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Title: Cardiovascular, mortality and renal outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes - a systematic review and meta-analysis of randomised trials

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Abstract: Background: Several glucagon-like peptide-1 (GLP-1) receptor agonists have been tested in clinical trials in patients with type 2 diabetes with different patient populations, cardiovascular outcomes and duration of follow-up. We planned a systematic review and meta-analysis of these trials, examining cardiovascular death, atherothrombotic cardiovascular events, heart failure, and death from any cause, as well as renal and key safety outcomes.
Methods: PubMed, Medline and the Cochrane central register of controlled trials were searched for eligible trials reporting major adverse cardiovascular events (MACE) i.e. cardiovascular death, stroke or myocardial infarction up to June 15, 2019. A meta-analysis was performed using a random-effects model to estimate overall hazard ratios (HR) for MACE, its components , death from any cause, hospital admission for heart failure, renal outcomes and key safety outcomes (severe hypoglycaemia, pancreatitis and pancreatic cancer). We also examined MACE in several patient subgroups based on patient population , glycated haemoglobin, trial duration, treatment dosing interval and structural homology.
Findings: Of 27 publications screened, 7 trials using GLP-1 receptor agonists, with a total of 56,006 patients, fulfilled the prespecified criteria and were included. Overall, GLP-1 receptor agonist treatment reduced MACE by 12% (HR 0.88; 95% CI 0.82, 0.94, p<0.001). There was no statistically significant heterogeneity across the subgroups examined.

GLP-1 receptor agonist treatment reduced all-cause mortality by 12% (0.88; 0.83, 0.95, p=0.001), hospital admission for heart failure by 9% (0.91; 0.83, 0.99, p=0.028) and a broad renal composite by 17% (0.83; 0.78, 0.89, p<0.001). There was no increase in risk of severe hypoglycaemia, pancreatitis or pancreatic cancer.
Interpretation: GLP-1 receptor agonists reduced 3-component MACE, its individual components, all-cause mortality, risk of hospitalization for heart failure and worsening renal function (due mainly to reduction in

urinary albumin excretion) in patients with type 2 diabetes. There was no increase in risk of severe hypoglycaemia or pancreatic adverse effects.

Title: **Cardiovascular, mortality and renal outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes – a systematic review and meta-analysis of randomised trials**

Running title GLP-1 receptor agonists and CV outcomes

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ABSTRACT

Background: Several glucagon-like peptide-1 (GLP-1) receptor agonists have been tested in clinical trials in patients with type 2 diabetes with different patient populations, cardiovascular outcomes and duration of follow-up. We planned a systematic review and meta-analysis of these trials, examining cardiovascular death, atherothrombotic cardiovascular events, heart failure, and death from any cause, as well as renal and key safety outcomes.

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Interpretation: GLP-1 receptor agonists reduced 3-component MACE, its individual components, all-cause mortality, risk of hospitalization for heart failure and worsening renal function (due mainly to reduction in urinary albumin excretion) in patients with type 2 diabetes. There was no increase in risk of severe hypoglycaemia or pancreatic adverse effects.

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Keywords: diabetes, GLP-1 receptor agonists, MACE, heart failure

RESEARCH IN CONTEXT

Evidence before this study

Glucagon-like peptide-1 (GLP-1) receptor agonists effectively decrease glycated haemoglobin (HbA1c) in patients with type 2 diabetes mellitus. A variety of agents of this class with differing structures and durations of action have been studied in randomised placebo-controlled trials of varying size and with different patient populations and effects on cardiovascular outcomes. In light of these differences, we conducted a meta-analysis of all large placebo-controlled GLP-1 receptor agonist trials to obtain robust estimates on the effect of this class of agent on a range of cardiovascular and renal endpoints, and patient subgroups.

Medline (via PubMed) and the Cochrane Controlled Register of Trials (up to 15 June 2019) were searched for trials comparing a GLP-1 receptor agonist to placebo in >500 patients and reporting a primary outcome including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke using the search terms "glucagon-like peptide-1 receptor agonists", "cardiovascular mortality", "myocardial infarction", "stroke" and "heart failure", "exenatide", "liraglutide", "semaglutide", "albiglutide", "dulaglutide", "placebo", and "randomized clinical trial". 7 trials were identified; ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (extended release exenatide), Harmony Outcomes (albiglutide), REWIND (dulaglutide) and PIONEER 6 (oral semaglutide).

Added value of this study

GLP-1 receptor agonists reduce all-cause mortality, the composite of cardiovascular death, myocardial infarction and stroke (MACE), each of the components of this outcome, hospital admission for heart failure and a composite renal outcome of worsening of estimated glomerular filtration rate (eGFR), end stage renal disease, death attributable to renal causes, or new onset macroalbuminuria (data not available in Harmony Outcomes and PIONEER 6 for the latter two outcomes). The benefit on MACE was consistent across all but one subgroup (with a suggestion of less effect of exendin 4 based compounds). The incidence of severe

hypoglycaemia, pancreatitis and pancreatic cancer did not differ between GLP-1 receptor agonist treatment and placebo. The present meta-analysis is the largest pooled study of the effect of GLP-1 RA on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus. Furthermore, compared to previous meta-analyses, it includes a greater number of patients without established cardiovascular disease, a new agent within this class of glucose lowering agents (dulaglutide) and an oral formation of an agent previously only available as a subcutaneous injection (semaglutide).

Implications of all the available evidence

The cardioprotective effects of GLP-1 receptor agonists in patients with established cardiovascular disease and the reduction in risk of heart failure and worsening renal function represent an important treatment opportunity to reduce morbidity and mortality in patients with type 2 diabetes mellitus.

INTRODUCTION

Prevention of non-fatal and fatal cardiovascular events is a key goal of the management of patients with type 2 diabetes mellitus.[1,2] In addition to blood pressure and cholesterol-lowering therapies, two of the newer classes of anti-hyperglycaemic agents also reduce cardiovascular risk. One of these, the glucagon-like peptide-1 (GLP-1) receptor agonists, decrease glycated haemoglobin (HbA1c) by stimulating glucose-dependent insulin secretion and by reducing glucagon secretion, gastric emptying and appetite.[3,4] GLP-1 receptor agonists also lead to modest improvements in lipids, reductions in blood pressure and weight, and carry a low risk of hypoglycaemia. Agents in this class, however, differ in structure and duration of action and have been studied in trials of varying size and with different patient populations and in individual trials the effects on cardiovascular outcomes have not been consistent.[5-15] In view of this we conducted a meta-analysis of all the large placebo-controlled GLP-1 receptor agonist trials, to obtain robust estimates of the effect of this class of agents on different cardiovascular endpoints and patient subgroups. We have also examined renal outcomes and key safety endpoints. Such a systematic review is helpful in supporting guideline recommendations on use of glucose lowering therapies to reduce macrovascular and renal outcomes in adults with type 2 diabetes.[1,2]

METHODS

Search strategy and study selection: We identified published randomised placebo-controlled trials (RCTs) testing GLP-1 receptor agonists in patients with type 2 diabetes (Appendix Table 1). Both injectable and oral agents were included. We further restricted the search to trials with a primary outcome including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Medline (via PubMed), and the Cochrane Controlled Register of Trials (Up to 15 June 2019) was searched with the search terms including "glucagon-like peptide-1 receptor agonists", "cardiovascular mortality", "myocardial infarction", "stroke" and "heart failure", "exenatide", "liraglutide", "semaglutide", "albiglutide", "dulaglutide", "placebo", and "randomized clinical trial". We restricted our search to trials including >500 patients. Included trials were assessed for bias using the Cochrane Risk of Bias Tool (Appendix Table 2). A Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart detailing the selection process is presented in Figure 1.

Data extraction: Data were extracted by SLK and RR, with conflicts over study inclusion resolved by consensus.

Selection of outcomes: Cardiovascular outcomes of interest were major adverse cardiovascular events (MACE), a composite outcome comprised of cardiovascular death, myocardial infarction and stroke, each of the components of this outcome, hospital admission for heart failure and death from any cause. Renal and safety outcomes were also examined. Two renal outcomes were examined, as reported previously: a narrower composite consisting of worsening of estimated glomerular filtration rate (eGFR), and a broader one which included end-stage kidney disease, death due to kidney disease and new onset macroalbuminuria (Appendix Table 3). The four key safety outcomes of interest were severe hypoglycaemia, retinopathy, pancreatitis and pancreatic cancer

(Appendix Table 4). We also examined thyroid cancer (Appendix Table 5). In all 7 trials, local investigators were encouraged to manage participants in accordance with local guidelines (and could use most non-study glucose lowering treatments as desired). In 6 of the 7 trials, the mean between-treatment group difference in HbA1c was in the range 0.3% and 0.7%. We compared treatment effect in the following subgroups: primary versus secondary prevention, higher versus lower baseline HbA1c concentration (see footnote to Figure 3 for details), longer versus shorter duration of follow-up, drug-dosing daily versus weekly, human GLP-1 homology, body mass index <30 versus ≥30, age <65 years versus ≥65 years, baseline eGFR <60 vs ≥60 mL/min/m^2. All outcomes were adjudicated with the exception of severe hypoglycaemia, and event definitions for each trial are listed in the Appendix (Tables 1,3,4).

Data analysis: Summary statistics from the individual trials included were used, as individual level data were not available. HRs and 95% CIs from the trial papers, supplementary appendix or secondary publications were used. Estimates from each study were combined by use of inverse variance-weighted averages of logarithmic hazard ratios (HR) in random-effects analysis. Inter-study heterogeneity was assessed using the I^2 index and Cochran´s Q test. I^2 index values lower than 25% indicated low, 26-50% moderate and more than 50% high degree of heterogeneity, and Cochran´s Q statistic $p<0.05$ were considered indicators for significant heterogeneity. Number needed to treat (NNT) was calculated using the method of Altman and Andersen, and median duration of follow-up was estimated by a weighted average.[16]. The fragility index, the minimum number of events needing to change from a non-event to an event in order to render a significant result non-significant, was calculated for 3-component MACE outcomes using the method described by Walsh et al. (Appendix Table 6).[17] Interactions between treatment and subgroups were

examined using a test for heterogeneity, using $p<0.1$ as significant. All analyses were performed separately using Stata version 14 (Stata Corp. College Station, Texas, USA).

Role of the funding source: The study was planned and conducted by members of the Metabolic and Diabetes Research Group and Heart Failure research Group at the University of Glasgow (KFD, PSJ, MCP, NS and JJVMcM), the Department of Cardiology, Rigshospitalet University Hospital, Copenhagen (SLK, RR, LK) and the Nuffield Department of Public Health at the University of Oxford (DP) using institutional funds. No external funder was involved in the study.

RESULTS

Of 27 articles screened for eligibility, 7 trials with 56,006 patients were included in the meta-analysis (Figure 1). In order of reporting, these were: The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER), the preapproval Trial to Evaluate Cardiovascular and Other Long-term outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes), Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND), and a trial investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes (PIONEER 6).[6-14] All included trials were assessed for bias using the Cochrane risk of bias tool. The trials were assessed as high quality with a low risk of bias (Appendix, Table 2). The key trial and patient characteristics at baseline are presented in Tables 1 and Appendix Table 1.

All trials were of substantial size (>3000 patients). ELIXA enrolled patients with a recent acute cardiovascular syndrome whereas all other trials included patients with stable cardiovascular disease, cardiovascular risk factors or both. All trials, except ELIXA, had MACE as the primary endpoint; in ELIXA an expanded composite including hospitalization for unstable angina was used. Lixisenatide (ELIXA), liraglutide (LEADER), and oral semaglutide (PIONEER 6) were each administered daily, whereas the remaining GLP-1 receptor agonists were administered once weekly. PIONEER 6 differed from the remaining trials in that semaglutide was taken orally, compared with subcutaneous administration of the treatments used in the remaining studies.

Mean age at baseline ranged from 60 years in ELIXA to 66 years in PIONEER 6 and REWIND. The highest proportion of women was included in REWIND (46% compared with between 31 and 39% in the remaining trials). The proportion of patients with established cardiovascular disease at baseline ranged from 100% in ELIXA and Harmony Outcomes to 31% of those in REWIND (Table 1). Kidney function was similar across trials (with median estimated glomerular filtration rate ranging from 74 to 80 ml/min/m^2). Median HbA1c was lowest in REWIND and ELIXA (7.1% and 7.7%, respectively) and highest, at 8.7%, in LEADER, SUSTAIN-6 and Harmony Outcomes. REWIND had the lowest proportional use of insulin at baseline (24% compared with 39-61% in remaining trials). The median length of follow-up ranged from 1.3 years in PIONEER 6 to 5.4 years in REWIND; the estimated median follow-up was 3.2 years (Appendix Table 1). Treatment discontinuation and loss to follow-up is summarised in Appendix Table 7.

In the pooled analysis, treatment with a GLP-1 receptor agonist led to a 12% relative risk reduction in MACE (HR 0.88; 95% CI 0.82, 0.94; p<0.001) [Figure 2]. The NNT was 75 (95% CI 50, 151) over an estimated median follow-up of 3.2 years and the fragility index, overall, was 202 (Appendix Table 6). When assessing the components of the composite MACE endpoint separately, GLP-1 receptor agonist use led to a reduction in risk of death from cardiovascular causes (HR 0.88 95% CI 0.81, 0.96; p=0.001), fatal- or non-fatal stroke (HR 0.84; 95% CI 0.76, 0.93; p<0.001), and fatal or non-fatal MI (HR 0.91; 95% CI 0.84, 1.00; p=0.043) [Figure 2].

In subgroup analyses there was no statistical heterogeneity between the effect of a GLP-1 receptor agonist in “primary prevention” patients (those without established cardiovascular disease) and those with cardiovascular disease at baseline: HR 0.95 (95% CI 0.83, 1.08) for “primary prevention” and 0.86 (0.79, 0.94) for “secondary prevention” , p for interaction=0.22. Similarly, we found no heterogeneity for the effect of GLP-1 receptor agonist therapy when examined by baseline HbA1c (“low” compared with “high” median HbA1c), shorter compared with longer trial follow-up

(<3 years vs. ≥3 years median follow-up), drug dosing interval (daily compared with weekly dosing), reflecting duration of drug action. The one possible exception was the comparison of exendin 4-based compounds (lixisenatide and exenatide) and agents more homologous with human GLP-1 (all other drugs studied); this analysis suggested heterogeneity: HR 0.95 (95% CI 0.85, 1.06) for exendin 4-based, compared with 0.84 (0.79, 0.90) for GLP-1-based, p-value for interaction=0.06 (Figure 3).

Compared with placebo, treatment with a GLP-1 receptor agonist reduced the risk of death from any cause by 12% (HR 0.88; 95% CI 0.83, 0.95; p=0.001), giving a NNT of 108 (77, 260) [Figure 4].

The risk of HF hospitalization was also reduced in GLP-1 receptor agonist treated patients, by 9% (HR 0.91; 95% CI 0.83, 0.99; p=0.028), giving a NNT of 311 (164, 2797) [Figure 4].

Renal events were not available for Harmony Outcomes or PIONEER 6. Treatment with a GLP-1 receptor agonist reduced the broader composite renal outcome of worsening renal function, end-stage renal disease and renal death, including development of macroalbuminuria, by 17% (HR 0.83, 95% CI 0.78, 0.89) with a NNT of 62 (48, 96). There was a 13% reduction (HR 0.87, 0.73, 1.03) in the narrower worsening renal function outcome which was of borderline statistical significance; the corresponding NNT was 245 (118, -1064) (Figure 4).

The incidence of severe hypoglycaemia, pancreatitis and pancreatic cancer did not differ between GLP-1 receptor agonist treatment and placebo (Appendix Figure 1). The incidence of retinopathy did not differ between GLP-1 receptor agonist treated and placebo treated patients, but this outcome was not defined consistently among the trials (Appendix Figure 1). The rate of thyroid carcinoma was low and did not differ between the active treatment and placebo groups (Appendix Table 5).

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DISCUSSION

The present meta-analysis includes 13,084 (30%) more patients, 1394 (29%) more MACE endpoints, 1818 (95%) more renal events and approximately 56,000 more years of patient exposure than the largest prior study of this type.[18,19] The present report also includes 6709 (95%) more "primary prevention" patients (i.e. with cardiovascular risk factors rather than established cardiovascular disease), one additional agent in the class i.e. dulaglutide with homology to human GLP-1 and a long duration of action, and a novel oral formulation of semaglutide which was administered by sub-cutaneous injection in a previous trial.

