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

Matteo Monami a, Stefania Zannoni a, Laura Pala a, Antonio Silveri a, Francesco Andreozzi b, Giorgio Sesti b, Edoardo Mannucci a,⁎

a Diabetology, Azienda Ospedaliero-Universitaria Careggi and University of Florence, Florence, Italy
b Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy

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] 0.80 [0.81–0.81]; 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].

⁎ Corresponding author at: Diabetology, Azienda Ospedaliero-Universitaria Careggi, Via delle Oblate 4, 50141 Florence, Italy.
E-mail addresses: matteo.monami@unifi.it (M. Monami), edoardo.mannucci@unifi.it (E. Mannucci).
The aim of the present meta-analysis is to collect and synthesize 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, dulaglutide, or semaglutide) was performed, collecting all randomized clinical trials on humans published in English up to September 15th. 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 and 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 I² statistics. In order to estimate possible publication/disclosure bias we used funnel plots and the Begg adjusted rank correlation test [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.)

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 1 and 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 67 reported 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. I² 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. I² 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,
cardiovascular mortality was significantly reduced by GLP-1 receptor agonists in placebo-controlled trials; the difference was significant in trials with non-cardiovascular endpoints, but not in those with cardiovascular endpoints (Fig. 2).

When trials with a duration of treatment ≥52 weeks (n = 14) were analysed separately, MH-OR was 0.85[0.74–0.97], p = 0.017. Meta-regression analyses did not reveal any relevant effect of any of the moderators listed above (Table 3 Supplementary materials), with the exception of a non-significant trend for BMI at enrolment (Fig. 6 Supplementary materials).

3.3. Myocardial infarction

Information on myocardial infarction was reported for 91 trials, 48 of which with at least one event \( I^2 \) was < 0.001, suggesting no relevant heterogeneity. Funnel plot analysis (Fig. 7 Supplementary materials) and Kendall’s tau (0.13; p = 0.20) did not suggest any relevant publication bias. Trials reporting at least one event enrolled 22,990 and 19,412 patients in GLP-1 receptor agonist and comparator arms, respectively. The number of reported myocardial infarction was 674 (2.9%) for GLP-1 receptor agonists and 725 (3.7%) for comparators.

In the principal analysis, the effect of GLP-1 receptor agonists on the incidence of myocardial infarction reached a marginal statistical significance (MH-OR [95% CI] 0.90 [0.80–1.00], p = 0.050; Figure 8 Supplementary materials); a significant difference was observed in the sensitivity analysis with continuity correction (MH-OR [95% CI] 0.89 [0.80–0.99], p = 0.039). None of the molecules of the class, when analysed separately, was associated with a significant reduction in the incidence of myocardial infarction (Fig. 3). A non significant trend toward lower incidence of myocardial infarction with GLP-1 receptor agonists was observed in placebo-controlled studies; however, between-group difference did not reach statistical significance neither in studies with non-cardiovascular endpoints, nor in those with cardiovascular endpoint. In addition, no significant difference was detected in comparison with any class of active comparators (Fig. 4). In a separate analysis, including only trials with a duration of treatment ≥52 weeks (n = 21) were analysed separately, MH-OR was 0.90 [0.81–1.01], p = 0.083.

In meta-regression analyses, a higher mean BMI at enrolment was associated with a greater beneficial effect of GLP-1 receptor agonists on myocardial infarction (Fig. 9 Supplementary materials); non-significant trends were observed also for higher HbA1c at baseline and greater HbA1c reduction (Table 3 Supplementary materials).

3.4. Stroke

Information on stroke was reported by 92 studies, 43 of which with at least one event. \( I^2 \) was < 0.001, suggesting no relevant heterogeneity. Funnel plot analysis (Fig. 10 Supplementary materials) and Kendall’s tau (−0.05; p = 0.40) did not suggest any relevant publication bias. The principal analysis was therefore performed on 43 trials, enrolling 22,114 and 19,436 patients in GLP-1 receptor agonist and comparator arms, respectively. The number of reported stroke was 313 (1.4%) for GLP-1 receptor agonists and 340 (1.7%) for comparators.

