Current Diabetes Reviews, 2018, *14*, 273-279

REVIEW ARTICLE

Effect of Glucagon-like Peptide-1 Receptor Agonists on All-cause Mortality and Cardiovascular Outcomes: A Meta-analysis

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ARTICLE HISTORY

Received: February 13, 2017
Revised: March 27, 2017
Accepted: March 29, 2017

DOI:
10.2174/1573399813666170414101450

Abstract: ***Background*:** Cardiovascular disease is the leading cause of death in patients with type 2 diabetes.

***Objective*:** To assess the impact of glucagon-like peptide-1 receptor agonist (GLP1RA) therapy, compared to placebo, on clinically relevant outcomes including all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalizations for heart failure, in patients with type 2 diabetes.

***Methods*:** EMBASE, MEDLINE, and CENTRAL were searched (inception to September 2016) for randomized, double-blind, placebo-controlled trials of at least one year in duration that compared any GLP1RA to placebo in patients with type 2 diabetes. Both authors independently completed the literature search, data extraction, and risk of bias assessment. For each outcome, a Risk Ratio (RR) and 95% Confidence Interval (CI) were calculated using a Mantel-Haenszel random effects model.

***Results*:** Eight trials (three albiglutide, two lixisenatide, two liraglutide, one semaglutide) consisting of 21,135 patients were included. Most patients had, or were at high risk for, cardiovascular disease. Follow-up ranged from 1-3.8 years. Trials contributing the majority of data were deemed to have a low risk of bias. The risk of all-cause mortality was lowered by 11% in patients receiving a GLP1RA (RR 0.89, 95% CI 0.81-0.99). There was no statistically significant difference between groups with respect to cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalizations for heart failure.

***Conclusion*:** GLP1RA therapy when compared to placebo reduced all-cause mortality in high cardiovascular risk patients with type 2 diabetes. They did not impact cardiovascular mortality, nonfatal MI, nonfatal stroke, or heart failure hospitalizations.

Keywords: Glucagon-like peptide-1 receptor agonists, incretins, hypoglycemic agents, liraglutide, cardiovascular diseases, type 2 diabetes mellitus.

1. INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are antihyperglycemic agents indicated in the treatment of type 2 diabetes mellitus [1]. These agents increase glucose-dependent insulin secretion, decrease glucagon secretion, delay gastric emptying, increase satiety, and are administered daily or weekly via a subcutaneous injection. GLP-1 RAs currently approved by the United States Food and Drug Administration (FDA) include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide [2]. GLP-1 RAs have been demonstrated to lower glycosylated hemoglobin (A1c) by approximately 1% [3]. In addition, these agents promote weight loss (ranging from one to four kilograms) and carry a low risk of hypoglycemia. However, gastrointestinal adverse effects, such as nausea, vomiting, and diarrhea, limit their tolerability. Data on clinically relevant outcomes, such as long-term survival and cardiovascular (CV) events, are lacking.

Cardiovascular disease (CVD) is the leading cause of death in patients with type 2 diabetes mellitus [4, 5]. In response to the increase in myocardial infarction (MI) observed with rosiglitazone, in 2008 the FDA published a guidance document for manufacturers of new antidiabetic therapies [6]. This document mandated industry to conduct large non-inferiority trials to assess CV outcomes to ensure that new antidiabetic agents do not cause an unacceptable increase in CV risk.

Several meta-analyses of the effect of GLP-1 RA on CV events have previously been published [7-10]. These analyses did not detect any statistically significant effect of GLP-1 RA on mortality and major adverse CV events in diabetics. However, these publications were limited by the studies included. These studies were of short duration and designed to assess outcomes related to glucose control, which limits the

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ability to detect relevant CV events, as they occurred infrequently and may have been reported inaccurately. Following the aforementioned FDA mandate, further data has become available since these meta-analyses were conducted and further analysis is warranted. The objective of this systematic review and meta-analysis was to assess the effect of GLP-1 RAs on clinically relevant CV endpoints and mortality.

