trials with a duration of treatment of at least 12 weeks, enrolling patients with type 2 diabetes, comparing a GLP-1 receptor agonist with placebo or any other non-GLP-1 receptor agonist drug, provided that concurrent treatment was the same for all treatment arms, and that the doses of GLP-1 receptor agonist were among those approved by FDA and/or EMA.

2.3. Data extraction and quality assessment

Results of trials were retrieved from the primary publication and, if needed, from other publications referring to the same trial. When information were unavailable on published papers, data were retrieved (in this hierarchical order) from FDA Medical Reviews EMA Summaries of Product Characteristics, www.clinicaltrials.gov study results, and trial results on manufacturers' company websites. Data retrieval was performed by two of the investigators (A.S. and L.P.), and conflicts resolved by a third investigator (E.M.). Retrieved data included all outcomes reported below, plus the main features of each trial (concurrent therapy, principal endpoint, baseline characteristics of enrolled patients (age, BMI, duration of diabetes, HbA1c), and effects of treatment on HbA1c and BMI. The quality of trials was assessed using the Cochrane Collaboration's Tool for Assessing Risk of Bias in randomized controlled trials; quality was not used as a criterion for the selection of trials, but only for descriptive purposes.

2.4. Data synthesis and analysis

The principal outcome of this analysis was the effect of GLP-1 receptor agonists, compared with placebo or other active drugs, on all-cause and cardiovascular mortality, overall (fatal plus nonfatal) myocardial infarction, stroke, and heart failure (HF). For the latter outcome, hospitalization for HF was considered whenever available; when that information was not reported, heart failure reported as serious treatment-emergent adverse event was considered. The composite endpoint of major cardiovascular events (MACE) was not considered, because it is not usually reported as such in trials with non-cardiovascular principal endpoints, which were the majority of available studies. Heterogeneity (on all-cause mortality) was assessed by using I^2 statistics. In order to estimate possible publication/disclosure bias we used funnel plots and the Begg adjusted rank correlation test [8,9], including published and unpublished, but disclosed, trials. Considering the differences across trials in molecules, treatment schedules, inclusion criteria, and length of follow-up, a random-effects model was applied, calculating Mantel-Haenszel odds ratio with 95% Confidence Interval (MH-OR) for all the events defined above, on an intention-to-treat basis, excluding trials with zero events. For all the principal endpoints, a sensitivity analysis was performed with continuity correction, in order to avoid distortions due to the exclusion of trials with zero events. Subgroup analyses were performed for all endpoints for different drugs of the class, different classes of comparators, and trials with cardiovascular and non-cardiovascular endpoints. A post-hoc analysis was performed on all principal endpoints selecting only trials with a duration of at least 52 weeks. In addition, a post-hoc meta-regression analysis was performed, exploring the moderating effect of mean age, duration of diabetes, HbA1c, fasting glucose, and BMI at study entry, as well as reduction of HbA1c and BMI versus comparators. All analyses were performed using Comprehensive Meta-analysis Version 2.Biostat. (Englewood. NJ. USA).The meta-analysis was reported following the PRISMA checklist [10].

3. Results

Out of 1.147 and 532 items identified through MEDLINE/Embase, www.clinicaltrials.gov and FDA/EMA websites, respectively, 113 trials were selected, as summarized in Fig. 1 of Supplementary materials. The quality of trials (all with intention-to-treat analysis) was generally good (Table 1 Supplementary materials). The trials fulfilling the inclusion criteria enrolled 33,167 and 26,683 patients in GLP-1 receptor agonist and comparator arms, respectively, with a mean duration of treatment of 41.7 ± 38.2 weeks. The main characteristics of the selected trials, and the outcomes of interest in each study, are reported in Table 1and Table 1 of Supplementary materials. The search of www.clinicaltrials.gov website allowed the identification of 26 unpublished and undisclosed, although completed, trials (Table 2 Supplementary materials).

3.1. All-cause mortality

Of the 113 trials fulfilling the inclusion criteria, 14 did not report information on all-cause mortality, whereas 67reported zero events in all treatment groups. The principal analysis was therefore performed on 32 trials, enrolling 20,280 and 16,939 patients in GLP-1 receptor agonist and comparator arms, respectively. The number of reported deaths was 720 (3.6%) for GLP-1 receptor agonists and 785 (4.6%) for comparators.

I^2 was <0.001, suggesting no relevant heterogeneity. Funnel plot analysis (Fig. 2 Supplementary materials) and Kendall's tau (−0.08; $p = 0.51$) did not suggest any relevant publication bias.

In GLP-1 receptor agonist-treated patients, all-cause mortality was significantly lower than in comparators (MH-OR [95% CI] 0.88 [0.79–0.97]. $p = 0.015$; Fig. 3 Supplementary materials). This result was confirmed in the sensitivity analysis with continuity correction (MH-OR 0.88 [0.79–0.96]. $p = 0.012$). When trials with different molecules were analysed separately, the difference in mortality versus comparators was significant only with dulaglutide and liraglutide; however, when the trials with a cardiovascular endpoint were excluded, the result for liraglutide was no longer statistically significant (Fig. 1).

A subgroup analysis was performed for trials with different comparators (Fig. 2), showing a significant reduction of all-cause mortality only in placebo-controlled trials, driven by the cardiovascular outcome studies. When trials with a duration of treatment ≥52 weeks ($n = 20$) were analysed separately, MH-OR was 0.88[0.79–0.98], $p = 0.023$.

Meta-regression analyses did not detect a significant effect on all-cause mortality of any of the putative moderators explored (Table 3 Supplementary materials).

3.2. Cardiovascular mortality

Information on cardiovascular mortality was available for 83 trials, 25 of which with at least one event. I^2 was <0.001, suggesting no relevant heterogeneity. Funnel plot analysis (Fig. 4 Supplementary materials) and Kendall's tau (−0.05; $p = 0.73$) did not suggest any relevant publication bias.

The analysis was therefore performed on 25 trials, enrolling 16,656 and 15,175 patients in GLP-1 receptor agonist and comparator arms, respectively. The number of reported cardiovascular deaths was 438 (2.6%) for GLP-1 receptor agonists and 514 (3.4%) for comparators. Cardiovascular mortality was significantly reduced by GLP-1 receptor agonists (MH-OR [95% CI] 0.84 [0.74–0.96]. $p = 0.009$; Fig. 5 Supplementary materials). This result was confirmed by the sensitivity analysis with continuity correction (MH-OR [95% CI] 0.84 [0.74–0.95]. $p = 0.007$).

In separate analyses for different GLP-1 receptor agonists, none of the molecules of the class reached a statistically significant effect on cardiovascular mortality (Fig. 1). Differences from any class of active comparators did not reach statistical significance (Fig. 2). On the other hand,

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