Three-component MACE, the primary endpoint in 6 of the 7 trials, was reduced by 12%, reflecting a beneficial effect on death from cardiovascular causes (relative risk reduction 12%), as well as a reduction in risk of stroke (16% relative risk-reduction in fatal and non-fatal stroke). The reduction in myocardial infarction (9% relative risk-reduction in fatal and non-fatal myocardial infarction) was less robust though directionally concordant. The NNT for MACE was 75 (95% CI 50, 151) over an estimated median duration of follow-up of 3.2 years. The relative risk reduction in MACE in a recent sodium-glucose co-transporter 2 (SGLT2) inhibitor meta-analysis was 11 (4-17)% and the NNT 97 (63, 266) over an estimated median follow-up of 3.3 years, although this comparison should be made cautiously as it does not take account of differences in the patient populations studied.. The hazard ratio for death from any cause in GLP-1 receptor agonist trials was 0.88 (95% CI 0.83-0.95) and NNT 108 (77, 260); in the SGLT2 inhibitor meta-analysis the corresponding HR was 0.85 (95% CI 0.78-0.93) and NNT 101 (69,216).[20]

We undertook several subgroup analyses to address the explanations proposed for the different effects on cardiovascular outcomes observed among the various GLP-1 receptor agonist trials. These include differences in the specific molecule tested, in the patients randomized, and in the duration of follow-up. Albiglutide, dulaglutide, liraglutide, and semaglutide are more similar, structurally, to native GLP-1 whereas exenatide and lixisenatide are based, structurally, on exendin-4.[21,22] Duration of treatment effect also differs markedly between the agents studied, although this does not reflect structural homology, with some GLP-1 receptor agonists of each type having a short pharmacologic half-life (e.g. lixisenatide 2-3 hours and liraglutide 12 hours) and others a long half-life (e.g. dulaglutide 120 hours and subcutaneous semaglutide 170 hours), or available as a sustained release formulation (exenatide), reflected in daily versus weekly dosing.[23] The oral formulation of semaglutide used in PIONEER 6 required daily dosing. With the seven trials now available it was possible to examine whether these pharmacological characteristics, and their permutations, influence treatment efficacy. While duration of drug action did not seem to modify the treatment-effect, there was a suggestion of an interaction related to chemical structure, with a possibly smaller effect on MACE of agents based on exendin-4. This apparent interaction could be unduly influenced by ELIXA, which was unique in recruiting patients with a recent acute coronary syndrome (and also used a very short-acting agent, administered once daily), poor adherence in EXSCEL (40% permanent treatment discontinuation) or may be a chance finding. The ongoing Efpeglenatide on Cardiovascular Outcomes trail (AMPLITUDE-O - ClinicalTrials.gov unique identifier: NCT03496298), using a long-acting exendin-4 based GLP-1 receptor agonist in patients with established cardiovascular disease or cardiovascular risk factors will provide more evidence on this question.

The difference in patient population enrolled in the various GLP-1 receptor agonist trials has also been considered a potential explanation for the difference in outcomes among the studies.[24] In particular, the lack of clear reduction in the primary MACE endpoint in EXSCEL has been attributed to the higher proportion of patients without established cardiovascular disease randomized in that trial, compared with the preceding GLP-1 receptor agonists trials. The inclusion of PIONEER 6 and, especially, REWIND allowed us to examine this question, with an almost doubling in the number of "primary-prevention" patients, overall, exposed to a GLP-1 receptor agonist, although even with this, the number of participants with MACE in this subgroup was less than a third of that in most other subgroups. Consequently, this analysis may still be under powered and, although there was no heterogeneity for the effect of GLP-1 receptor agonist treatment, the statistical test for interaction is weak. Therefore we cannot be certain that the relative risk reduction in "primary prevention" patients was the same as in "secondary prevention" patients and even if it was, the absolute risk reduction in the "primary prevention" population will be smaller, and the treatment likely to be less cost-effective, because individuals without established cardiovascular disease are at lower baseline risk than "secondary prevention" patients. These additional data may, therefore, not be sufficiently robust to challenge the new guideline recommendations only to use GLP-1 receptor agonists in patients with established cardiovascular disease.[1,2]

Duration of follow-up was a further potential explanation for difference discrepancy in trial outcomes, with, for example, the much shorter follow-up in ELIXA (median 2.1 years) than LEADER (median 3.8 years) highlighted as an important difference between the first two large outcome trials with a GLP-1 receptor agonist. However, duration of follow-up did not seem to modify the benefit of treatment on the composite MACE outcome.

Two of the other subgroups merit discussion. The effect of GLP-1 receptor agonist treatment was consistent according to age and renal function. Because older age and lower eGFR were associated with higher rates of MACE, the absolute benefit was larger in these individuals.

This updated meta-analysis also shows for the first time that treatment with a GLP-1 receptor agonist reduces the risk of heart failure hospitalization, although the reduction in risk was small in relative (9%, 95% CI 1-17%) and absolute (NNT 311; 95% CI 164, 2797) terms and was not statistically robust. This effect was also, clearly, much smaller than seen with SGLT2 inhibitors, which showed a relative risk reduction of 31 (21-39)% and a NNT of 100 (79, 147) over a similar median duration of follow-up (3.2 vs 3.3 years). Nevertheless, a GLP-1 receptor agonist may be an alternative in a patient with heart failure (or renal impairment) who cannot take a SGLT2 inhibitor.[20] The explanation for why GLP-1 receptor agonists should reduce this endpoint is not clear, especially as these agents has not demonstrated any benefit in trials in patients with established heart failure with reduced ejection fraction.[25,26] One possibility is that this favourable effect in the meta-analysis is secondary to reduction in myocardial infarction, a common precursor of heart failure. In this context, is notable that the largest reductions in heart failure were in the two trials (Harmony Outcomes and LEADER) with the greatest reduction in myocardial infarction. This hypothesis, however, needs further investigation, for example with examination of the time sequence of cardiovascular events in individual patients.

It is clear, overall, that GLP-1 receptor agonists are cardioprotective agents. The time course of their effects, apparent in the individual trials, and the types of cardiovascular events prevented suggest that GLP-1 receptor agonists have primarily an anti-atherothrombotic effect. This profile is distinct from the SGLT 2 inhibitors which exhibit an effect much more rapidly and which is more

pronounced on heart failure, raising the possibility of therapeutic synergy from the combination of these two classes of drug.[27]

This may also be true for renal outcomes. While we found that GLP-1 receptor agonists clearly reduced the risk of worsening of kidney function when assessed using a composite outcome driven by an increase in urinary albumin excretion, the benefit on a composite including a significant decline in eGFR (or increase in creatinine) was less clear, of borderline statistical significance and not as pronounced as seen with SGLT2 inhibitors.[18,27] The relative risk reduction in the "harder" renal endpoint in the three large, broadly inclusive, SGLT2 inhibitor trials was 45 (36-52)% with a NNT of 79 (69, 99), compared with 13 (27-+3)% and 245 (118, -1064) in the present meta-analysis.[18]

Lastly, this meta-analysis suggests that prior concerns about pancreatitis and pancreatic cancer with GLP-1 receptor agonists seem unfounded and there was also no increase in risk of severe hypoglycaemia. We also so no overall increase in adverse eye-outcomes, although these were inconsistently defined in the trials, a deficit that should be remedied in future studies. The outcomes reported did not require systematic eye examination and this too is required for a full understanding of the effect of any glucose-lowering therapy on eye health. A dedicated trial of this type is currently underway with semaglutide (FOCUS - ClinicalTrials.gov unique identifier: NCT03811561). Our study has other limitations, including lack of patient-level data, restriction of subgroup analyses to the primary 3-component MACE endpoint, and ability to examine only the secondary endpoints and adverse events of special interest reported by the investigators of the trials included.

In conclusion, in this meta-analysis, we show that in patients with type 2 diabetes, GLP-1 receptor agonists reduced 3-component MACE, its individual components of, all-cause mortality and risk of hospitalization for heart failure. Treatment with a GLP-1 receptor agonist also reduces the risk of worsening renal function, due mainly to a decrease in development of macroalbuminuria. These benefits were obtained without an increase in risk of severe hypoglycaemia, pancreatic adverse effects, or thyroid cancer.

Contributors:

Data extraction was carried out by RR and SLK and the analyses were conducted by SLK and replicated by KFD, supervised by PSJ. All authors were involved in data interpretation, manuscript writing or editing. All authors had full access to all data required to complete the analysis and agreed to submit the study for publication.

Declaration of interest:

SLK, RR, KFD, LK report no conflict of interest. NS has consulted for AstraZeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Napp Pharmaceuticals, and Sanofi, and has received grant support from Boehringer Ingelheim. DP is an investigator on the EMPA-KIDNEY trial (investigating SGLT2 inhibition in patients with chronic kidney disease), funded by a grant from Boehringer Ingelheim to the University of Oxford, but he obtains no salary support from the grant; CTSU, University of Oxford has a staff policy of not accepting honoraria or consultancy fees from industry. PSJ has received advisory board or speaker fees from Novartis, Boehringer Ingelheim and Cytokinetics, research grants from Boehringer Ingelheim. His employer, the University of Glasgow, has received payment for his work on trials sponsored by AstraZeneca. MCP reports consultancy for Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Napp Pharmaceuticals and Eli Lilly. JJVMcM's employer, the University of Glasgow, has been paid by Abbvie, Amgen, AstraZeneca,

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Table 1: Baseline characteristics and use of glucose lowering agents across trials

	ELIXA n=6068	LEADER n=9340	SUSTAIN-6 n=3297	EXSCEL n=14752	HARMONY n=9463	REWIND n=9903	PIONEER 6 n=3183
Drug studied	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide
Structural basis	Exendin-4 based	Human GLP-1 based	Human GLP-1 based	Exendin-4 based	Human GLP-1 based	Human GLP-1 based	Human GLP-1 based
Administration route	subcutaneous	subcutaneous	subcutaneous	subcutaneous	subcutaneous	subcutaneous	oral
Dose	20 ug/day	1.8 mg/day	0.5 or 1 mg/week	2 mg/week	30 or 50 mg/week	1.5 mg/week	14 mg/day
Age, mean – years	60±10	64±7	65±7	62±9	64±7	66±7	66±7
Female sex, no. (%)	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)	2894 (31%)	4589 (46%)	1007 (32%)
BMI (kg/m^2)	30.1±5.6	32.5±6.3	32.8±6.2	32.7±6.4	32.3±5.9	32.3±5.7	32.3±6.5
Caucasian	4576 (75%)	7238 (78%)	2736 (83%)	11175 (76%)	6583 (70%)	7498 (76%)	2300 (72%)
Diabetes duration, years	9.2±8.2	12.8±8.0	13.9±8.1	13.1±8.3	14.2±8.8	10.6±7.2	14.9±8.5
HbA1c (%)	7.7±1.3	8.7±1.6	8.7±1.5	8.1±1.0	8.7±1.5	7.3±1.1	8.2±1.6
Proportion with CVD	6068 (100%)	7598 (81%)	2735 (83%)	11175 (76%)	6678 (71%)	3114 (31%)	2692 (85%)
Proportion with HF	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	852 (9%)	388 (12%)
Systolic blood pressure (mmHg)	129±17	136±18	136±17	135±17	135±17	137±17	136±18
eGFR, mL/min per 1.73 m^2	78±21	80 (SD not given)	80 (61, 92)	77 (61,92)	79±25	75±24	74±21
Glucose lowering agents. (%)							
Insulin	2374 (39%)	4159 (45%)	1913 (58%)	6838 (46%)	5597 (59%)	2398 (24%)	1943 (61%)
Biguanides	4021 (66%)	7136 (76%)	2414 (73%)	11295 (77%)	7970 (84%)	8016 (81%)	2437 (77%)
Sulfonylurea	2004 (33%)	4721 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	5644 (57%)	1007 (32%)
Thiazolidinedione	95 (2%)	573 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	N/A
DPP4-inhibitor	NA	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	88 (1%)	0
SGLT2 inhibitor	NA	NA	5 (<1%)	77 (1%)	575 (6%)	12 (0%)	301 (10%)

BMI – body mass index, HbA1c – haemoglobin A1c, CVD – cardiovascular disease, HF – heart failure, eGFR – estimated glomerular filtration rate, DPP4-inhibitor – dipeptidyl peptidase 4 inhibitor, SGLT-2 inhibitor – sodium/glucose co transporter 2 inhibitor.

Figure 1: PRISMA flow diagram of included trials.

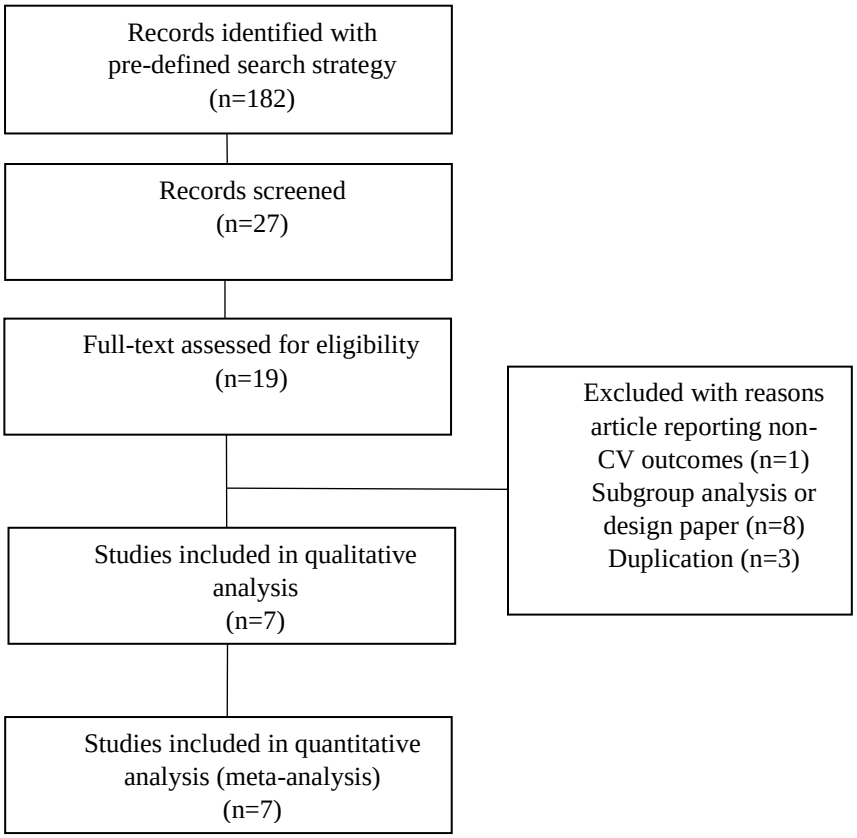
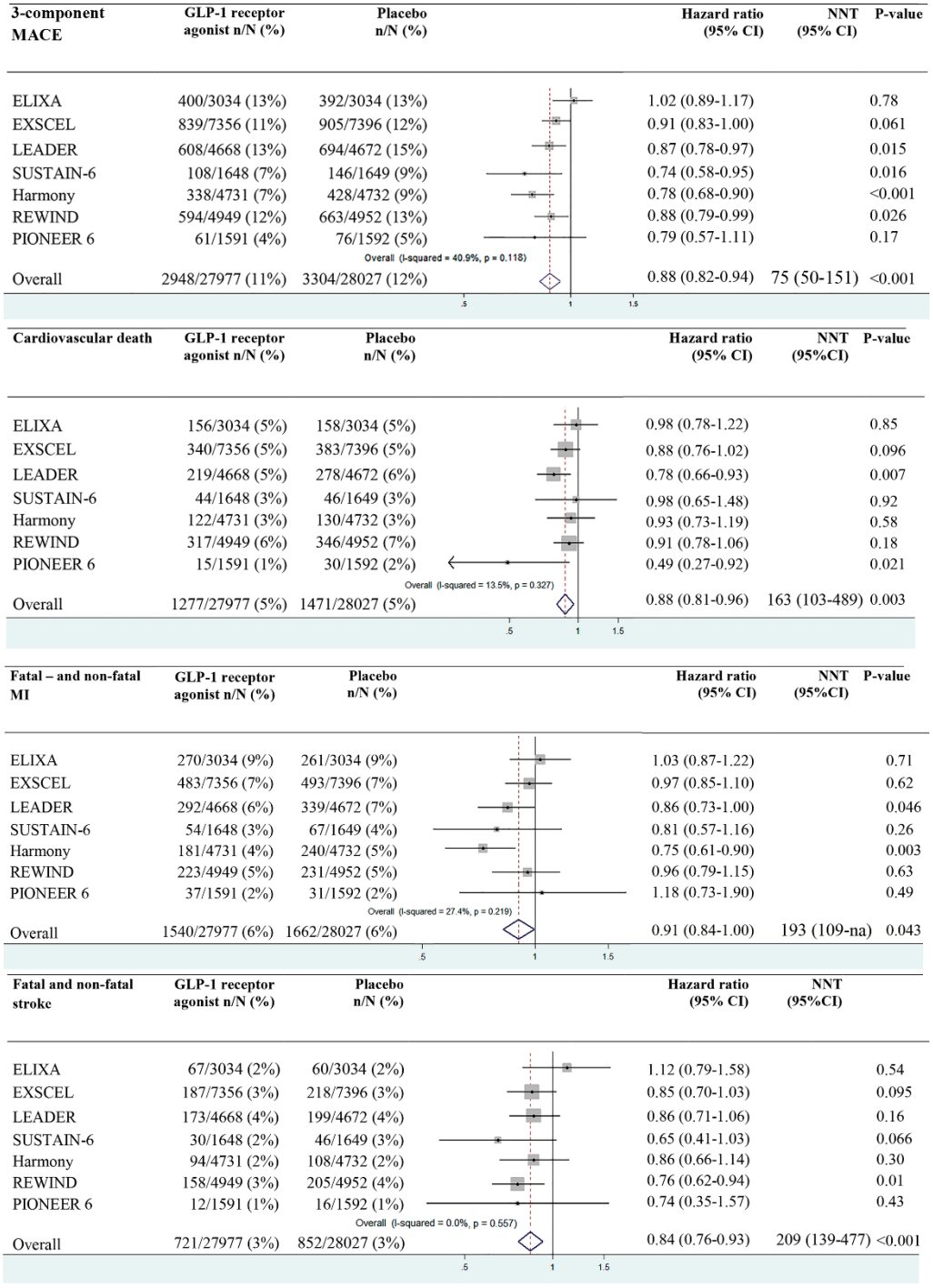
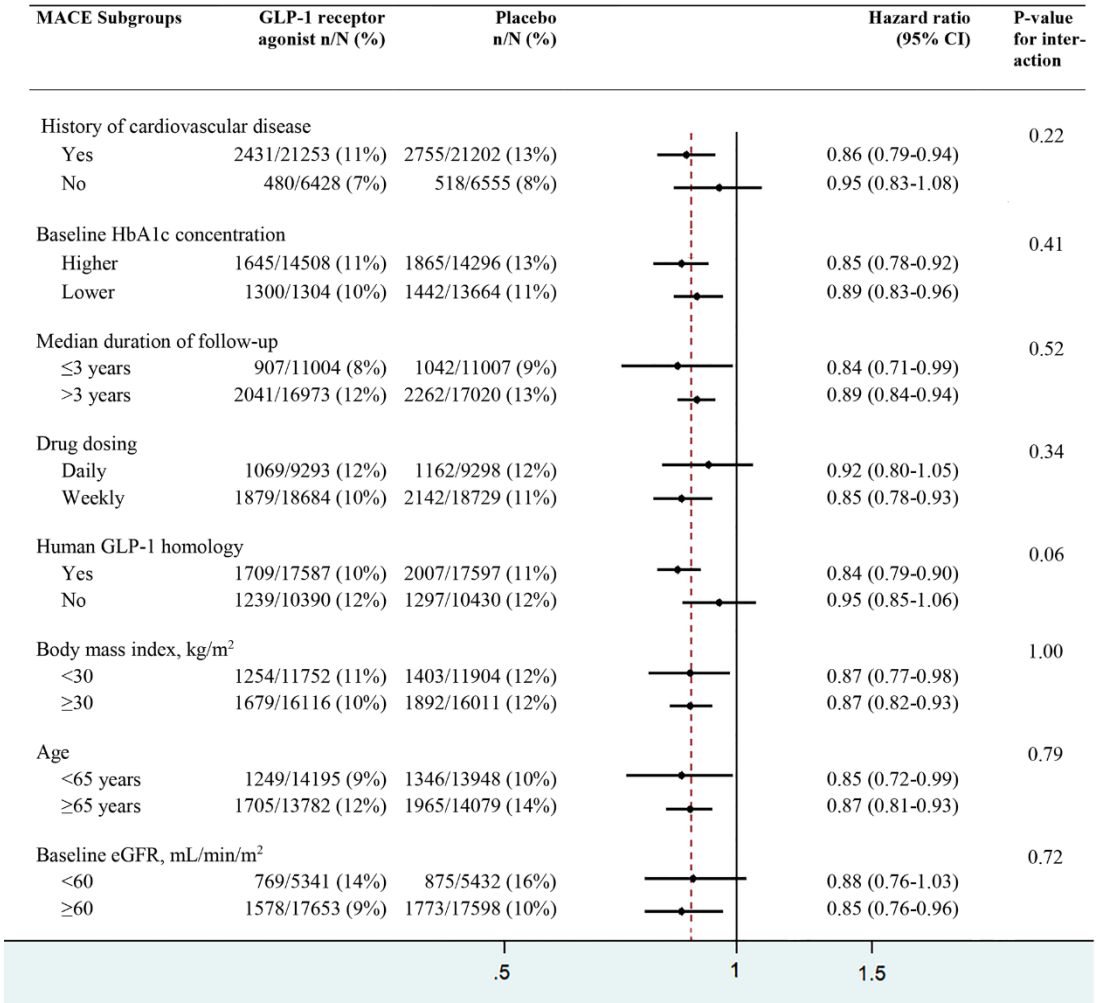