2. MATERIALS AND METHODS

2.1. Search Strategy and Selection Criteria

The following databases were searched using the OVID platform: MEDLINE (1946 to September 2016), EMBASE (1974 to September 2016) and CENTRAL (to August 2016). The following keywords were utilized: *glucagon-like peptide-1*, *albiglutide*, *dulaglutide*, *exenatide*, *liraglutide*, *lixisenatide*, and *semaglutide*. The search was limited to phase 2 or 3 randomized controlled trials conducted in humans with type 2 diabetes mellitus. No language restrictions were applied. Included were prospective, double-blind, randomized trials that compared any GLP-1 RA to placebo and reported at least one outcome of interest, defined as all-cause mortality, CV death, nonfatal MI, nonfatal stroke, or hospitalization due to heart failure. If data for one or more endpoints was not available in the published article or appendices, the corresponding author was contacted via email to request this information. As the aim of this meta-analysis was to assess long-term effects, only trials of one year in duration or longer were included.

2.2. Study Selection and Data Extraction

Two investigators (SCP and ARB) independently performed the systematic search, study selection, data extraction, and assessment of internal validity of each trial using the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled trials [11]. Discrepancies in study selection, risk of bias assessment, and data extraction were resolved by consensus. Publication bias was assessed using a funnel plot if the search identified 10 or more randomized controlled trials.

2.3. Statistical Analysis

Outcome data were entered into Review Manager (version 5.3, Cochrane Collaboration, London, England). For each outcome of interest, a risk ratio (RR) and 95% confidence interval (CI) were calculated using a Mantel-Haenszel random effects model, which was selected to account for potential heterogeneous effects of different GLP-1 RAs. Heterogeneity was quantified using the χ^2 and I^2 statistic, and assessed graphically using a forest plot. Heterogeneity was pre-defined as $p<0.1$ for the χ^2 test. If heterogeneity was detected by the χ^2 test, the degree of heterogeneity was defined as low ($I^2 \leq 25\%$), moderate ($I^2 \leq 50\%$) and high ($I^2 \geq 75\%$) [12]. No prespecified subgroup or sensitivity analyses were planned.

3. RESULTS

The search identified 647 citations, and 359 non-duplicate records were reviewed based on title and/or abstract. Of those, 10 studies were identified and reviewed in full. Two trials were excluded, as they were conducted in non-diabetic patients. Thus, a total of eight randomized controlled trials consisting of 21,135 patients were included [13-20]. Fig. (**1**) depicts the flow diagram of included trials. Study characteristics are described in Table **1**. All randomized controlled trials included patients with type 2 diabetes mellitus—four trials included patients with inadequate glycemic control on first- or second-line therapy [13-16], three trials included patients with established, or at high risk of, CVD [18-20], and one trial included overweight patients [17]. In all trials, the majority of patients continued their pre-existing antidiabetic agents while receiving the intervention (GLP-1 RA) or control (placebo). Three trials assessed albiglutide [14-16], two trials each assessed lixisenatide [13, 18] and liraglutide [17, 19], and one trial investigated semaglutide [20]. Only four trials reported all of the outcomes of interest [17-20]. Data for CV endpoints was not available in four trials, and attempts to obtain this information by contacting the corresponding authors via email went unanswered. Risk of publication bias was not assessed, as there were less than 10 studies included in the quantitative analysis.