The incidence of stroke with GLP-1 receptor agonists was not significantly different from that of comparator groups, neither in the main analysis (MH-OR [95% CI] 0.89 [0.76–1.04], p = 0.16; Fig. 11 Supplementary materials) nor in the sensitivity analysis with continuity correction (MH-OR [95% CI] 0.88 [0.76–1.02], p = 0.088). When trials with a duration of treatment ≥52 weeks (n = 20) were analysed separately, MH-OR was 0.89[0.75–1.04], p = 0.14.

No significant differences were observed in subgroup analyses with different molecules (with the only exception of semaglutide) or with different comparators (Figs. 3 and 4). No significant effect of moderators was detected in meta-regression analyses (Table 3 Supplementary materials).

3.5. Heart failure

Information on heart failure was reported by 80 studies, 32 of which with at least one event. \( I^2 \) was < 0.001, suggesting no relevant heterogeneity. Funnel plot analysis (Fig. 12 Supplementary materials) and Kendall’s tau (−0.04; p = 0.77) did not suggest any relevant publication bias. Trials reporting at least one event enrolled 18,861 and 16,082 patients in GLP-1 receptor agonist and comparator arms, respectively. The number of reported heart failure was 427 (2.3%) for GLP-1 receptor agonists and 452 (2.8%) for comparators.

GLP-1 receptor agonists did not appear to produce any effect on heart failure (MH-OR [95% CI] 0.92 [0.81–1.06], p = 0.25; Fig. 13 Supplementary materials); this result was confirmed by the analysis with continuity correction (MH-OR [95% CI] 0.92 [0.81–1.06], p = 0.24). In a separate analysis, including only trials with a duration of treatment ≥52 weeks (n = 19) were analysed separately, MH-OR was 0.92 [0.80–1.06], p = 0.25.

No significant differences were observed in subgroup analyses with different molecules or with different comparators (Figs. 3 and 4). No
Table 1: Description of the outcomes considered in the present meta-analysis.

<table>
<thead>
<tr>
<th>First author (year)*</th>
<th>Comparator</th>
<th>Drug</th>
<th>Dose GLP-1RA</th>
<th>Trial duration</th>
<th>Number of patients</th>
<th>All cause death</th>
<th>Cardiovascular death</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albigger 2016 (4)</td>
<td>Placebo</td>
<td>Motone</td>
<td>30 mg</td>
<td>12 weeks</td>
<td>282</td>
<td>3.7</td>
<td>2.3</td>
<td>1.5</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Reusch 2014 (8)</td>
<td>NCT01769378 (19)</td>
<td>Placebo</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>250</td>
<td>3.5</td>
<td>2.5</td>
<td>1.4</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Home 2015 (10)</td>
<td>Placebo</td>
<td>Glimepiride</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>271</td>
<td>3.5</td>
<td>2.5</td>
<td>1.4</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Placebo</td>
<td>Glibenclamide</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>50</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Placebo</td>
<td>Glimepiride</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>271</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chaudhuri 2012 (24)</td>
<td>Placebo</td>
<td>Glibenclamide</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>50</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gudipati 2014 (25)</td>
<td>Placebo</td>
<td>Glibenclamide</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>271</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Miyagawa 2015 (13)</td>
<td>Placebo</td>
<td>Glibenclamide</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>50</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Araki 2015 (14)</td>
<td>Placebo</td>
<td>Glibenclamide</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>271</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vauzou 2016 (27)</td>
<td>Placebo</td>
<td>Glibenclamide</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>271</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bergrenner 2012 (22)</td>
<td>Placebo</td>
<td>Glibenclamide</td>
<td>0.75 mg</td>
<td>12 weeks</td>
<td>271</td>
<td>3.4</td>
<td>2.4</td>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Author (year) format: Last name, Year (Number).
significant effect of moderators was detected in meta-regression analyses (Table 3 Supplementary materials).