Figure 2: Risk of MACE and each of its components



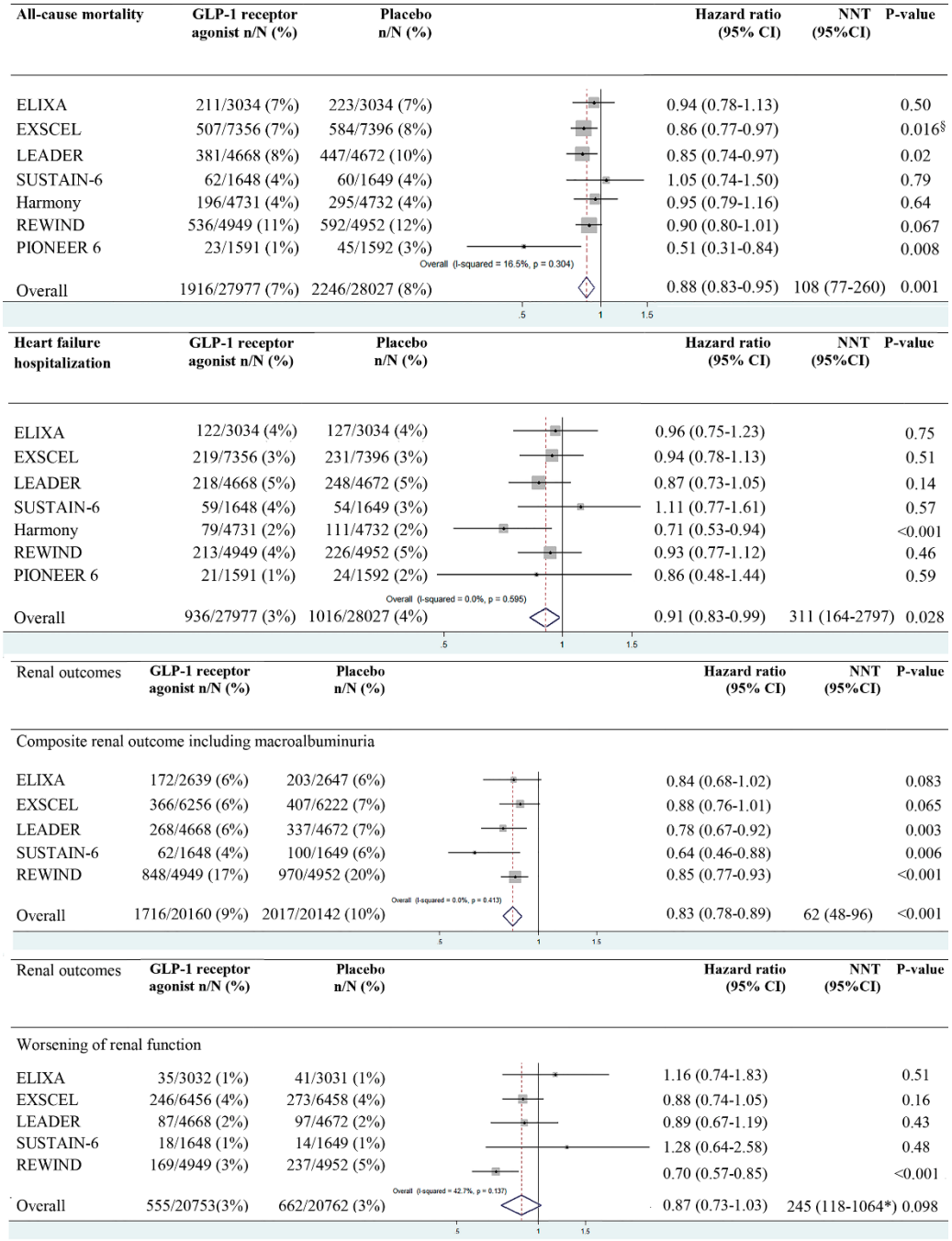
For PIONEER 6, fatal and non-fatal MI and stroke was not available, hence numbers and estimates refer to non-fatal MI, and non-fatal stroke exclusively.

Figure 3: Cardiovascular outcome of GLP-1 receptor agonists for selected subgroups



Higher baseline HbA1c" defined as: >7.5% in ELIXA, >8.0% in EXSCEL, >8.3% in LEADER, >8.5% in SUSTAIN-6, >8.0% in Harmony, >7.2% in REWIND and >8.5% in PIONEER 6. In REWIND, patients were divided by BMI>32 / BMI ≤32, and agegroups <66 / ≥66 years. In LEADER agegroups were <60/≥60 years.

Figure 4: All-cause mortality, heart failure hospitalization, and renal outcomes



*not regarded statistically significant due to hierarchical statistical testing plan. §number needed to harm. Data on renal outcomes were not available in Harmony Outcomes and PIONEER 6. The broader "composite renal outcome" consisted of development of macroalbuminuria, doubling of serum creatinine or ≥40% decline in eGFR, development of end-stage renal disease or death due to renal disease. The narrower "worsening of renal function" outcome was defined as either doubling of serum creatinine or ≥40% decline in eGFR. Exact definitions of renal outcomes are detailed in Appendix Table 2.

*Manuscript with revisions highlighted

Title: ~~Use~~Cardiovascular, mortality and renal outcomes with ~~of~~ ~~G~~glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes~~LP-1 receptor agonists in type 2 diabetes and cardiovascular outcomes~~ – **a systematic review and meta-analysis of randomi~~s~~zed trials**

Running title GLP-1 receptor agonists and CV outcomes

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ABSTRACT

Background: ~~A variety of~~Several glucagon-like peptide-1 (GLP-1) receptor agonists have been tested in clinical trials in patients with type 2 diabetes with different patient populations, cardiovascular outcomes and duration of follow-up. We planned a systematic review and meta-analysis of these trials, examining cardiovascular death, atherothrombotic cardiovascular events, heart failure, and death from any cause, as well as renal and key safety outcomes.

Methods: ~~We pooled data from trials using albiglutide, dulaglutide, exenatide extended release, liraglutide, lixisenatide, liraglutide, and semaglutide in adult patients with type 2 diabetes reporting major adverse cardiovascular events (MACE) i.e. death from cardiovascular death, stroke or myocardial infarction.~~ PubMed, Medline and the Cochrane central register of controlled trials were searched for eligible trials reporting major adverse cardiovascular events (MACE) i.e. cardiovascular death, stroke or myocardial infarction up to June 15, 2019. A meta-analysis was performed using a random-effects model to estimate overall hazard ratios (HR) for MACE, ~~each of the~~its components ~~of this composite~~, death from any cause, hospital admission for heart failure, renal outcomes and key safety outcomes (severe hypoglycaemia, pancreatitis and pancreatic cancer). We also examined MACE in several patient subgroups based on patient population ~~(primary versus secondary prevention),~~ glycated haemoglobin ~~concentration ("higher" versus "lower")~~, trial duration ~~(shorter versus longer follow-up)~~, treatment dosing interval ~~(daily versus, weekly, reflecting duration of drug action) a~~ and structural homology. ~~(exendin-4 based versus GLP-1 based).~~

~~Result~~Findings: Of 27 publications screened, 7 trials using GLP-1 receptor agonists, with a total of 56,006 patients, fulfilled the prespecified criteria and were included. Overall, GLP-1 receptor agonist treatment reduced MACE by 12% (HR 0.88; 95% CI 0.82, 0.94, p<0.001). There was no statistically significant heterogeneity across the subgroups examined.

GLP-1 receptor agonist treatment reduced all-cause mortality by 12% (0.88; 0.83, 0.95, p=0.001), hospital admission for heart failure by 9% (0.91; 0.83, 0.99, p=0.028) and a broad renal composite by 17% (0.83; 0.78, 0.89, p<0.001). There was no increase in risk of severe hypoglycaemia, pancreatitis or pancreatic cancer. ~~any of the safety outcomes examined.~~

~~**Conclusion**~~**Interpretation:** GLP-1 receptor agonists reduced -3-component MACE, its individual components, all-cause mortality, ~~and~~ risk of hospitalization for heart failure and worsening renal function (due mainly to reduction in urinary albumin excretion) in patients with type 2 diabetes. ~~This type of treatment also reduces the risk of worsening renal function (due mainly to reduction in urinary albumin reduction) and these benefits were obtained without an~~There was no increase in risk of severe hypoglycaemia or pancreatic adverse effects.

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Keywords: diabetes, GLP-1 receptor agonists, MACE, heart failure

RESEARCH IN CONTEXT

Evidence before this study

Glucagon-like peptide-1 (GLP-1) receptor agonists effectively decrease glycated haemoglobin (HbA1c) in patients with type 2 diabetes mellitus. A variety of agents of this class with differing structures and durations of action have been studied in randomised placebo-controlled trials of varying size and with different patient populations and effects on cardiovascular outcomes. In light of these differences, we conducted a meta-analysis of all large placebo-controlled GLP-1 receptor agonist trials to obtain robust estimates on the effect of this class of agent on a range of cardiovascular and renal endpoints, and patient subgroups.

Medline (via PubMed) and the Cochrane Controlled Register of Trials (up to 1~~2~~5 June 2019) were searched for trials comparing a GLP-1 receptor agonist to placebo in >500 patients and reporting a primary outcome including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke using the search terms "glucagon-like peptide-1 receptor agonists", "cardiovascular mortality", "myocardial infarction", "stroke" and "heart failure", "exenatide", "liraglutide", "semaglutide", "albiglutide", "dulaglutide", "placebo", and "randomized clinical trial". 7 trials were identified; ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (extended release exenatide), Harmony Outcomes (albiglutide), REWIND (dulaglutide) and PIONEER 6 (oral semaglutide).

Added value of this study

GLP-1 receptor agonists reduce all-cause mortality, the composite of cardiovascular death, myocardial infarction and stroke (MACE), each of the components of this outcome, hospital admission for heart failure and a composite renal outcome of worsening of estimated glomerular filtration rate (eGFR), end stage renal disease, death attributable to renal causes, or new onset macroalbuminuria (data not available in Harmony Outcomes and PIONEER 6 for the latter two outcomes). The benefit on MACE was consistent across all but one subgroup (with a suggestion of less effect of exendin 4 based compounds). The incidence of severe

hypoglycaemia, pancreatitis and pancreatic cancer did not differ between GLP-1 receptor agonist treatment and placebo. The present meta-analysis is the largest pooled study of the effect of GLP-1 RA on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus. Furthermore, compared to previous meta-analyses, it includes a greater number of patients without established cardiovascular disease, a new agent within this class of glucose lowering agents (dulaglutide) and an oral formation of an agent previously only available as a subcutaneous injection (semaglutide).

Implications of all the available evidence

The cardioprotective effects of GLP-1 receptor agonists in ~~-~~patients with ~~and possibly without~~ established cardiovascular disease and the reduction in risk of heart failure and worsening renal function represent an important treatment opportunity to reduce morbidity and mortality in patients with type 2 diabetes mellitus ~~to reduce morbidity and mortality~~.

INTRODUCTION

Prevention of non-fatal and fatal cardiovascular events is a key goal of the management of patients with type 2 diabetes mellitus ~~(T2D)~~.[1,2] In addition to blood pressure and cholesterol-lowering therapies, two of the newer classes of anti-hyperglycaemic agents also reduce cardiovascular risk. One of these, the glucagon-like peptide-1 (GLP-1) receptor agonists, decrease glycated haemoglobin (HbA1c) by stimulating glucose-dependent insulin secretion and by reducing glucagon secretion, gastric emptying and appetite.[3,4] GLP-1 receptor agonists also lead to modest improvements in lipids, reductions in blood pressure and weight, and carry a low risk of hypoglycaemia. Agents in this class, however, differ in structure and duration of action and have been studied in trials of varying size and with different patient populations and in individual trials the effects on cardiovascular outcomes have not been consistent.[5-15] In view of this we conducted a meta-analysis of all the large placebo-controlled GLP-1 receptor agonist trials, to obtain robust estimates of the effect of this class of agents on different cardiovascular endpoints and patient subgroups. We have also examined renal outcomes and key safety endpoints. Such a systematic review is helpful in supporting guideline recommendations on use of glucose lowering therapies to reduce macrovascular and renal outcomes in adults with type 2 diabetes.[1,2]

METHODS

Search strategy and study selection: We identified published randomised placebo-controlled trials (RCTs) testing GLP-1 receptor agonists in patients with type 2 diabetes (Appendix Table 1). Both injectable and oral agents were included. We further restricted the search to trials with a primary outcome including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Medline (via PubMed), and the Cochrane Controlled Register of Trials (Up to 15 June 2019) was searched with the search terms including "glucagon-like peptide-1 receptor agonists", "cardiovascular mortality", "myocardial infarction", "stroke" and "heart failure", "exenatide", "liraglutide", "semaglutide", "albiglutide", "dulaglutide", "placebo", and "randomized clinical trial". We restricted our search to trials including >500 patients. Included trials were assessed for bias using the Cochrane Risk of Bias Tool (Appendix Table 2). A Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart detailing the selection process is presented in Figure 1.

Data extraction: Data were extracted by SLK and RR, with conflicts over study inclusion resolved by consensus.

Selection of outcomes: Cardiovascular outcomes of interest were major adverse cardiovascular events (MACE), a composite outcome comprised of cardiovascular death, myocardial infarction and stroke, each of the components of this outcome, hospital admission for heart failure and death from any cause. Renal and safety outcomes were also examined. Two renal outcomes were examined, as reported previously: a narrower composite consisting of worsening of estimated glomerular filtration rate (eGFR), and a broader one which included end-stage kidney disease, death due to kidney disease and new onset macroalbuminuria (Appendix Table ~~1~~3). The four key safety outcomes of interest were severe hypoglycaemia, retinopathy, pancreatitis and pancreatic cancer

(Appendix Table ~~2~~4). We also examined thyroid cancer (Appendix Table ~~3~~5). In all 7 trials, local investigators were encouraged to manage participants in accordance with local guidelines (and could use most non-study glucose lowering treatments as desired). In 6 of the 7 trials, the mean between-treatment group difference in HbA1c was in the range 0.3% and 0.7%. We compared treatment effect in the following subgroups: primary versus secondary prevention, higher versus lower baseline HbA1c concentration (see footnote to Figure 3 for details), longer versus shorter duration of follow-up, drug-dosing daily versus weekly, human GLP-1 homology, body mass index <30 versus ≥30, age <65 years versus ≥65 years, baseline eGFR <60 vs ≥60 mL/min/m^2. All outcomes were adjudicated with the exception of severe hypoglycaemia, and event definitions for each trial are listed in the Appendix (Tables 1,3,4).~~appendix~~.