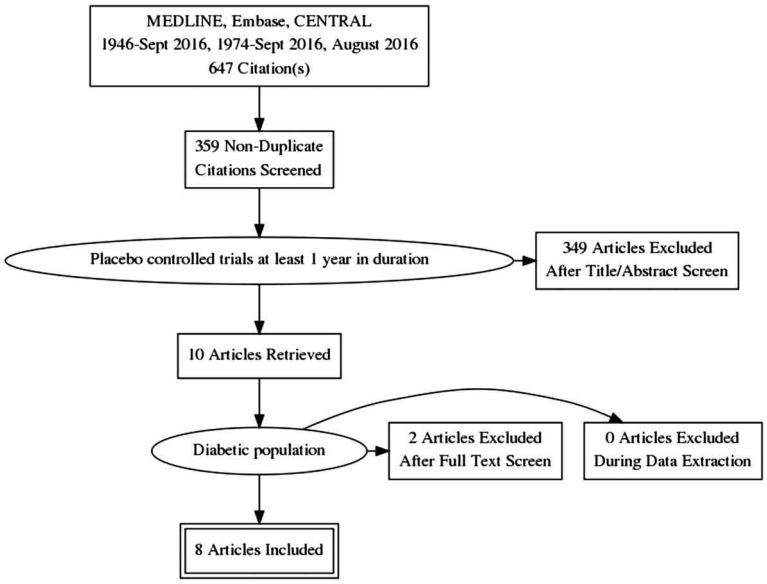

Fig. (1). Study flow diagram.

Table 1. Summary of included trials.

Trial	Year of publication	Population	N	Intervention	Comparator	Duration
GetGoal-F1 [13]	2014	T2DM and A1c 7-10% on metformin	466	Lixisenatide 20 mcg SC daily	Placebo	52 weeks
HARMONY 1 [14]	2014	T2DM and A1c 7-10% on pioglitazone	310	Albiglutide 30 mg SC weekly	Placebo	52 weeks
HARMONY 3 [15]	2014	T2DM and A1c 7-10% on metformin	403	Albiglutide 30 mg SC weekly	Placebo	104 weeks
HARMONY 5 [16]	2015	T2DM and A1c 7-10% on metformin and sulfonylurea	386	Albiglutide 30 mg SC weekly	Placebo	52 weeks
SCALE [17]	2015	T2DM and BMI ≥27 kg/m^2	844	Liraglutide 1.8 mg SC daily	Placebo	56 weeks
ELIXA [18]	2015	T2DM and MI or UA within 180 days	6068	Lixisenatide up to 20 mcg SC daily	Placebo	25 months
LEADER [19]	2016	T2DM and age >50 years with CVD or age >60 years with ≥1 CV risk factor	9340	Liraglutide 1.8 mg SC daily	Placebo	3.8 years
SUSTAIN-6 [20]	2016	T2DM and age >50 years with CVD, CHF or CKD or age >60 years with ≥1 CV risk factor	3297	Semaglutide 0.5 mg or 1 mg SC weekly	Placebo	109 weeks

Abbreviations: A1c=Glycosylated Hemoglobin; BMI=Body Mass Index; CHF=Congestive Heart Failure; CKD=Chronic Kidney Disease; CV=Cardiovascular; CVD=Cardiovascular Disease; MI=Myocardial Infarction; SC=Subcutaneously; T2DM=Type 2 Diabetes Mellitus; UA=Unstable Angina.

3.1. Risk of Bias Assessment

The risk of bias assessment of the included studies is summarized in Fig. (**2**). All trials were double-blind and placebo-controlled. Four larger trials that reported on all outcomes of interest were deemed to be at low risk of bias [17-20], while the remaining smaller trials had a more variable risk of bias [13-16]. Only three trials adequately described allocation concealment [17, 18, 20], and outcome assessment may not have been blinded in three trials [13, 15, 16]. There was no evidence of selective outcome reporting in any of the trials, yet two trials did not report outcome data for all participants [13, 16]. One trial excluded non-adherent patients and reported that some patients were terminated by the sponsor or investigators without providing rationale—this trial was deemed to be at high risk of selection bias [15].