### 4. Discussion

The publication of the results of the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) and Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trials suggested a possible beneficial effect of the class of GLP-1 receptor agonists on cardiovascular morbidity and mortality (Section 2.3). In the present meta-analysis, the incidence of major cardiovascular events (MACE), which was the principal endpoint of both those trials, was not considered, because time to first event cannot be reliably assessed when including studies with non-cardiovascular endpoints. However, a significant effect was detected for two of the components of MACE, i.e., cardiovascular mortality and myocardial infarction.

This result is not surprising, considering that a relevant proportion (approximately

---

**Table 1 (continued)**

<table>
<thead>
<tr>
<th>First author (year)*</th>
<th>Comparator</th>
<th>Dose GLP-1RA</th>
<th>Trial duration</th>
<th>Number of patients</th>
<th>All cause death</th>
<th>Cardiovascular death</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamant 2012 (64)</td>
<td>Glargine</td>
<td>2</td>
<td>84</td>
<td>233 223</td>
<td>0 0</td>
<td>0 0</td>
<td>1 0</td>
<td>1 0</td>
<td>0 0</td>
</tr>
<tr>
<td>NCT01652729 (65)</td>
<td>Placebo</td>
<td>2</td>
<td>28</td>
<td>181 61</td>
<td>NR NR</td>
<td>NR NR</td>
<td>0 0</td>
<td>1 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Davies 2013 (66)</td>
<td>Sitagliptin</td>
<td>2</td>
<td>52</td>
<td>181 122</td>
<td>NR NR</td>
<td>NR NR</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Inagaki 2012 (67)</td>
<td>Glargine</td>
<td>2</td>
<td>52</td>
<td>215 212</td>
<td>1 0</td>
<td>1 0</td>
<td>0 0</td>
<td>1 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Russell-Jones 2012 (68)</td>
<td>Metformin</td>
<td>2</td>
<td>26</td>
<td>248 409</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 0</td>
<td>0 0</td>
</tr>
</tbody>
</table>