Data analysis: Summary statistics from the individual trials included were used, as individual level data were not available. HRs and 95% CIs from the trial papers, supplementary appendix or secondary publications were used. Estimates from each study were combined by use of inverse variance-weighted averages of logarithmic hazard ratios (HR) in random-effects analysis. Inter-study heterogeneity was assessed using the I^2 index and Cochran´s Q test. I^2 index values lower than 25% indicated low, 26-50% moderate and more than 50% high degree of heterogeneity, and Cochran´s Q statistic $p<0.05$ were considered indicators for significant heterogeneity. Number needed to treat (NNT) was calculated using the method of Altman and Andersen, and median duration of follow-up was estimated by a weighted average.[16]. ~~For subgroups without heterogeneity, we used overall estimates of treatment effects.~~ The fragility index, the minimum number of events needing to change from a non-event to an event in order to render a significant result non-significant, was calculated for 3-component MACE outcomes using the method described by Walsh et al. (Appendix Table ~~5~~6).[17] Interactions between treatment and subgroups were examined using a

test for heterogeneity, using $p<0.1$ as significant. All analyses were performed separately using Stata version 14 (Stata Corp. College Station, Texas, USA).

Role of the funding source: The study was planned and conducted by members of the Metabolic and Diabetes Research Group and Heart Failure research Group at the University of Glasgow (KFD, PSJ, MCP, NS and JJVMcM), the Department of Cardiology, Rigshospitalet University Hospital, Copenhagen (SLK, RR, LK) and the Nuffield Department of Public Health at the University of Oxford (DP) using institutional funds. No external funder was involved in the study.

RESULTS

~~Trials included:~~ ~~Of~~ Of 27 articles screened for eligibility, 7 trials with 56,006 patients were included in the meta-analysis (Figure 1). In order of reporting, these were: The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER), the preapproval Trial to Evaluate Cardiovascular and Other Long-term outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes), Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND), and a trial investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes (PIONEER 6).[6-14] All included trials were assessed for bias using the Cochrane risk of bias tool. The trials were assessed as high quality with a low risk of bias (~~Supplementary appendix 4~~Appendix, Table 2). The key trial and patient characteristics at baseline are presented in Tables 1 and Appendix Table ~~2~~1.

~~Trial design and treatment:~~ ~~All~~ All trials were of substantial size (>3000 patients). ELIXA enrolled patients with a recent acute cardiovascular syndrome whereas all other trials included patients with stable cardiovascular disease, cardiovascular risk factors or both. All trials, except ELIXA, had MACE as the primary endpoint; in ELIXA an expanded composite including hospitalization for unstable angina ~~was used~~the primary endpoint. Lixisenatide (ELIXA), liraglutide (LEADER), and oral semaglutide (PIONEER 6) were each administered daily, whereas the remaining GLP-1 receptor agonists were administered once weekly. PIONEER 6 differed from the remaining trials in that semaglutide was taken orally, compared with subcutaneous administration of the treatments used in the remaining studies.

~~Patient characteristics:~~ Mean age at baseline ranged from 60 years in ELIXA to 66 years in PIONEER 6 and REWIND. The highest proportion of women was included in REWIND (46% compared with between 31 and 39% in the remaining trials). The proportion of patients with established cardiovascular disease at baseline ranged from ~~in~~ 100% in ELIXA and Harmony Outcomes to 31% of those in REWIND (Table 1~~2~~). Kidney function was similar across trials (with median estimated glomerular filtration rate ranging from 74 to 80 ml/min/m^2). Median HbA1c was lowest in REWIND and ELIXA (7.1% and 7.7%, respectively) and highest, at 8.7%, in LEADER, SUSTAIN-6 and Harmony Outcomes. REWIND had the lowest proportional use of insulin at baseline (24% compared with 39-61% in remaining trials). The median length of follow-up ranged from 1.3 years in PIONEER 6 to 5.4 years in REWIND; the estimated median follow-up was 3.2 years (Appendix Table 1). Treatment discontinuation and loss to follow-up is summarised in Appendix Table ~~6~~7.

~~Effect of GLP-1 receptor agonists on MACE and its components:~~ In the pooled analysis, treatment with a GLP-1 receptor agonist led to a 12% relative risk reduction in MACE (HR 0.88; 95% CI 0.82, 0.94; p<0.001) [Figure 2]. The NNT was 75 (95% CI 50, 151) over an estimated median follow-up of 3.2 years and the fragility index, overall, was 202 (Appendix Table ~~5~~6). When assessing the components of the composite MACE endpoint separately, GLP-1 receptor agonist use led to a reduction in risk of death from cardiovascular causes (HR 0.88 95% CI 0.81, 0.96; p=0.001), fatal- or non-fatal stroke (HR 0.84; 95% CI 0.76, 0.93; p<0.001), and fatal or non-fatal MI (HR 0.91; 95% CI 0.84, 1.00; p=0.043) [Figure 2].

~~Subgroup analyses for MACE:~~ In subgroup analyses ~~T~~there was no statistical heterogeneity between the effect of a GLP-1 receptor agonist in "primary prevention" patients (those without established cardiovascular disease) and those with cardiovascular disease at baseline: HR 0.95 (95% CI 0.83, 1.08) for "primary prevention" and 0.86 (0.79, 0.94) for "secondary prevention"~~,~~

~~respectively~~, p for interaction=0.22. Similarly, we found no heterogeneity for the effect of GLP-1 receptor agonist therapy when examined by baseline HbA1c ("low" compared with "high" median HbA1c), shorter compared with longer trial follow-up (<3 years vs. ≥3 years median follow-up), drug dosing interval (daily compared with weekly dosing), reflecting duration of drug action. The one possible exception was the comparison of exendin 4-based compounds (lixisenatide and exenatide) and agents more homologous with human GLP-1 (all other drugs studied); this analysis suggested heterogeneity: HR 0.95 (95% CI 0.85, 1.06) for exendin 4-based, compared with 0.84 (0.79, 0.90) for GLP-1-based~~, respectively~~, p-value for interaction~~-~~=0.06 (Figure 3).

~~**Death from any cause:**~~ Compared with placebo, treatment with a GLP-1 receptor agonist reduced the risk of death from any cause by 12% (HR 0.88; 95% CI 0.83, 0.95; p=0.001), giving a NNT of 108 (77, 260) [Figure 4].

~~**Hospital admission for heart failure:**~~ The risk of HF hospitalization was also reduced in GLP-1 receptor agonist treated patients, by 9% (HR 0.91; 95% CI 0.83, 0.99; p=0.028), giving a NNT of 311 (164, 2797) [Figure ~~4~~5].

~~**Effect of GLP-1 receptor agonists on renal outcomes:**~~ Renal events were not available for Harmony Outcomes or PIONEER 6. Treatment with a GLP-1 receptor agonist reduced the broader composite renal outcome of worsening renal function, end-stage renal disease and renal death, including development of macroalbuminuria, by 17% (HR 0.83, 95% CI 0.78, 0.89) with a NNT of 62 (48, 96). There was a 13% reduction (HR 0.87, 0.73, 1.03) in the narrower ~~outcome of~~ worsening renal function outcome ~~of 13% (HR 0.87, 0.73, 1.03)~~ which was of borderline statistical significance; the corresponding NNT was 245 (118, -1064) (Figure ~~6~~4).

~~**Safety outcomes:**~~ The incidence of severe hypoglycaemia, pancreatitis and pancreatic cancer did not differ between GLP-1 receptor agonist treatment and placebo (Appendix Figure ~~1~~7). The

incidence of retinopathy did not differ between GLP-1 receptor agonist treated and placebo treated patients, but this outcome was not defined consistently among the trials (Appendix Figure 1). ~~Event rates~~The rate of thyroid carcinoma ~~were~~ was low and did not differ between the active treatment and placebo groups (Appendix Table ~~3~~5).

DISCUSSION

The present meta-analysis includes 13,084 (30%) more patients, 1394 (29%) more MACE endpoints, 1818 (95%) more renal events and approximately 56,000 more years of patient exposure than the largest prior study of this type.[18,19] The present report also includes 6709 (95%) more "primary prevention" patients (i.e. with cardiovascular risk factors rather than established cardiovascular disease), one additional agent in the class i.e. dulaglutide with homology to human GLP-1 and a long duration of action, and a novel oral formulation of semaglutide which was administered by sub-cutaneous injection in a previous trial.

Three-component MACE, the primary endpoint in 6 of the 7 trials, was reduced by 12%, reflecting a beneficial effect on death from cardiovascular causes (relative risk reduction 12%), as well as a reduction in risk of stroke (16% relative risk-reduction in fatal and non-fatal stroke). The reduction in myocardial infarction (9% relative risk-reduction in fatal and non-fatal myocardial infarction) was less robust though directionally concordant. The NNT for MACE was 75 (95% CI 50, 151) over an estimated median duration of follow-up of 3.2 years. The relative risk reduction in MACE in a recent sodium-glucose co-transporter 2 (SGLT2) inhibitor meta-analysis was 11 (4-17)% and the NNT 97 (63, 266) over an estimated median follow-up of 3.3 years, although this comparison should be made cautiously as it does not take account of differences in the patient populations studied~~. and duration of follow-up.~~ ,. The hazard ratio for death from any cause in GLP-1 receptor agonist trials was 0.88 (95% CI 0.83-0.95) and NNT 108 (77, 260); in the SGLT2 inhibitor meta-analysis the corresponding HR was 0.85 (95% CI 0.78-0.93) and NNT 101 (69,216).[20]

We undertook several subgroup analyses to address the explanations proposed for the different effects on cardiovascular outcomes observed among the various GLP-1 receptor agonist trials. These include differences in the specific molecule tested, in the patients randomized, and in the duration of follow-up. Albiglutide, dulaglutide, liraglutide, and semaglutide are more similar, structurally, to native GLP-1 whereas exenatide and lixisenatide are based, structurally, on exendin-4.[21,22] Duration of treatment effect also differs markedly between the agents studied, although this does not reflect structural homology, with some GLP-1 receptor agonists of each type having a short pharmacologic half-life (e.g. lixisenatide 2-3 hours and liraglutide 12 hours) and others a long half-life (e.g. dulaglutide 120 hours and subcutaneous semaglutide 170 hours), or available as a sustained release formulation (exenatide), reflected in daily versus weekly dosing.[23] The oral formulation of semaglutide used in PIONEER 6 required daily dosing. With the seven trials now available it was possible to examine whether these pharmacological characteristics, and their permutations, influence treatment efficacy. While duration of drug action did not seem to modify the treatment-effect, there was a suggestion of an interaction related to chemical structure, with a possibly smaller effect on MACE of agents based on exendin-4. This apparent interaction could be unduly influenced by ELIXA, which was unique in recruiting patients with a recent acute coronary syndrome (and also used a very short-acting agent, administered once daily), poor adherence in EXSCEL (40% permanent treatment discontinuation) or may be a chance finding. The ongoing Efpeglenatide on Cardiovascular Outcomes trail (AMPLITUDE-O - ClinicalTrials.gov unique identifier: NCT03496298), using a long-acting exendin-4 based GLP-~~1~~1 receptor agonist in patients with established cardiovascular disease or cardiovascular risk factors will provide more evidence on this question.

The difference in patient population enrolled in the various GLP-1 receptor agonist trials has also been considered a potential explanation for the difference in outcomes among the studies.[24] In particular, the lack of clear reduction in the primary MACE endpoint in EXSCEL has been attributed to the higher proportion of patients without established cardiovascular disease randomized in that trial, compared with the preceding GLP-1 receptor agonists trials. The inclusion of PIONEER 6 and, especially, REWIND allowed us to examine this question, with an almost doubling in the number of "primary-prevention" patients, overall, exposed to a GLP-1 receptor agonist, although even with this, the number of participants with MACE in this subgroup was less than a third of that in most other subgroups. Consequently, this analysis may still be under powered and, although there was no heterogeneity for the effect of GLP-1 receptor agonist treatment, the statistical test for interaction is weak. Therefore we cannot be certain that the relative risk reduction in "primary prevention" patients was the same as in "secondary prevention" patients and even if it was, the absolute risk reduction in the "primary prevention" population will be smaller, and the treatment likely to be less cost-effective, because individuals without established cardiovascular disease are at lower baseline risk than "secondary prevention" patients. These additional data may, therefore, not be sufficiently robust to challenge the new guideline recommendations only to use GLP-1 receptor agonists in patients with established cardiovascular disease.[1,2] ~~The inclusion of PIONEER 6 and, especially, REWIND allowed us to examine this question, with an almost doubling in the number of "primary prevention" patients, overall, exposed to GLP-1 receptor agonists treatment. . We did not show any statistical heterogeneity of the effect of GLP-1 receptor agonist treatment on MACE according to whether patients had, or did not have, established cardiovascular disease at baseline. However, the number of patients with a major adverse cardiovascular event in the "primary prevention" prevention subgroup was less than half that in any other subgroup (and less than a third in most subgroups). Therefore, this subgroup may still be~~

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~~under powered, although our findings do at least challenge the new guideline recommendations only to use GLP-1 receptor agonists in patients with established cardiovascular disease.~~[1,2] ~~However, even if the relative risk reduction with treatment is consistent in patients with and without established cardiovascular disease, the absolute risk reduction in the latter will be smaller and the treatment less cost-effective~~

Duration of follow-up was a further potential explanation for difference discrepancy in trial outcomes, with, for example, the much shorter follow-up in ELIXA (median 2.1 years) than LEADER (median 3.8 years) highlighted as an important difference between the first two large outcome trials with a GLP-1 receptor agonist. However, duration of follow-up did not seem to modify the benefit of treatment on the composite MACE outcome.

Two of the other subgroups merit discussion. The effect of GLP-1 receptor agonist treatment was consistent according to age and renal function. Because older age and lower eGFR were associated with higher rates of MACE, the absolute benefit was larger in these individuals. ~~(as demonstrated by a smaller NNT).~~

This updated meta-analysis also shows for the first time that treatment with a GLP-1 receptor agonist reduces the risk of heart failure hospitalization, although the reduction in risk was small in relative (9%, 95% CI 1-17%) and absolute (NNT 311; 95% CI 164, 2797) terms and was not statistically robust. This effect was also, clearly, much smaller than seen with SGLT2 inhibitors, which showed a relative risk reduction of 31 (21-39)% and a NNT of 100 (79, 147) over a similar median duration of follow-up (3.2 vs 3.3 years). Nevertheless, a GLP-1 receptor agonist may be an ~~useful~~ alternative in a patient with heart failure (or renal impairment) who cannot take a SGLT2 inhibitor.[20] The explanation for why GLP-1 receptor agonists should reduce this endpoint is not clear, especially as these agents has not demonstrated any benefit in trials in patients with

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established heart failure with reduced ejection fraction.[25,26] One possibility is that this favourable effect in the meta-analysis is secondary to reduction in myocardial infarction, a common precursor of heart failure. In this context, is notable that the largest reductions in heart failure were in the two trials (Harmony Outcomes and LEADER) with the greatest reduction in myocardial infarction. This hypothesis, however, needs further investigation, for example with examination of the time sequence of cardiovascular events in individual patients.

It is clear, overall, that GLP-1 receptor agonists are cardioprotective agents. The time course of their effects, apparent in the individual trials, and the types of cardiovascular events prevented suggest that GLP-1 receptor agonists have primarily an anti-atherothrombotic effect. This profile is distinct from the ~~sodium-glucose co-transporter-2 (~~SGLT 2~~)~~ inhibitors which exhibit an effect much more rapidly and which is more pronounced on heart failure, raising the possibility of therapeutic synergy from the combination of these two classes of drug.[27]

This may also be true for renal outcomes. While we found that GLP-1 receptor agonists clearly reduced the risk of worsening of kidney function when assessed using a composite outcome driven by an increase in urinary albumin excretion, the benefit on a composite including a significant decline in eGFR (or increase in creatinine) was less clear, of borderline statistical significance and not as pronounced as seen with SGLT2 inhibitors.[18,27] The relative risk reduction in the "harder" renal endpoint in the three large, broadly inclusive, SGLT2 inhibitor trials was 45 (36-52)% with a NNT of 79 (69, 99), compared with 13 (27-+3)% and 245 (118, -1064) in the present meta-analysis.[18]

Lastly, this meta-analysis suggests that prior concerns about pancreatitis and pancreatic cancer with GLP-1 receptor agonists seem unfounded and there was also no increase in risk of severe hypoglycaemia. We also so no overall increase in adverse eye-outcomes, although these were inconsistently defined in the trials, a deficit that should be remedied in future studies. The outcomes reported did not require systematic eye examination and this too is required for a full understanding of the effect of any glucose-lowering therapy on eye health. A dedicated trial of this type is currently underway with semaglutide (FOCUS - ClinicalTrials.gov unique identifier: NCT03811561). Our study has other limitations, including lack of patient-level data, restriction of subgroup analyses to the primary 3-component MACE endpoint, and ability to examine only the secondary endpoints and adverse events of special interest reported by the investigators of the trials included.

In conclusion, in this meta-analysis, we show that in patients with type 2 diabetes, GLP-1 receptor agonists reduced 3-component MACE, its individual components of, all-cause mortality and risk of hospitalization for heart failure. Treatment with a GLP-1 receptor agonist also reduces the risk of worsening renal function, due mainly to a decrease in development of macroalbuminuria. These benefits were obtained without an increase in risk of severe hypoglycaemia, pancreatic adverse effects, or thyroid cancer.