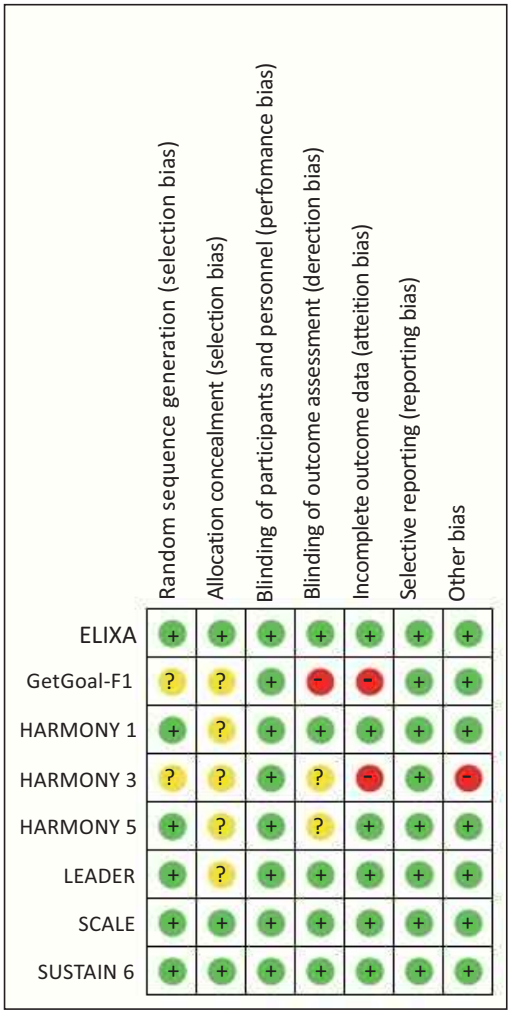

Fig. (2). Risk of bias assessment.

3.2. All-cause Mortality

All eight included trials reported all-cause mortality. Aside from the LEADER trial, there was no statistically significant difference in mortality between GLP-1 RA therapy and placebo. The LEADER trial reported a statistically significant reduction in all-cause mortality in patients receiving liraglutide [19]. In the pooled analysis, all-cause mortality was significantly reduced in patients receiving a GLP-1 RA compared to placebo by a relative 11% (RR 0.89, 95% CI 0.81-0.99, p=0.03). (Fig. **3**) There was no significant heterogeneity among the included data (χ^2 =4.38, p=0.63).

3.3 Cardiovascular Death

Four of the eight trials reported CV death, and the outcome definitions were similar across the trials [17-20]. The LEADER trial [19] demonstrated a significant reduction in CV death with liraglutide; however, the pooled data did not

show a statistically significant reduction in CV death with GLP-1 RAs versus placebo (RR 0.88, 95% CI 0.75-1.03, p=0.12). (Fig. **4**) There was no significant heterogeneity among the included data (χ^2 =2.79, p=0.25).

3.4. Nonfatal MI

Four of the eight trials reported nonfatal MI, and the outcome definitions were approximately consistent across the trials [17-20]. There was no statistically significant reduction in nonfatal MI with GLP-1 RA therapy over placebo observed in any of the individual trials, which was consistent with the pooled analysis (RR 0.92, 95% CI 0.80-1.06, p=0.24) with no significant heterogeneity in the data (χ^2 =3.86, p=0.28) (Fig. **5**).

3.5. Nonfatal Stroke

Four of the eight trials reported nonfatal stroke with a consistent definition across the trials [17-20]. Only the SUSTAIN-6 trial demonstrated a statistically significant reduction in nonfatal stroke with semaglutide [20]. However, the pooled data did not show a statistically significant reduction in nonfatal stroke with GLP-1 RAs versus placebo (RR 0.89, 95% CI 0.72-1.09, p=0.26) (Fig. **6**). There was no significant heterogeneity among the data included (χ^2 =3.57, p=0.31).