**Table 1**

<table>
<thead>
<tr>
<th>First author (year)*</th>
<th>Comparator</th>
<th>Dose GLP-1RA</th>
<th>Trial duration</th>
<th>Number of patients</th>
<th>All cause death</th>
<th>Cardiovascular death</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pratley 2011 (69)</td>
<td>Sitagliptin</td>
<td>1.2–1.8</td>
<td>52</td>
<td>446 219</td>
<td>1 2</td>
<td>0 2</td>
<td>2 1</td>
<td>0 0</td>
<td>2 0</td>
</tr>
<tr>
<td>Mathieu 2014 (70)</td>
<td>Aspart</td>
<td>0.6–28</td>
<td>28</td>
<td>88 89</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 0</td>
<td>0 0</td>
</tr>
<tr>
<td>D’Alessio 2015 (71)</td>
<td>Glargine</td>
<td>0.6–24</td>
<td>24</td>
<td>489 489</td>
<td>NR NR</td>
<td>NR NR</td>
<td>0 0</td>
<td>2 0</td>
<td>2 0</td>
</tr>
<tr>
<td>De Wit 2014 (72)</td>
<td>None</td>
<td>0.6–24</td>
<td>24</td>
<td>64 60</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Lind 2015 (73)</td>
<td>Placebo</td>
<td>0.6–24</td>
<td>24</td>
<td>695 114</td>
<td>0 0</td>
<td>0 0</td>
<td>3 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Marre 2007 (74)</td>
<td>Rosiglitazone</td>
<td>26</td>
<td>26</td>
<td>695 232</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>3 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Nauck 2009 (75)</td>
<td>Glimepiride</td>
<td>0.6–1.8</td>
<td>104</td>
<td>724 242</td>
<td>1 0</td>
<td>0 0</td>
<td>5 3</td>
<td>2 0</td>
<td>2 0</td>
</tr>
<tr>
<td>Garber 2011 (76)</td>
<td>Glimepiride</td>
<td>1.2–1.8</td>
<td>104</td>
<td>498 248</td>
<td>0 1</td>
<td>0 0</td>
<td>2 2</td>
<td>0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Zinman 2009 (77)</td>
<td>Placebo</td>
<td>1.2–1.8</td>
<td>26</td>
<td>355 175</td>
<td>0 0</td>
<td>0 0</td>
<td>1 0</td>
<td>0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Russell-Jones 2009 (78)</td>
<td>Placebo</td>
<td>1.8</td>
<td>26</td>
<td>230 232</td>
<td>1 2</td>
<td>0 2</td>
<td>1 2</td>
<td>0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Marso 2016 (79)</td>
<td>Placebo</td>
<td>1.8</td>
<td>198</td>
<td>2058 4672</td>
<td>181 447</td>
<td>219 278</td>
<td>292 339</td>
<td>173 199</td>
<td>218 248</td>
</tr>
<tr>
<td>Davies 2016 (80)</td>
<td>Placebo</td>
<td>1.8</td>
<td>26</td>
<td>140 139</td>
<td>4 1</td>
<td>0 0</td>
<td>5 2</td>
<td>0 0</td>
<td>2 0</td>
</tr>
<tr>
<td>Forst 2012 (81)</td>
<td>None</td>
<td>1.8</td>
<td>12</td>
<td>21 19</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
</tr>
<tr>
<td>Seino 2010 (82)</td>
<td>Glimepiride</td>
<td>0.9</td>
<td>52</td>
<td>268 132</td>
<td>1 0</td>
<td>0 0</td>
<td>3 1</td>
<td>0 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Kaku 2010 (83)</td>
<td>Placebo</td>
<td>0.6</td>
<td>52</td>
<td>88 88</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>NCT00614120 (84)</td>
<td>Glimepiride</td>
<td>0.6–1.8</td>
<td>16</td>
<td>698 231</td>
<td>0 0</td>
<td>1 0</td>
<td>1 0</td>
<td>0 1</td>
<td>0 0</td>
</tr>
<tr>
<td>D’Alessio 2014 (85)</td>
<td>Glimepiride</td>
<td>1.8–2.6</td>
<td>104</td>
<td>522 225</td>
<td>0 0</td>
<td>1 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>NCT01907854 (86)</td>
<td>Glimepiride</td>
<td>0.6–26</td>
<td>26</td>
<td>202 204</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Zang 2016 (87)</td>
<td>Sitagliptin</td>
<td>1.8</td>
<td>26</td>
<td>183 184</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Yang 2011 (88)</td>
<td>Glimepiride</td>
<td>0.6–1.8</td>
<td>16</td>
<td>698 231</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
<td>NR NR</td>
</tr>
<tr>
<td>Li 2012 (89)</td>
<td>Placebo</td>
<td>1.8</td>
<td>56</td>
<td>211 212</td>
<td>0 0</td>
<td>0 0</td>
<td>NR NR</td>
<td>2 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Davies 2013 (90)</td>
<td>Placebo</td>
<td>1.8</td>
<td>26</td>
<td>16 16</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Nandy 2014 (91)</td>
<td>Glimepiride</td>
<td>1.8</td>
<td>12</td>
<td>16 17</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Idom 2016 (92)</td>
<td>None</td>
<td>1.8</td>
<td>12</td>
<td>25 22</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>vonScholten 2016 (93)</td>
<td>None</td>
<td>1.8</td>
<td>12</td>
<td>32 32</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Retnakaran 2014 (94)</td>
<td>None</td>
<td>1.8</td>
<td>26</td>
<td>25 25</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Vanderheiden 2016 (95)</td>
<td>None</td>
<td>1.8</td>
<td>26</td>
<td>35 36</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Kumarathurai 2016 (96)</td>
<td>None</td>
<td>1.8</td>
<td>12</td>
<td>39 39</td>
<td>0 0</td>
<td>0 0</td>
<td>2 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Charbonnel 2013 (97)</td>
<td>Sitagliptin</td>
<td>1.2</td>
<td>26</td>
<td>327 326</td>
<td>0 1</td>
<td>0 0</td>
<td>0 1</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Smiths 2016 (98)</td>
<td>Placebo</td>
<td>1.8</td>
<td>12</td>
<td>19 17</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
</tbody>
</table>