Contributors:

Data extraction was carried out by RR and SLK and the analyses were conducted by SLK and replicated by KFD, supervised by PSJ. All authors were involved in data interpretation, manuscript writing or editing. All authors had full access to all data required to complete the analysis and agreed to submit the study for publication.

Declaration of interest:

SLK, RR, KFD, LK report no conflict of interest. NS has consulted for AstraZeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Napp Pharmaceuticals, and Sanofi, and has received grant support from Boehringer Ingelheim. DP is an investigator on the EMPA-KIDNEY trial (investigating SGLT2 inhibition in patients with chronic kidney disease), funded by a grant from Boehringer Ingelheim to the University of Oxford, but he obtains no salary support from the grant; CTSU, University of Oxford has a staff policy of not accepting honoraria or consultancy fees from industry. PSJ has received advisory board or speaker fees from Novartis, Boehringer Ingelheim and Cytokinetics, research grants from Boehringer Ingelheim. His employer, the University of Glasgow, has received payment for his work on trials sponsored by AstraZeneca. MCP reports consultancy for Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Napp Pharmaceuticals and Eli Lilly. JJVMcM's employer, the University of Glasgow, has been paid by Abbvie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, DalCor, GSK, Merck Sharp & Dohme, Novartis, Resverlogix and Theracos for his participation in clinical trials and by Alnylam, AstraZeneca, Cardurion, Novartis and Pfizer for consultancies, advisory boards and/or lectures.

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Table 1: Study inclusion criteria, glycaemia management and outcomes

	ELIXA n=6068	LEADER n=9340	SUSTAIN 6 n=3297	EXSCEL n=14752	HARMONY n=9463	REWIND n=9903	PIONEER 6 n=3183
Drug studied	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide
Key inclusion criteria	HbA1c 5.5-11.0%, ACS within 180 days; age≥30 years	HbA1c≥7.0% age≥50 years with CVD/HF/CKD or age≥60 years with ≥1 CVD risk factor	HbA1c≥7.0% age≥50 years with CVD/HF/CKD or age≥60 years with ≥1 CVD risk factor	HbA1c 6.5-10.0% established CVD and primary prevention age≥18 years	HbA1c≥7.0%, age ≥40 years, established CVD	HbA1c≤9.5%, ≤2 antidiabetic drugs age≥50/55/60 years with CVD/ subclinical vascular/ risk factors	age≥50 years with CVD/HF/CKD or age≥60 years with ≥1 CVD risk factor
Key safety exclusion criteria	Unexplained pancreatitis, multiple endocrine neoplasia syndrome	Chronic or acute pancreatitis, multiple endocrine neoplasia syndrome. calcitonin≥50 ng/L	Chronic or acute pancreatitis, multiple endocrine neoplasia syndrome. calcitonin≥50 ng/L	Chronic or acute pancreatitis, multiple endocrine neoplasia syndrome. calcitonin≥40 ng/L	eGFR<30 mL/min per 1.73m^2, pancreatitis, multiple endocrine neoplasia syndrome	eGFR<15 mL/min per 1.73m^2, liver disease, pancreatitis, multiple endocrine neoplasia syndrome	eGFR<30 mL/min per 1.73m^2, pancreatitis, multiple endocrine neoplasia syndrome
Glycaemic management	If screening HbA1c<8.5% downtitration of insulin or sulfonylurea. GLP-1 RA and DPP4-I prohibited	If screening HbA1c<8.0% downtitration of insulin. dose escalation over 2 weeks. GLP-1 RA and DPP4-I prohibited	If screening HbA1c<8.0% downtitration of insulin. dose escalation over 2 weeks. GLP-1 RA and DPP4-I prohibited	At physicians´ discretion according to guidelines. . GLP-1 prohibited but DPP4-I allowed	At physician´s discretion according to local guidelines	At physician´s discretion according to local guidelines	At physician´s discretion according to local guidelines. DPP4-I prohibited
Statistical analysis	Primary analysis simultaneous assessment of non-inferiority and superiority	Primary analysis non-inferiority. Hierarchical testing for superiority, secondary CV endpoints	Primary analysis non-inferiority. Superiority testing was not pre-specified	Primary analysis non-inferiority. Hierarchical testing for superiority, secondary CV endpoints	Primary analysis non-inferiority. Then secondary testing for superiority, secondary CV endpoints	Primary outcome MACE, Secondary outcomes CV endpoints and microvascular composite	Primary analysis non-inferiority. Then secondary testing for superiority, secondary CV endpoints
Median duration of follow-up, years	2.1	3.8	2.1	3.2	1.6	5.4	1.3
Primary outcome	MACE-4 (non-inf)	MACE-3 (non-inf)	MACE-3 (non-inf)	MACE-3 (superiority)	MACE-3 (non-inf)	MACE-3 (superiority)	MACE-3 (non-inf)
Participants with a primary outcome*	792*	1302	254	1744	766	1257	137
Event rate per 100 py (active/placebo)	6.3/6.2	3.4/3.9	3.2/4.4	3.7/4.0	4.6/5.9	2.4/2.7	2.9/3.7

*For ELIXA we used a 3-component MACE outcomes (without hospitalisation for unstable angina) similar to other trials. HbA1c – haemoglobin A1c, ACS – acute coronary syndrome, CVD- cardiovascular disease, HF – heart failure, CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate, GLP-1 RA – glucagon like receptor-1 agonist, DPP4-I, dipeptidyl peptidase-4 inhibitors, MACE – major adverse cardiac events, UAH – unstable angina pectoris.

Table 1: Baseline characteristics and use of glucose lowering agents across trials

	ELIXA n=6068	LEADER n=9340	SUSTAIN-6 n=3297	EXSCEL n=14752	HARMONY n=9463	REWIND n=9903	PIONEER 6 n=3183
Drug studied	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide
Structural basis	Exendin-4 based	Human GLP-1 based	Human GLP-1 based	Exendin-4 based	Human GLP-1 based	Human GLP-1 based	Human GLP-1 based
Administration route	subcutaneous	subcutaneous	subcutaneous	subcutaneous	subcutaneous	subcutaneous	oral
Dose	20 ug/day	1.8 mg/day	0.5 or 1 mg/week	2 mg/week	30 or 50 mg/week	1.5 mg/week	14 mg/day
Age, mean – years	60±10	64±7	65±7	62±9	64±7	66±7	66±7
Female sex, no. (%)	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)	2894 (31%)	4589 (46%)	1007 (32%)
BMI (kg/m^2)	30.1±5.6	32.5±6.3	32.8±6.2	32.7±6.4	32.3±5.9	32.3±5.7	32.3±6.5
Caucasian	4576 (75%)	7238 (78%)	2736 (83%)	11175 (76%)	6583 (70%)	7498 (76%)	2300 (72%)
Diabetes duration, years	9.2±8.2	12.8±8.0	13.9±8.1	13.1±8.3	14.2±8.8	10.6±7.2	14.9±8.5
HbA1c (%)	7.7±1.3	8.7±1.6	8.7±1.5	8.1±1.0	8.7±1.5	7.3±1.1	8.2±1.6
Proportion with CVD	6068 (100%)	7598 (81%)	2735 (83%)	11175 (76%)	6678 (71%)	3114 (31%)	2692 (85%)
Proportion with HF	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	852 (9%)	388 (12%)
Systolic blood pressure (mmHg)	129±17	136±18	136±17	135±17	135±17	137±17	136±18
eGFR, mL/min per 1.73 m^2	78±21	80 (SD not given)	80 (61, 92)	77 (61,92)	79±25	75±24	74±21
Glucose lowering agents. (%)							
Insulin	2374 (39%)	4159 (45%)	1913 (58%)	6838 (46%)	5597 (59%)	2398 (24%)	1943 (61%)
Biguanides	4021 (66%)	7136 (76%)	2414 (73%)	11295 (77%)	7970 (84%)	8016 (81%)	2437 (77%)
Sulfonylurea	2004 (33%)	4721 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	5644 (57%)	1007 (32%)
Thiazolidinedione	95 (2%)	573 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	N/A
DPP4-inhibitor	NA	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	88 (1%)	0
SGLT2 inhibitor	NA	NA	5 (<1%)	77 (1%)	575 (6%)	12 (0%)	301 (10%)

BMI – body mass index, HbA1c – haemoglobin A1c, CVD – cardiovascular disease, HF – heart failure, eGFR – estimated glomerular filtration rate, DPP4-inhibitor – dipeptidyl peptidase 4 inhibitor, SGLT-2 inhibitor – sodium/glucose co transporter 2 inhibitor.

Figure 1: PRISMA flow diagram of included trials.

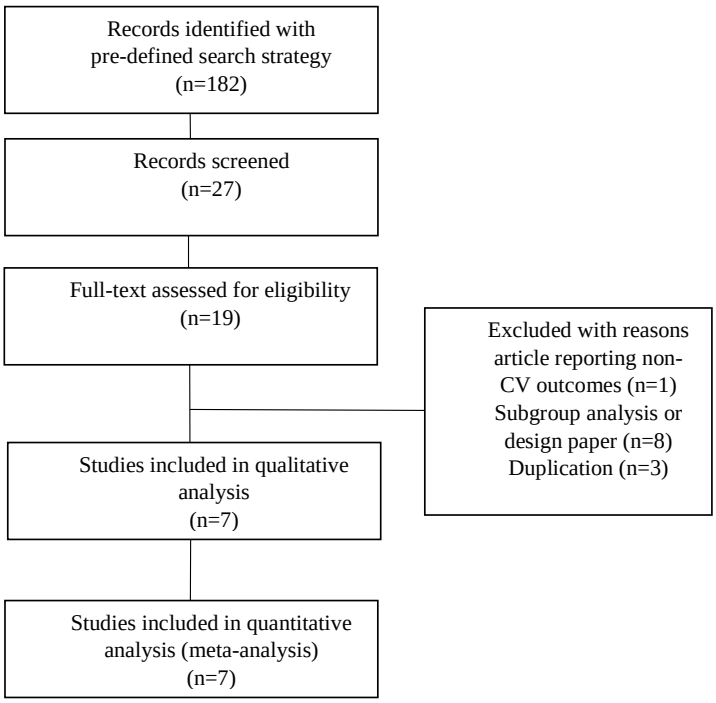
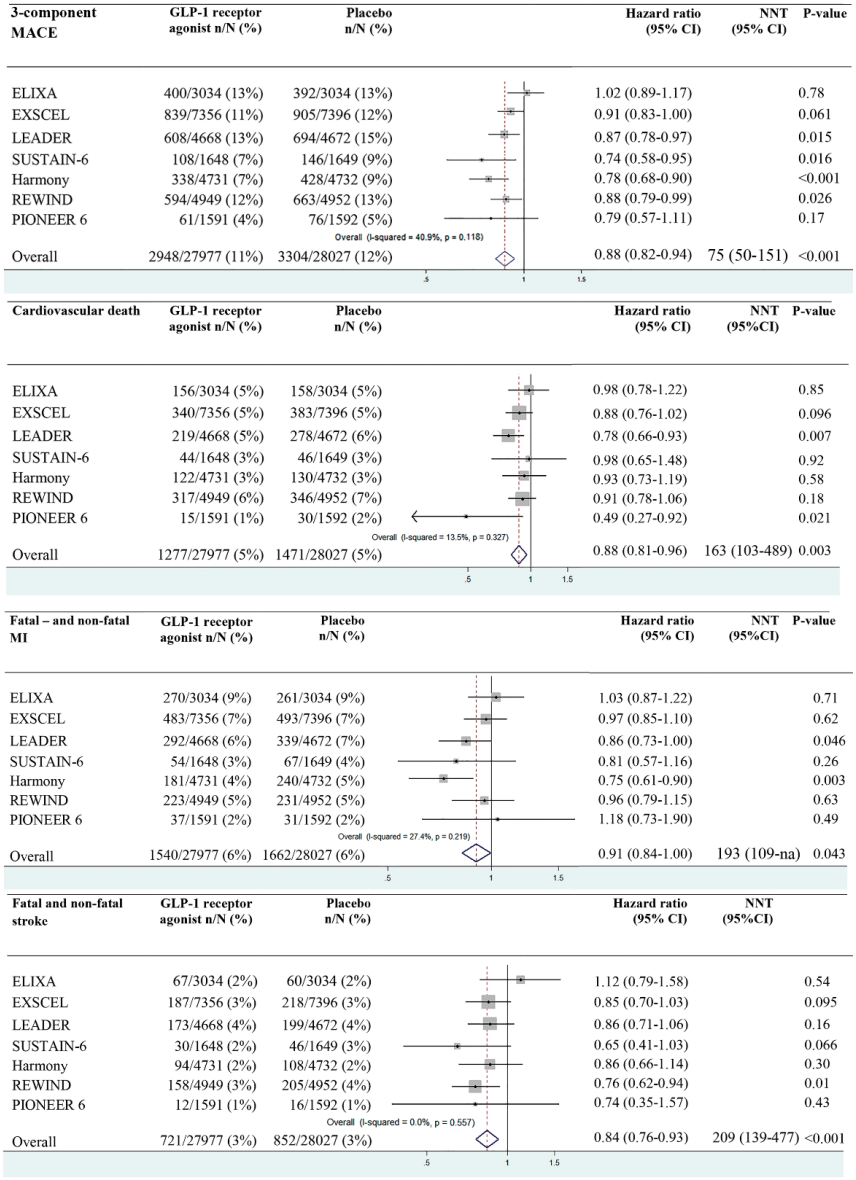
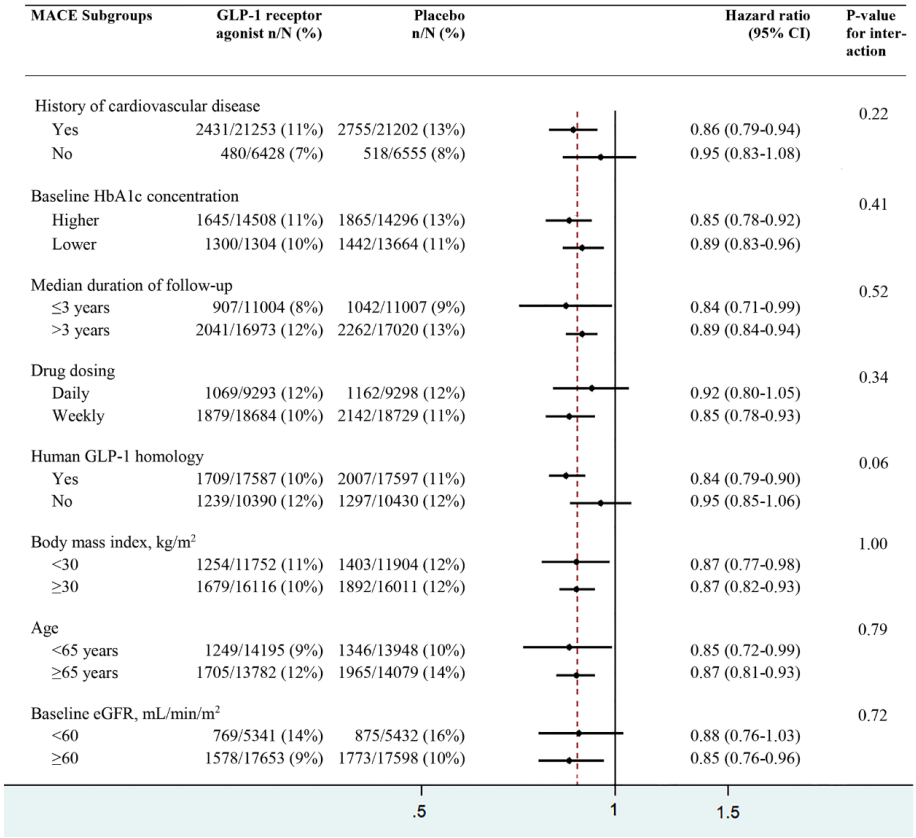


Figure 2: Risk of MACE and each of its components



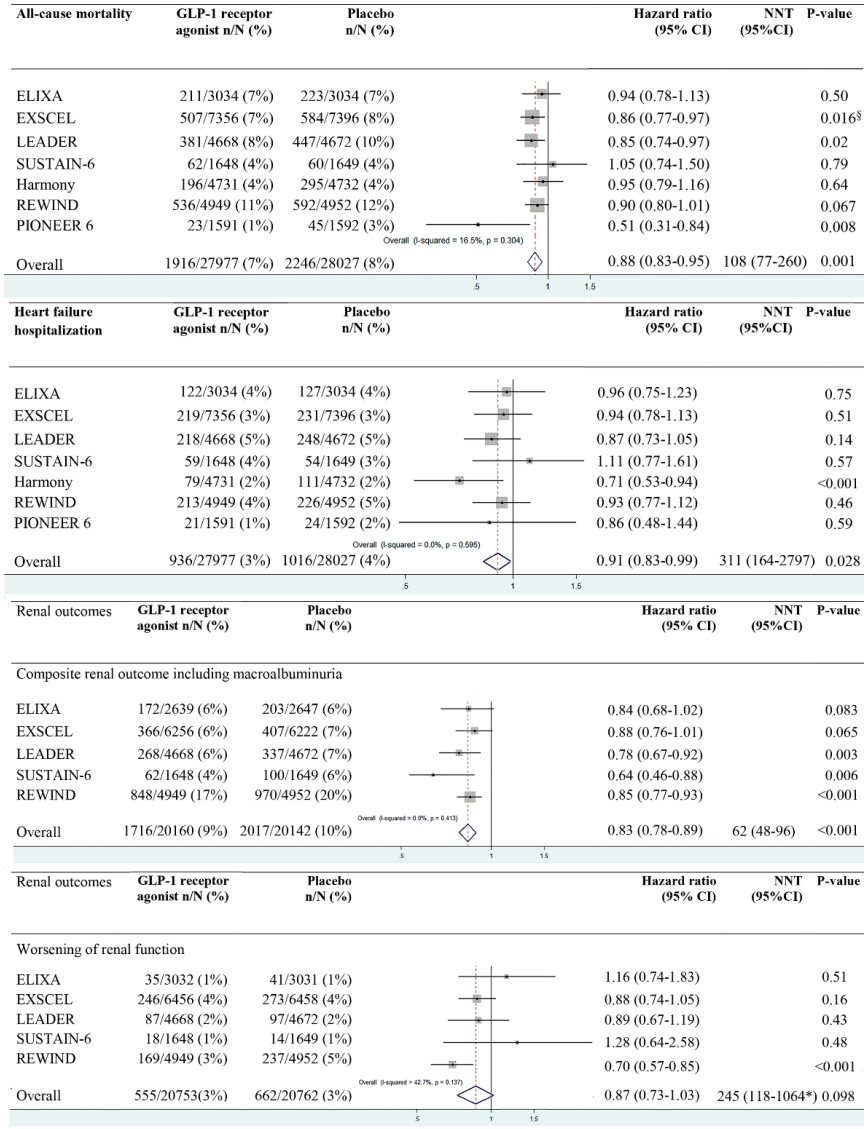
For PIONEER 6, fatal and non-fatal MI and stroke was not available, hence numbers and estimates refer to non-fatal MI, and non-fatal stroke exclusively.