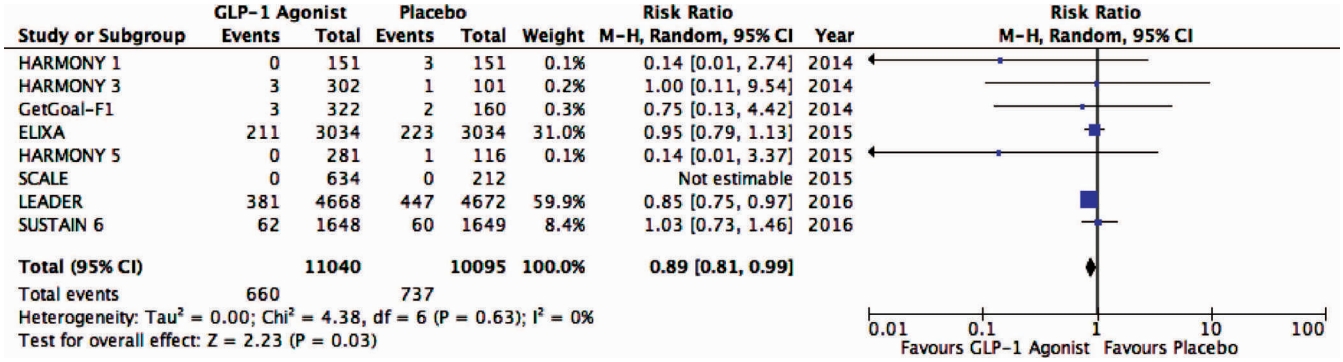

Fig. (3). Forest plot of all-cause mortality.

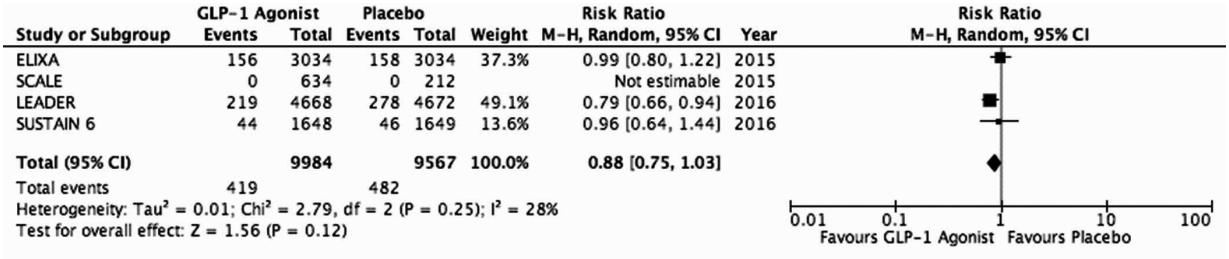

Fig. (4). Forest plot of cardiovascular death.

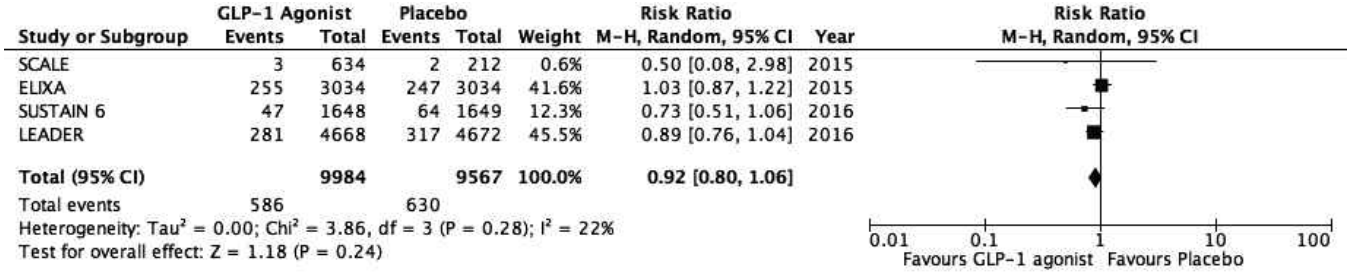

Fig. (5). Forest plot of nonfatal myocardial infarction.