*See references in Supplementary materials; GLP-1RA: Glucagon-like Peptide-1 Receptor Agonists; ID: Investigational Drug (GLP-1RA); Comp.: Comparator; NR: Not reported.
34 and 53% of cardiovascular deaths and incident myocardial infarctions, respectively) of reported events derived from the LEADER and SUSTAIN-6 trials.

The relative risk reduction for myocardial infarction and cardiovascular mortality (10 and 14%, respectively) may seem relatively small. However, it should be considered that the majority of events was observed in cardiovascular outcome trials, in which a large proportion of the patients enrolled was already treated with other drugs for cardiovascular protection, such as statins, antiplatelet agents, beta blockers, and ACE inhibitors or angiotensin receptor blockers [1–3]. Therefore, the protective effect of GLP-1 receptor agonists appears to be additive to that of current cardiovascular treatments. In addition, the protocol of cardiovascular outcome studies is designed in such a way as to minimize between-group differences in glycemic control; in fact, investigators were invited to adjust concurrent hypoglycemic treatments with the aim of reaching and maintaining good glycemic control in all patients [1–3]. This particular design may lead to an underestimation of the actual beneficial effects of experimental drugs.

Overall, the results of the present meta-analysis are consistent with those of pooled analyses of patient-level data on cardiovascular events observed in phase 3 trials. Such analysis showed either no effect [11] or a trend toward a reduction of risk [12,13], which did not reach statistical significance due to the limited size of the samples studied. In fact, the number of events observed in non-cardiovascular, phase 3 trials is too small to allow any definitive conclusion.

It is conceivable that multiple mechanisms are involved in the reduction of cardiovascular risk during treatment with GLP-1 receptor agonists. The improvement of glucose control [14] and of other risk factors, such as blood pressure, body weight and lipid profile [15,16], could play a major role. However, direct effects of GLP-1 agonists on the cardiovascular system are also plausible [17].

One of the main issues in the interpretation of cardiovascular outcome trials with GLP-1 receptor agonists is the identification of reasons underlying differences in results between the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study [1] and the two other trials cited above (Section 2.3). In the cardiovascular trial with lixisenatide, patients were enrolled within 180 days from an acute coronary syndrome; a majority of those patients had undergone a coronary revascularization shortly before the initiation of treatment [1]. Those patients represent a population at very high cardiovascular risk, which could be less sensitive to some therapeutic interventions for longer-term prevention of cardiovascular disease. Therefore, the lack of beneficial actions on MACE in the ELIXA trial could be the effect of the selection of population, rather than of the lack of efficacy of the drug. In this respect, data from other trials with lixisenatide, in different patient populations, could be very interesting. Unfortunately, the number of events observed in the trials with lixisenatide different from ELIXA is too small to draw any conclusion on this point.

On the other hand, differences between cardiovascular trials with liraglutide and semaglutide, on one side, and lixisenatide on the other,
The number of patients undergoing hospitalization for heart failure is not usually detectable. This result should be interpreted with caution, because the number of cardiovascular trials with GLP-1 receptor agonists, the heart failure rate for GLP-1 receptor agonists versus placebo or other active comparators.

The mean duration of the studies included in the meta-analysis is relatively short; therefore, the cardiovascular effects of GLP-1 receptor agonists in the longer term deserve further investigation. Notably, differences in cardiovascular events between the active drug and placebo in both LEADER and SUSTAIN-6 trials [23,24] were evident only after several months of treatment. Therefore, it is possible that the present meta-analysis, which includes a large number of shorter-term trials, underestimates the actual beneficial effects of GLP-1 receptor agonists. On the other hand, when trials with a duration of one year or more were analysed separately, the results did not differ from those of the main analysis; this suggests that the distortion introduced by the inclusion of shorter-term trials is not very relevant.