Figure 3: Cardiovascular outcome of GLP-1 receptor agonists for selected subgroups



Higher baseline HbA1c" defined as: >7.5% in ELIXA, >8.0% in EXSCEL, >8.3% in LEADER, >8.5% in SUSTAIN-6, >8.0% in Harmony, >7.2% in REWIND and >8.5% in PIONEER 6. In REWIND, patients were divided by BMI>32 / BMI ≤32, and agegroups <66 / ≥66 years. In LEADER agegroups were <60/≥60 years.

Figure 4: All-cause mortality, heart failure hospitalization, and renal outcomes



*not regarded statistically significant due to hierarchical statistical testing plan. §number needed to harm. Data on renal outcomes were not available in Harmony Outcomes and PIONEER 6. The broader "composite renal outcome" consisted of development of macroalbuminuria, doubling of serum creatinine or ≥40% decline in eGFR, development of end-stage renal disease or death due to renal disease. The narrower "worsening of renal function" outcome was defined as either doubling of serum creatinine or ≥40% decline in eGFR. Exact definitions of renal outcomes are detailed in Appendix Table 2.

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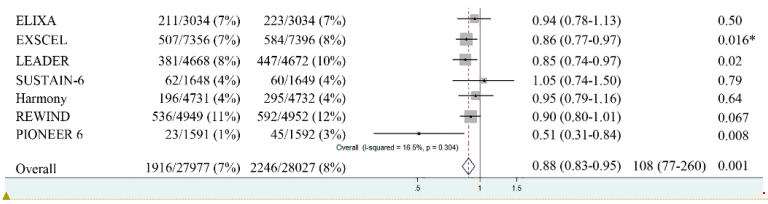
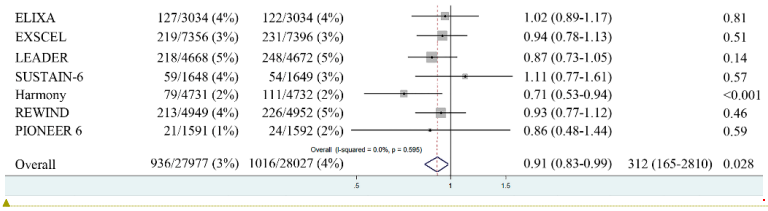
All-cause mortality	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95%CI)	P-value
ELIXA	211/3034 (7%)	223/3034 (7%)	0.94 (0.78-1.13)		0.50
EXSCEL	507/7356 (7%)	584/7396 (8%)	0.86 (0.77-0.97)		0.016*
LEADER	381/4668 (8%)	447/4672 (10%)	0.85 (0.74-0.97)		0.02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1.05 (0.74-1.50)		0.79
Harmony	196/4731 (4%)	295/4732 (4%)	0.95 (0.79-1.16)		0.64
REWIND	536/4949 (11%)	592/4952 (12%)	0.90 (0.80-1.01)		0.067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0.51 (0.31-0.84)		0.008
Overall	1916/27977 (7%)	2246/28027 (8%)	0.88 (0.83-0.95)	108 (77-260)	0.001



~~*not regarded statistically significant due to hierarchical statistical testing plan~~

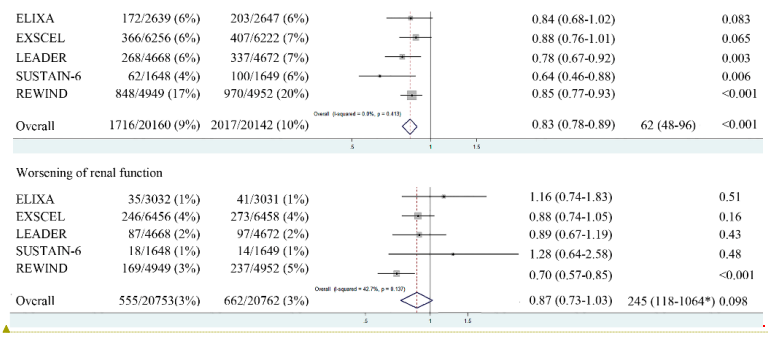
~~Figure 5: Heart failure hospitalization~~

Heart failure hospitalization	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95%CI)	P-value
ELIXA	127/3034 (4%)	122/3034 (4%)	1.02 (0.89-1.17)		0.81
EXSCEL	219/7356 (3%)	231/7396 (3%)	0.94 (0.78-1.13)		0.51
LEADER	218/4668 (5%)	248/4672 (5%)	0.87 (0.73-1.05)		0.14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1.11 (0.77-1.61)		0.57
Harmony	79/4731 (2%)	111/4732 (2%)	0.71 (0.53-0.94)		<0.001
REWIND	213/4949 (4%)	226/4952 (5%)	0.93 (0.77-1.12)		0.46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0.86 (0.48-1.44)		0.59
Overall	936/27977 (3%)	1016/28027 (4%)	0.91 (0.83-0.99)	312 (165-2810)	0.028



~~Figure 6: Renal outcomes~~

Renal outcomes	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95%CI)	P-value
Composite renal outcome including macroalbuminuria					
ELIXA	172/2639 (6%)	203/2647 (6%)	0.84 (0.68-1.02)		0.083
EXSCEL	366/6256 (6%)	407/6222 (7%)	0.88 (0.76-1.01)		0.065
LEADER	268/4668 (6%)	337/4672 (7%)	0.78 (0.67-0.92)		0.003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0.64 (0.46-0.88)		0.006
REWIND	848/4949 (17%)	970/4952 (20%)	0.85 (0.77-0.93)		<0.001
Overall	1716/20160 (9%)	2017/20142 (10%)	0.83 (0.78-0.89)	62 (48-96)	<0.001
Worsening of renal function					
ELIXA	35/3032 (1%)	41/3031 (1%)	1.16 (0.74-1.83)		0.51
EXSCEL	246/6456 (4%)	273/6458 (4%)	0.88 (0.74-1.05)		0.16
LEADER	87/4668 (2%)	97/4672 (2%)	0.89 (0.67-1.19)		0.43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1.28 (0.64-2.58)		0.48
REWIND	169/4949 (3%)	237/4952 (5%)	0.70 (0.57-0.85)		<0.001
Overall	555/20753(3%)	662/20762 (3%)	0.87 (0.73-1.03)	245 (118-1064*)	0.098



~~Data on renal outcomes were not available in Harmony Outcomes and PIONEER 6. The broader "composite renal outcome" consisted of development of macroalbuminuria, doubling of serum creatinine or ≥40% decline in eGFR, development of end-stage renal disease or death due to renal disease. The narrower "worsening of renal function" outcome was defined as either doubling of serum creatinine or ≥40% decline in eGFR. Exact definitions of renal outcomes are detailed in Appendix Table 1. * number needed to harm~~

~~Figure 7: Safety outcomes~~

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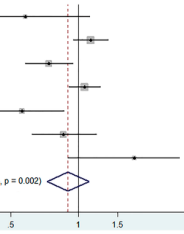
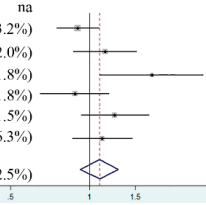
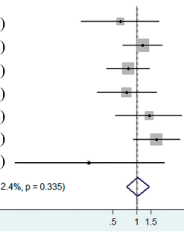
Severe hypoglycemia	GLP-receptor agonist n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
ELIXA	14/3034 (<1%)	24/3034 (1%)	0.58 (0.30-1.13)	0.11
EXSCEL	247/7356 (3%)	219/7396 (3%)	1.14 (0.95-1.37	0.17
LEADER	114/4668 (2%)	153/4672 (3%)	0.74 (0.58-0.95)	0.016
SUSTAIN-6	369/1648 (22%)	350/1649 (21%)	1.07 (0.91-1.26)	0.42
Harmony	31/4731 (1%)	55/4732 (1%)	0.56 (0.36-0.87)	0.009
REWIND	64/4949 (1%)	74/4952 (2%)	0.86 (0.62-1.21)	0.38
PIONEER 6	23/1591 (1%)	13/1592 (1%)	1.78 (0.90-3.53)	0.32
Overall		Overall (I-squared = 71.2%, p = 0.002)	0.90 (0.73-1.12)	0.34



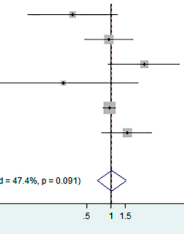
Retinopathy	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
ELIXA	na	na	na	na
EXSCEL	214/7344 (2.9%)	238/7389 (3.2%)	0.90 (0.75-1.09)	0.25
LEADER	106/4668 (2.3%)	92/4672 (2.0%)	1.15 (0.87-1.52)	0.33
SUSTAIN-6	50/1648 (3.0%)	29/1649 (1.8%)	1.73 (1.09-2.72)	0.02
Harmony	78/4717 (1.7%)	89/4715 (1.8%)	0.88 (0.65-1.19)	0.41
REWIND	95/4949 (1.9%)	76/4952 (1.5%)	1.25 (0.93-1.69)	0.14
PIONEER 6	113/1591 (7.1%)	101/1592 (6.3%)	1.12 (0.86-1.46)	0.40
Overall	656/24917 (2.6%)	625/24969 (2.5%)	1.09 (0.92-1.29)	0.30



Pancreatitis	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
ELIXA	5/3034 (<1%)	8/3034 (<1%)	0.62 (0.20-1.91)	0.41
EXSCEL	26/7356 (<1%)	22/7396 (<1%)	1.19 (0.67-2.10)	0.55
LEADER	18/4668 (<1%)	23/4672 (<1%)	0.78 (0.42-1.45)	0.44
SUSTAIN-6	9/1648 (1%)	12/1649 (1%)	0.75 (0.32-1.78)	0.51
Harmony	10/4731 (<1%)	7/4732 (<1%)	1.43 (0.54-3.75)	0.46
REWIND	23/4949 (1%)	13/4952 (<1%)	1.77 (0.90-3.51)	0.11
PIONEER 6	1/1591 (<1%)	3/1592 (<1%)	0.25 (0.03-2.24)	0.20
Overall		Overall (I-squared = 12.4%, p = 0.335)	1.03 (0.74-1.42)	0.86



Pancreatic cancer	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
ELIXA	3/3034 (<1%)	9/3034 (<1%)	0.33 (0.09-1.23)	0.50
EXSCEL	15/7356 (<1%)	16/7396 (<1%)	0.94 (0.47-1.91	0.87
LEADER	13/4668 (<1%)	5/4672 (<1%)	2.61 (0.93-7.32)	0.069
SUSTAIN-6	1/1648 (<1%)	4/1649 (<1%)	0.25 (0.03-2.24)	0.22
Harmony	6/4731 (<1%)	5/4715 (4%)	0.95 (0.79-1.16)	0.644
REWIND	19/4949 (<1%)	12/4952 (<1%)	1.59 (0.77-3.27)	0.22
PIONEER 6	na	na	na	na
Overall		Overall (I-squared = 47.4%, p = 0.091)	1.03 (0.67-1.58)	0.897



~~For definitions of safety outcomes, please see Appendix Table 2. The definition of severe hypoglycaemia in all trials included clinical symptoms and the need for help from another person for treatment. SUSTAIN-6 also included symptomatic hypoglycemia as confirmed on plasma glucose testing (<3.1 mmol per litre [56 mg per deciliter]~~

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***Reply to Reviewers Comments**

Manuscript reference number: THELANCETDE-D-19-00502R1
Title: Use of GLP-1 receptor agonists in type 2 diabetes and cardiovascular outcomes - a systematic review and meta-analysis of randomized trials

Dear Dr. Mcmurray,

Thank you for submitting your paper to The Lancet Diabetes & Endocrinology. Following a discussion with the editorial team, I am pleased to tell you that we have decided to invite you to submit a revised version of your manuscript that addresses the editors' and reviewers' comments below. We usually ask that authors of research papers return their revised manuscript within 4-5 working days. If you cannot make this deadline, please let me know by email as soon as possible.

In your point-by-point responses to the reviewer and editorial comments, please state the page number and paragraph of the manuscript where changes have been made as a result. It can be helpful to tabulate your responses with columns labelled (left to right) as follows: Reviewer comments; author response and changes made; page number in revised paper where the change can be found. Please provide a 'clean' version of the manuscript, incorporating changes, and a 'tracked' changes version (highlighting additions and deletions - please use the 'Track changes' function in Word). IMPORTANT: where a reviewer has asked for clarification, it is usually necessary to amend the manuscript as well as answering the question directly in the point-by-point response document - where no changes have been made to the manuscript, please provide justification.

I look forward to hearing from you.

Kind regards,
Neil Bennet

Senior Editor
The Lancet Diabetes & Endocrinology
Email: neil.bennet@lancet.com

Thank you – we hope our responses, provided below, and our revised manuscript is now satisfactory. We think it is definitely improved from the original and represents a fair an balanced update on field.

EDITORS' SPECIFIC POINTS:

*In addition to responding to the re-reviewers' comments, we require authors to respond to the general editorial comments listed below - we require responses to each of these points individually, to ensure all have been addressed. For example, as detailed in these general points, there is a limit on the number of non-text items (figures and tables) of 5-6: currently there are 9 such items in the paper. As such we need the authors to attempt to reduce this number, either by combining certain figures with similar layout, or by moving certain items to a separate appendix Word file (we would suggest the latter for table 1, and possibly figure 1 if necessary). Additionally, as detailed in the general editorial points, we require the figures (excluding any moved to an appendix file) to be supplied in an editable format. To ensure that the revised paper meets these and other requirements necessary for acceptance, please ensure that you go through and respond to all the points listed.

We have replied to each point, individually, as requested. We have reduced the number of non-text items to 5, as requested. We have complied with the general editorial points.

*Based on the re-review comments from Reviewer #6, some further toning down may be required with respect to the subgroup analysis. This may also require some more detailed results reporting in the abstract (eg, so that readers of the abstract can see the actual HRs for subgroups (eg, primary and secondary prevention), as well as heterogeneity p values, with carefully worded interpretation.

We have tried to address the somewhat conflicting comments of Reviewers #1 and #6 in our revised manuscript. Specifically, we have provided an estimated median follow-up for the NNTs and removed NNTs (based on the overall relative risk reduction) from the subgroup figure. We think it is best to simply state in the abstract that *"There was no statistically significant heterogeneity across the subgroups examined."* To just show the primary vs. secondary prevention subgroup in the abstract would look rather strange. Alternatively, to include all subgroups would exceed the word limit, considerably. The most abbreviated way of describing these we could come up with was: "Overall, there was no statistically significant heterogeneity across the subgroups examined: HR for MACE in patients with a history of cardiovascular disease: yes 0.86 (95% CI 0.79, 0.94), no 0.95 (0.83, 1.08), (interaction p=0.22); glycated haemoglobin level: higher 0.85 (0.78, 0.92), lower 0.89 (0.83,0.96), (p=0.41); trial duration: shorter 0.84 (0.71,0.99), longer 0.89 (0.84,0.94), (p=0.52); dosing: daily 0.92 (0.80,1.05), weekly 0.85 (0.78,0.93) (p=0.34); GLP-1 homology: yes 0.84 (0.79,0.90), no 0.95 (0.85,1.06), (p=0.06); body mass index: lower 0.87 (0.77,0.98), higher 0.87 (0.82,0.93), (p=1.00); age: younger 0.85 (0.72,0.99), older 0.87 (0.81,0.93) (p=0.79); renal function: better 0.88 (0.76,1.03), worse 0.85 (0.76,0.96), (p=0.72)." That is a total of 98 words. We think simply saying *"There was no statistically significant heterogeneity across the subgroups examined."* is best – it is succinct and accurate.

*We believe the title would read better as "Cardiovascular, mortality, and renal outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials" [NOTE: you can of course amend this as needed, eg, if you do not think it is appropriate to list these three groups of outcomes; structurally though, it is best to mention the outcomes analyses first, as in this suggestion]

We have amended the title, as suggested.