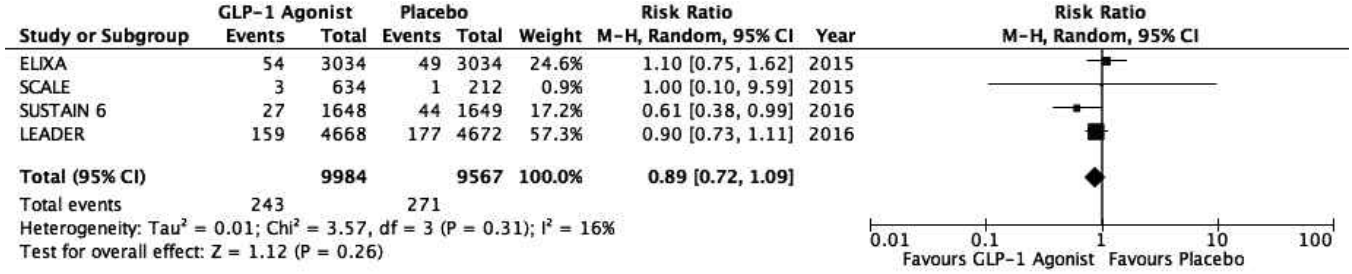

Fig. (6). Forest plot of nonfatal stroke.

3.6. Hospitalizations for Heart Failure

Four of the eight trials reported hospitalizations for heart failure [17-20]; however, the outcome definitions used in these trials were variable. No individual trial demonstrated a statistically significant reduction in hospitalizations for heart failure with GLP-1 RA therapy compared to placebo. This was also observed with the pooled data (RR 0.93, 95% CI 0.81-1.06, p=0.29) with no significant heterogeneity (χ^2=1.21, p=0.75) (Fig. **7**).

3.7. Sensitivity Analysis

A sensitivity analysis was performed using only the data from the three largest trials: LEADER, SUSTAIN-6, and ELIXA [18-20]. The results of the sensitivity analysis were consistent with our primary results for all outcomes, including all-cause mortality (RR 0.89, 95% CI 0.80-0.98, p=0.03). Combining the results with a fixed effects model gave consistent results for all-cause mortality, nonfatal MI, nonfatal stroke, and hospitalizations for heart failure, but demonstrated a significant difference in CV death, which was lower in patients receiving GLP-1 RA therapy (RR 0.86, 95% CI 0.75-0.99, p=0.03).

4. DISCUSSION

The results of this meta-analysis suggest that GLP-1 RAs, as compared to placebo, reduce all-cause mortality in patients with type 2 diabetes mellitus, but do not influence CV death or clinically relevant CV outcomes including nonfatal MI, nonfatal stroke, or hospitalizations for heart failure. The majority of the data was derived from large, well-designed randomized controlled trials that were deemed to be at low risk of bias using the Cochrane Collaboration tool. Pooling of the data from each individual trial was deemed to be appropriate, as there was no statistical heterogeneity in any of the analyses.

This is the first meta-analysis of GLP-1 RAs to demonstrate a reduction in all-cause mortality. The findings differ from previous meta-analyses, as it is the first to include the recently published large, randomized control trials assessing the impact of GLP-1 RA on all-cause mortality and CV events. Otherwise, this analysis is methodologically similar to previous analyses [7-9].

It is interesting that the reduction in all-cause mortality was not accompanied by a reduction in CV mortality in our primary analysis. This finding may be explained by a lack of power to detect a statistically significant reduction in CV death, lack of accurate reporting of CV events, or that GLP-1 RAs prolong survival by a non-CV mechanism. The exact mechanism by which GLP-1 RAs may reduce mortality is otherwise unclear, as CV events are the primary cause of death in patients with type 2 diabetes mellitus. In the LEADER and ELIXA trials, there was no significant difference in non-CV mortality [18, 19]. The observed reduction in all-cause mortality does not appear to be related to cancer. While there were significantly fewer patients with prostate cancer or leukemia in the liraglutide group of the LEADER trial, there was a numerically higher (though not statistically significant) incidence of total neoplasms with liraglutide compared to placebo [19]. As well, in the ELIXA and SUSTAIN-6 trials, there was a numerically higher rate of neoplasm with lixisenatide and semaglutide, respectively, compared to placebo [18, 20]. In contrast to the primary analysis, a statistically significant reduction in CV mortality was observed in the sensitivity analysis using a fixed effects model. Given these findings, further long-term studies are required to clearly establish the effect of GLP-1 RAs on CV mortality.