A further limitation of this meta-analysis is the lack of adjudication of cardiovascular events and cardiovascular mortality in many of the smaller studies, with the possibility of misclassifications. In addition, despite the efforts at collecting all available evidence, including that derived from the so-called "grey literature", data from some completed trials could not be retrieved. The possibility of distortions determined by selective disclosure cannot be entirely ruled out.

Meta-regression analyses were performed post-hoc, as a tool for detecting possible moderators of the cardiovascular effects of GLP-1 receptor agonists. Interestingly, this class of drugs appeared to produce a greater reduction of cardiovascular mortality and of the incidence of myocardial infarction in patients with a higher BMI. This suggests that subjects with a higher degree of obesity could benefit more from GLP-1 receptor agonist treatment, although this difference was not detected in the LEADER and SUSTAIN-6 trials (Section 2.3). The interpretation of this result should be very cautious because of the risk of ecological fallacy, i.e. the possibility of confounding factors, unaccounted for in this analysis, associated with a higher BMI: for example, we did not consider ethnicity, which has a relevant impact on body mass index, and which could moderate the biological effects of GLP-1 receptor agonists.

4.1. Conclusions

Overall, the agents of this class appear to reduce all-cause and cardiovascular mortality, and the incidence of myocardial infarction at mid-term follow up. Available data suggest differences across molecules of the class, but they are insufficient to verify whether these differences are due to kinetics or other features of individual drugs. The possibility that patients with a higher degree of obesity have greater cardiovascular benefits with GLP-1 receptor agonists deserves further investigation.

Please cite this article as: M. Monami et al., Effects of glucagon-like peptide-1 receptor agonists on mortality and cardiovascular events: A comprehensive meta-analysis of rand..., Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.03.163
Declaration of interests
Matteo Monami has received speaking fees from Bristol Myers Squibb, Eli-Lilly, Merck, Novonordisk, Merck, and Takeda, and research grants from Bristol Myers Squibb. Stefania Zannoni, Laura Pala, Antonio Silverii, and Francesco Andreozzi have no conflicts of interest.

Giorgio Sesti has received consultancy fees from Servier, Intarcia, Novo Nordisk, Janssen, BoehringerIngelheim, Eli Lilly, Astra Zeneca, MSD Italy, Sanofi, Pfizer, and Abbott, and speaking fees from Novo Nordisk, MSD Italy, Boehringer Ingelheim, Eli Lilly, Janssen, Astra Zeneca, TherasLifeTetch and Takeda.

Edoardo Mannucci has received consultancy fees from Merck and Novartis, speaking fees from Astra Zeneca, Bristol Myers Squibb, Merck, and Novartis, and research grants from Merck, Novartis, and Takeda.

Contributor statements
Matteo Monami was involved in each of the following points:
1. Design
2. Data Collection
3. Analysis
4. Writing manuscript
Stefania Zannoni, Laura Pala, Antonio Silverii, and Francesco Andreozzi were involved in each of the following points:
1. Data Collection
2. Manuscript revision

Giorgio Sesti was involved in each of the following points:
1. Design
2. Reviewing manuscript

Edoardo Mannucci was involved in each of the following points:
1. Design
2. Data Collection
3. Analysis
4. Writing manuscript

All the authors approved the final version of this manuscript.

Acknowledgements and statements
This research was performed independently of any funding, as part of the institutional activity of the investigators. Human and animal rights. Informed consent was not necessary because of no experimentation with human subjects was performed.

Appendix A. Supplementary data
Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.03.163.

References

Please cite this article as: M. Monani, et al., Effects of glucagon-like peptide-1 receptor agonists on mortality and cardiovascular events: A comprehensive meta-analysis of rand... Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.03.163