REVIEWERS' COMMENTS:

Reviewer #1: The main changes to the manuscript since the previous review are that the authors have toned down their comments regarding GLP-1R agonists in primary prevention and added numbers needed to treat to the article.

In their discussion of the lack of any statistical differences (page 16 lines 1-14), they seem to have the right idea but there are a lot of negatives ("did not show", "However", "although", and "however" in consecutive sentences) making it hard to fully understand. Perhaps best to focus on what is clear: i) they do not cause notable cardiovascular harm in primary prevention and may reduce risk; ii) the absolute benefit is likely smaller in primary than secondary prevention, largely because absolute risk is higher in secondary prevention; iii) even when combining the current set of trials there is a lack of power to accurately determine if there is a beneficial effect if one restricts to primary prevention populations.

We have rewritten the relevant section of the Discussion in keeping with the Reviewer's suggestion. It now says:

"The inclusion of PIONEER 6 and, especially, REWIND allowed us to examine this question, with an almost doubling in the number of "primary-prevention" patients, overall, exposed to a GLP-1 receptor agonist, although even with this, the number of participants with MACE in this subgroup was less than a third of that in most other subgroups. Consequently, this analysis may still be under powered and, although there was no heterogeneity for the effect of GLP-1 receptor agonist treatment, the statistical test for interaction is weak. Therefore we cannot be certain that the relative risk reduction in "primary prevention" patients was the same as in "secondary prevention" patients and even if it was, the absolute risk reduction in the "primary prevention" population will be smaller, and the treatment likely to be less cost-effective, because individuals without established cardiovascular disease are at lower baseline risk than "secondary prevention" patients. These additional data may, therefore, not be sufficiently robust to challenge the new guideline recommendations only to use GLP-1 receptor agonists in patients with established cardiovascular disease."

Their analyses of NNT suffer from two problems:
i) they should give some indication of a time frame over which the NNT is relevant, e.g. perhaps the median/mean follow-up time. As the treatment gradually accrues cardiovascular benefit over time an NNT without a time reference is effectively meaningless (even if they have been published for SGLT2is). I realise some assumptions or back-of-the-envelope calculations may be required to give an approximate time-frame, but that is better than having a statistic which is largely meaningless.

We agree and had written caveats stating this when originally asked by another Reviewer to add NNTs. We have added an estimated median follow-up, as suggested – this was 3.2 years. On balance, we think even with their limitations, the NNTs do succeed in making the point we believe the Reviewer who requested them wished to make – that the absolute treatment effects with these drugs are relatively modest. However, we would be happy to remove NNTs if that is the Editor's preference.

ii) In Figures 3 they present NNT calculated using an "overall" hazard ratio, next to subgroup hazard ratios. I think this is misleading as there is a reasonable expectation that the HR and NNT in the same row of the Figure relate to one another and would have been calculated on the same set of data. So I suggest they are (actually I feel quite strongly that these should be) removed from this particular figure (e.g. as they have done for individual trials with differing follow-up durations in other figures where the NNT likewise would have been misleading).

We have removed NNTs for subgroups from the figure.

Reviewer #4: Thank you for addressing all issues raised including providing NNTs. In aggregate, I feel the manuscript has improved considerably and gives novel and practically relevant information.

Thank you.

Reviewer #6: Manuscript re-reviewed without access to a track changes version. This version mostly addresses the concerns expressed in my original review. I do find the manuscript marginal in priority because it offers almost no insights not already provided by the included trials. I still think the authors over-emphasize the potential role of GLP-1 agonists in primary prevention. Although there is no "statistical heterogeneity" the analysis is severely underpowered for this assessment. I must point out that the HR in the primary prevention population is 0.95 with an upper CI of 1.08. The lack of an interaction P value likely represents a lack of power. In general the authors over-emphasize subgroup analyses which leads to potentially misleading conclusions. The subgroup "human GLP-1

homology" is HIGHLY confounded by differences in drug pharmacokinetics UNRELATED to homology. I would request that the authors go further in explaining that these analyses are potentially unreliable. In the words of a very prominent statistician: "let me study enough subgroups and I'll show you anything you want."

We have “toned down” our comments about primary prevention in response to the Reviewers’ and Editor’s comments (see above).

Regarding "human GLP-1 homology", we examined a modest number of subgroups (eight in total) and, in fact, some of these were added at the request of the Reviewers. We think we have made it very clear in the text of the Discussion that this is a potentially confounded subgroup (as indeed is any univariate subgroup). However, it does address one suggestion put forward to explain apparent differences between the trials and therefore is of interest. We believe that we have both addressed the question and given a balanced and detailed discussion of the answer, including the complexities of its interpretation.

Figure1 esp GLP

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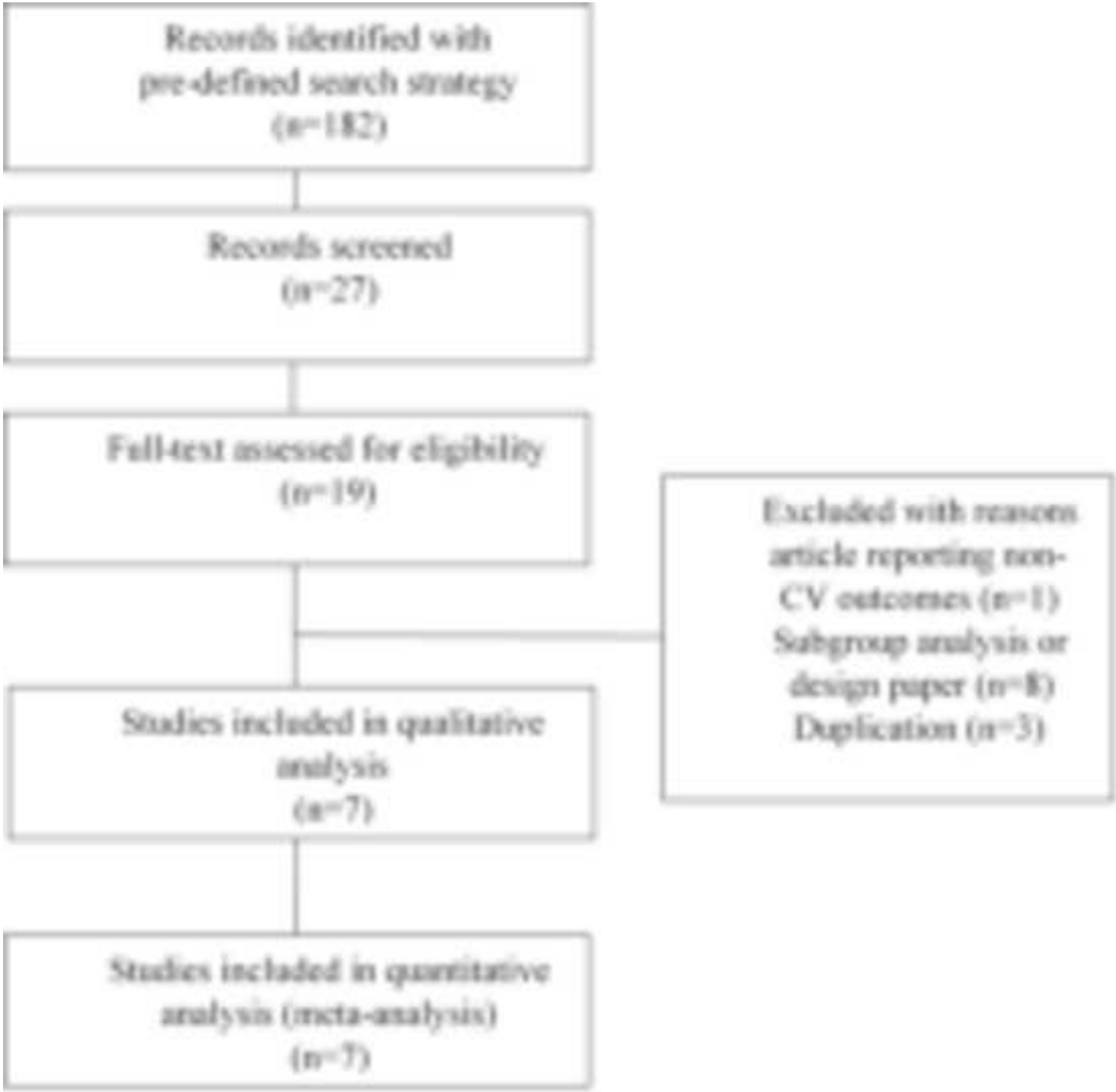

Figure 2 CV death GLP

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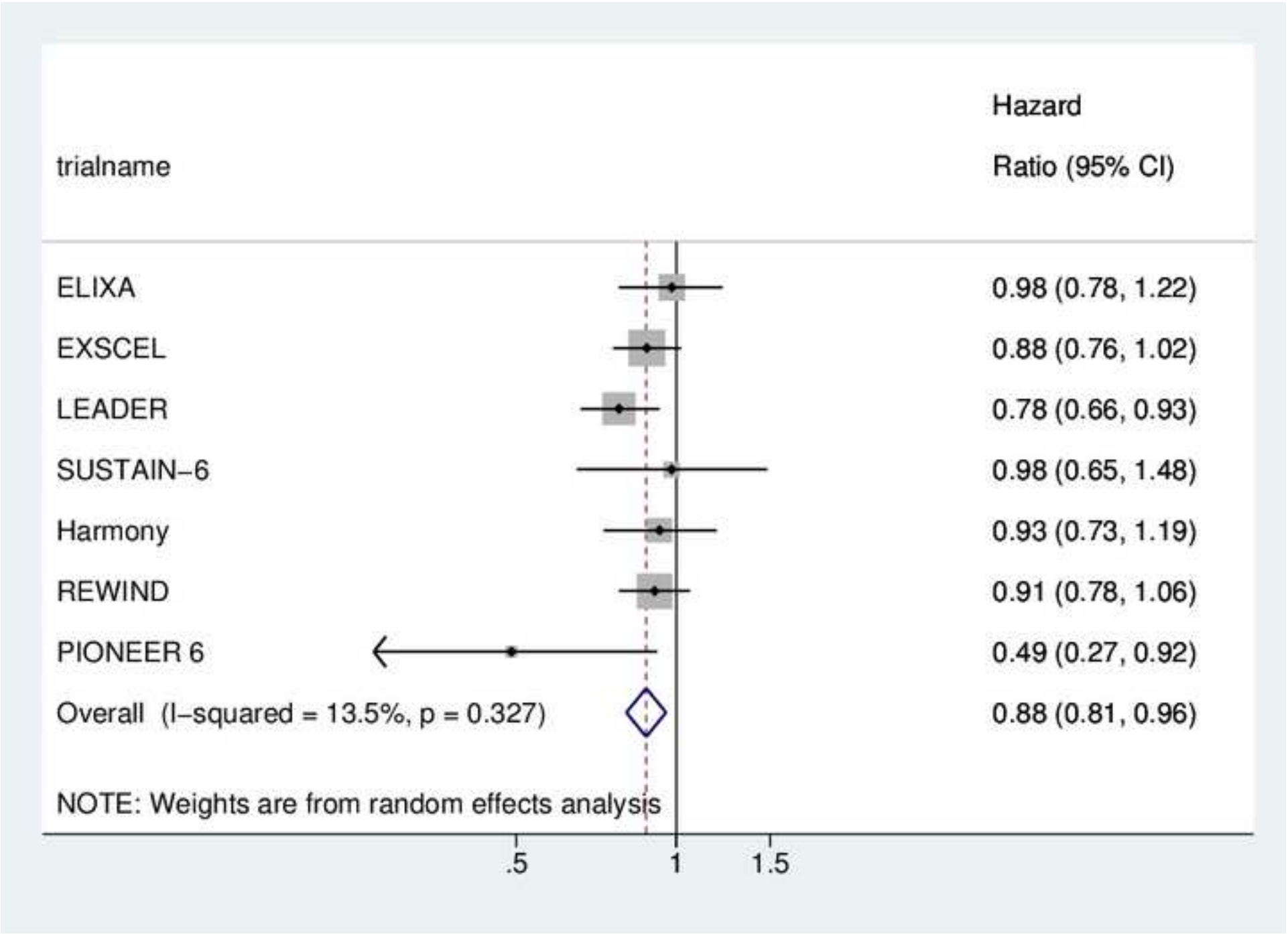

Figure 2 MI

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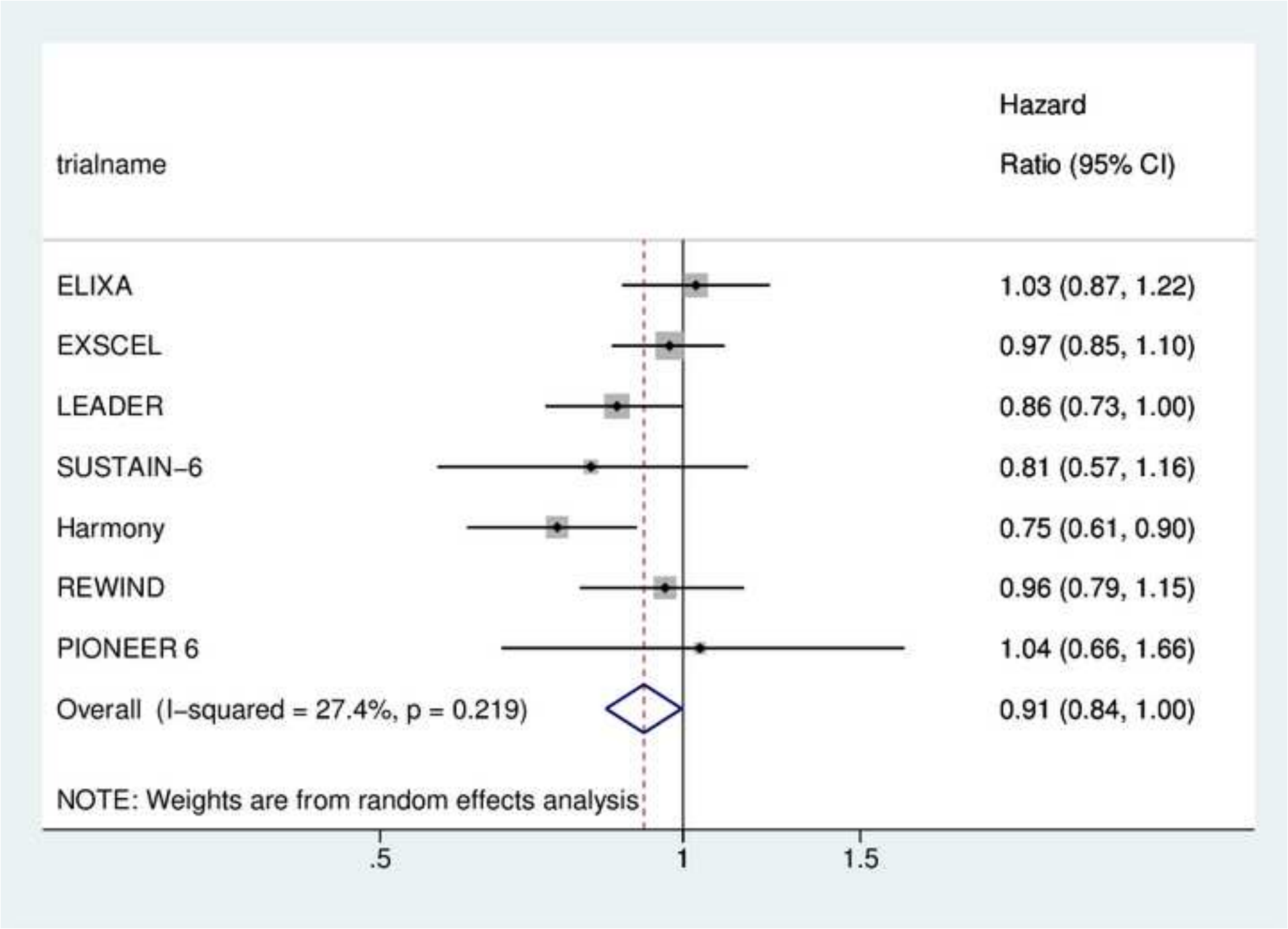