Despite the incongruent findings regarding CV mortality, a reduction in all-cause mortality is perhaps the most robust and meaningful clinical outcome. This is because it is a high priority for almost all patients with diabetes, and the outcome definition cannot vary between trials. Few antidiabetic agents have been shown to reduce all-cause mortality. Formerly, metformin was the only antidiabetic agent to reduce all-cause mortality in patients with type 2 diabetics mellitus [21]. However, a recently published randomized controlled trial demonstrated a reduction in all-cause mortality in patients at high CV risk with the sodium-glucose transport protein 2 inhibitor empagliflozin [22]. This trial also found a statistically significant reduction in death from CV causes in the patients receiving empagliflozin.

Given the current body of evidence for treatment of type 2 diabetes mellitus and the results of this analysis, it is reasonable to consider GLP-1 RAs in addition to first-line therapy, particularly for patients at high CV risk. However, as the long-term safety of these agents has yet to be clearly established, further pharmacovigilance data is required before the agents can be considered first-line.

GLP-1 RA therapy was not found to effect nonfatal MI, nonfatal stroke, or hospitalizations for heart failure. One could consider these findings reassuring given the concern about the CV safety of other incretin agents, specifically dipeptidyl peptidase-4 inhibitors and the risk of hospitalizations heart failure [23]. In the present meta-analysis, heart failure hospitalizations were neither decreased nor increased. It should be noted that although the definitions for heart failure hospitalizations were different among the four included

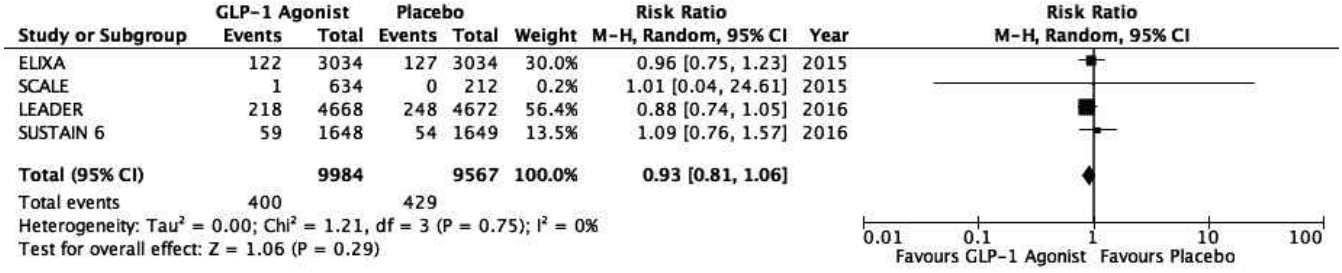

Fig. (7). Forest plot of hospitalizations for heart failure.

trials, they were deemed to be similar enough to allow for a combined quantitative analysis.

There are several limitations to this meta-analysis that warrant discussion. First, only four of the eight included trials reported CV outcomes. Attempts were made to obtain this data from the other four trials, but were unsuccessful. However, our analysis included over 21,000 patients and 1730 cardiovascular events. Furthermore, all of the included trials were well-designed, and our outcomes of interest were clinically significant with a low risk of inappropriate or missing adjudication. Second, the trial populations included in this meta-analysis were heterogeneous with respect to their CV risk, though the majority of patients had established, or were at high risk for, CVD. It is not unreasonable to extrapolate these results to younger, healthier patients with type 2 diabetes mellitus acknowledging that the absolute risk reduction in all-cause mortality would likely be lower due to their lower baseline risk. Third, this meta-analysis assumes that GLP-1 RAs as a class have a consistent impact on the outcomes of interest, despite the variability in the pharmacokinetics and pharmacodynamics of these agents. However, the lack of heterogeneity observed among the outcomes supports this assumption. Fourth, the trials varied in size. The LEADER and ELIXA trials included 9340 and 6068 patients, respectively, which far exceeded any of the other included trials. For this reason, the results of this meta-analysis were largely driven by the results of these two trials. We also acknowledge that the short duration of the included trials (1-4 years) limits our ability to appreciate the long-term effects of GLP-1 RA agonist therapy on CV events and mortality. Finally, this meta-analysis does not address the non-CV safety of GLP-1 RAs, which have been associated with adverse pancreatic and thyroid conditions [24]. These outcomes were not investigated to avoid performing multiple statistical analyses, which would have increased the risk of a chance finding.

There are currently two randomized, placebo-controlled trials underway investigating the CV safety of once weekly GLP-1 RA therapy in patients with type 2 diabetes mellitus. The EXSCEL trial (NCT01144338) is investigating exenatide [25], and the REWIND trial (NCT01394952) is investigating dulaglutide [26]. The primary outcome of both trials is a composite of CV death, nonfatal MI, and nonfatal stroke. Both trials are estimated to be completed in 2018.

CONCLUSION

This analysis supports that GLP-1 RAs reduce all-cause mortality in patients with type 2 diabetes at high CV risk, as compared to placebo. However, they did not reduce the rates of CV death, nonfatal stroke, nonfatal MI, or hospitalizations for heart failure. Further long-term studies are required to clearly establish the effect of GLP-1 RA on CV endpoints.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICTS OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Frias JP, Edelman SV. Incretins and their role in the management of diabetes. Curr Opin Endocrinol Diabetes Obes 2007; 14: 269-76.

[2] United States Food and Drug Administration. Drugs@FDA website. Accessed on: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. [Cited: 26th Sept 2016]

[3] Trujilo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. Ther Adv Endocrinol Metab 2015; 6(1): 19-28.

[4] American Diabetes Association. 5. Glycemic targets. Diabetes Care 2016; 39(Suppl 1): S39-S46.

[5] Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013; 37(suppl 1): S1-S212.

[6] United States Food and Drug Administration. FDA guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Accessed on: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. [Cited 8th Aug 2016].

[7] Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes, Obes Metab 2014; 16(1): 38-47.

[8] Monami M, Cremasco F, Lamanna C, *et al*. Glucagon-like peptide-1 receptor agonists and cardiovascular events: A meta-analysis of randomized clinical trials. Exp Diabetes Res 2011; 2011: 215764.

[9] Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. Eur J Endocrinol 2009; 160: 909-17.

[10] Fischer M, Petrie MC, Ambery PD, Donaldson J, Ye J, McMurray JJV. Cardiovascular safety of albiglutide in the Harmony programme: A meta-analysis. Lancet Diabetes Endocrinol 2015; 3(9): 697-703.

[11] Higgins JP, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.

[12] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.

[13] Bolli GB, Munteanu M, Dotsenko S, *et al*. Efficacy and safety of lixisenatide once daily *vs.* placebo in people with type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabet Med 2014; 31: 176-84.

[14] Reusch J, Stewart MW, Perkins CM, *et al*. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. Diabetes Obes Metab 2014; 16(12): 1257-64.

[15] Ahren B, Johnson SL, Stewart M, *et al*. HARMONY 3: 104-week randomized, double-blind, placebo-and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care 2014; 37(8): 2141-8.

[16] Home PD, Shamanna P, Stewart M, *et al*. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes taking metformin and glimerpiride: HARMONY 5. Diabetes Obes Metab 2015; 17(2): 179-87.

[17] Davies MJ, Bergenstal R, Bode B, *et al*. Efficacy of liraglutide for weight loss among patient with type 2 diabetes. JAMA 2015; 314(7): 687-99.

[18] Pfeffer MA, Clagget B, Diaz R, *et al*. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015; 373(23): 2247-57.

[19] Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375(4): 311-22.

[20] Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375: 1834-44.

[21] UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352(9131): 854-65.

[22] Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. N Engl J Med 2015; 373(22): 2117-28.

[23] Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. Cardiovasc Ther 2014; 32(4): 147-58.

[24] Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011; 10: CD006423.

[25] Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus. Clinical Trials. gov website. https://clinicaltrials.gov/ct2/show/NCT01144338. (Accessed on: October 7, 2016).

[26] Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01394952. [Cited 7th Oct 2016].