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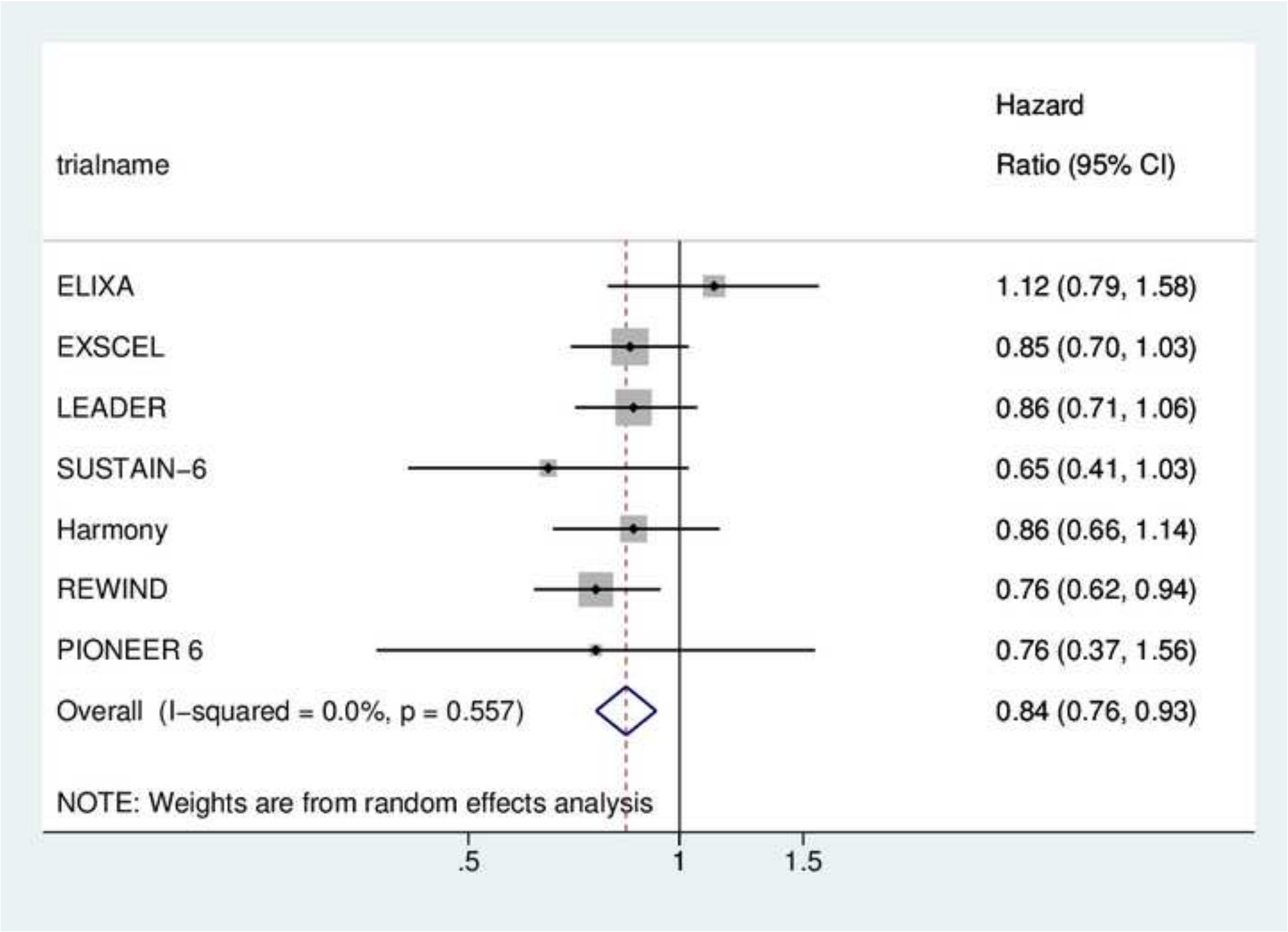

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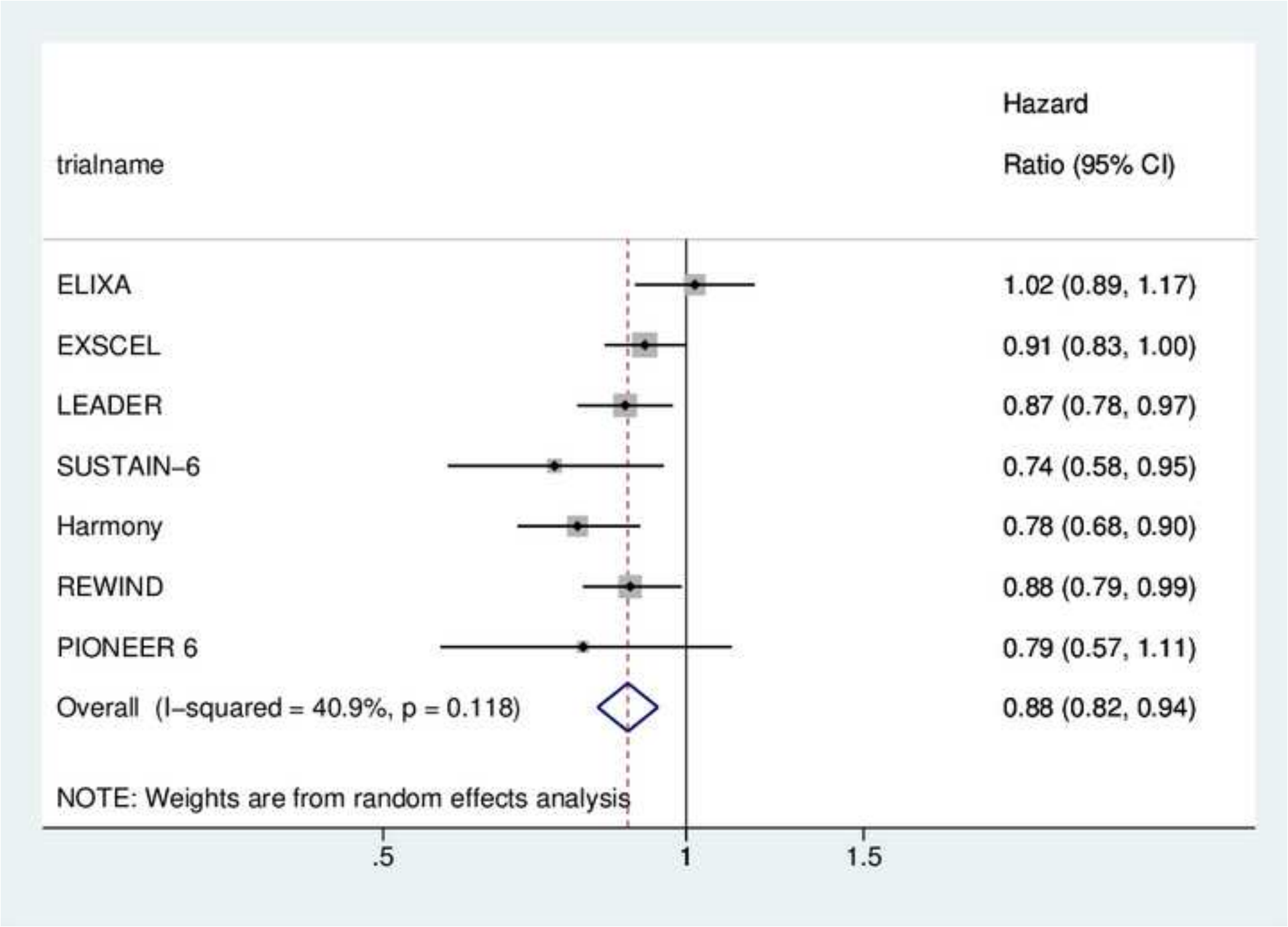

Figure 3 subgroups

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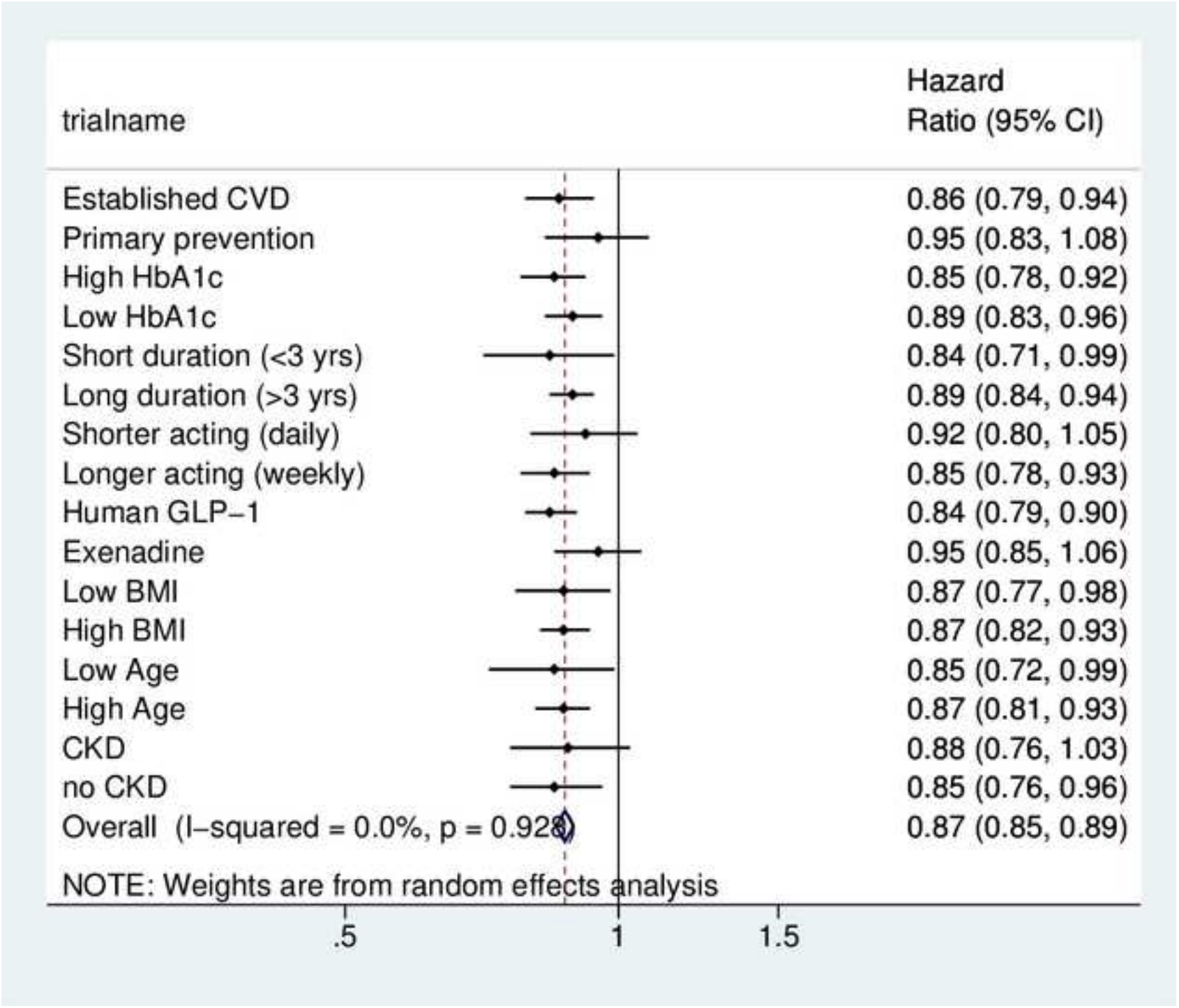

Figure 4 all cause

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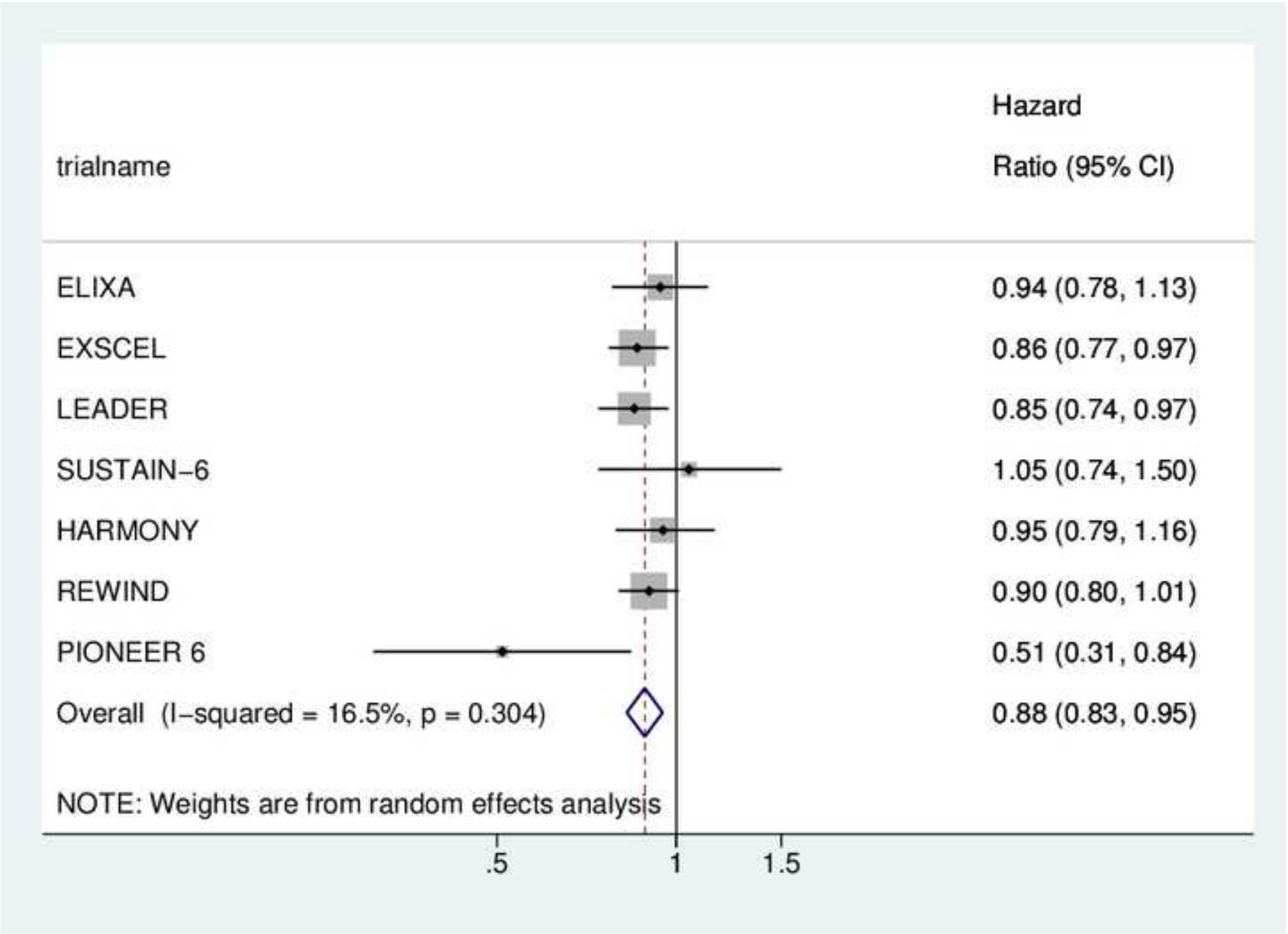

Figure 4 composite

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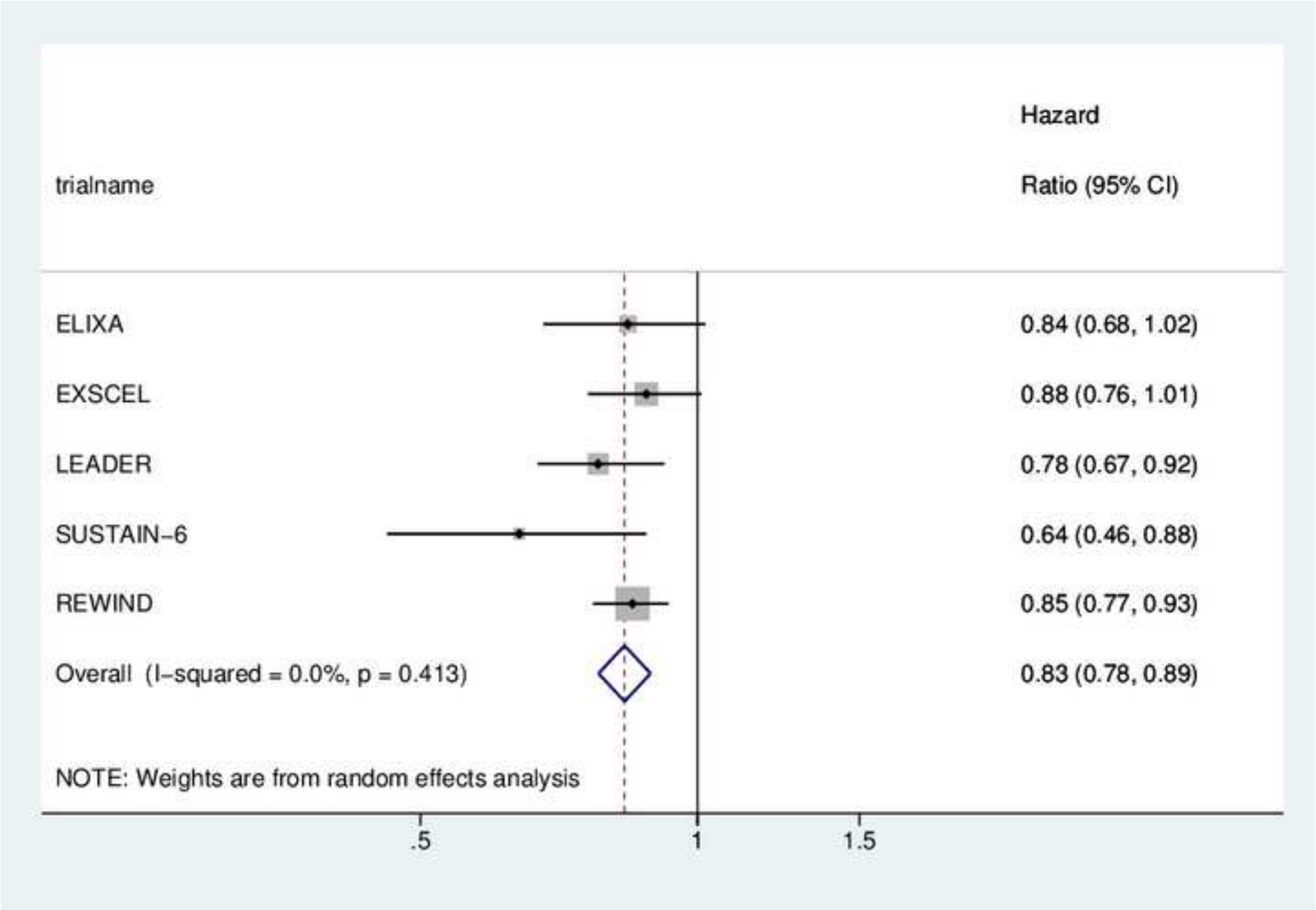

Figure 4 HF hosp.

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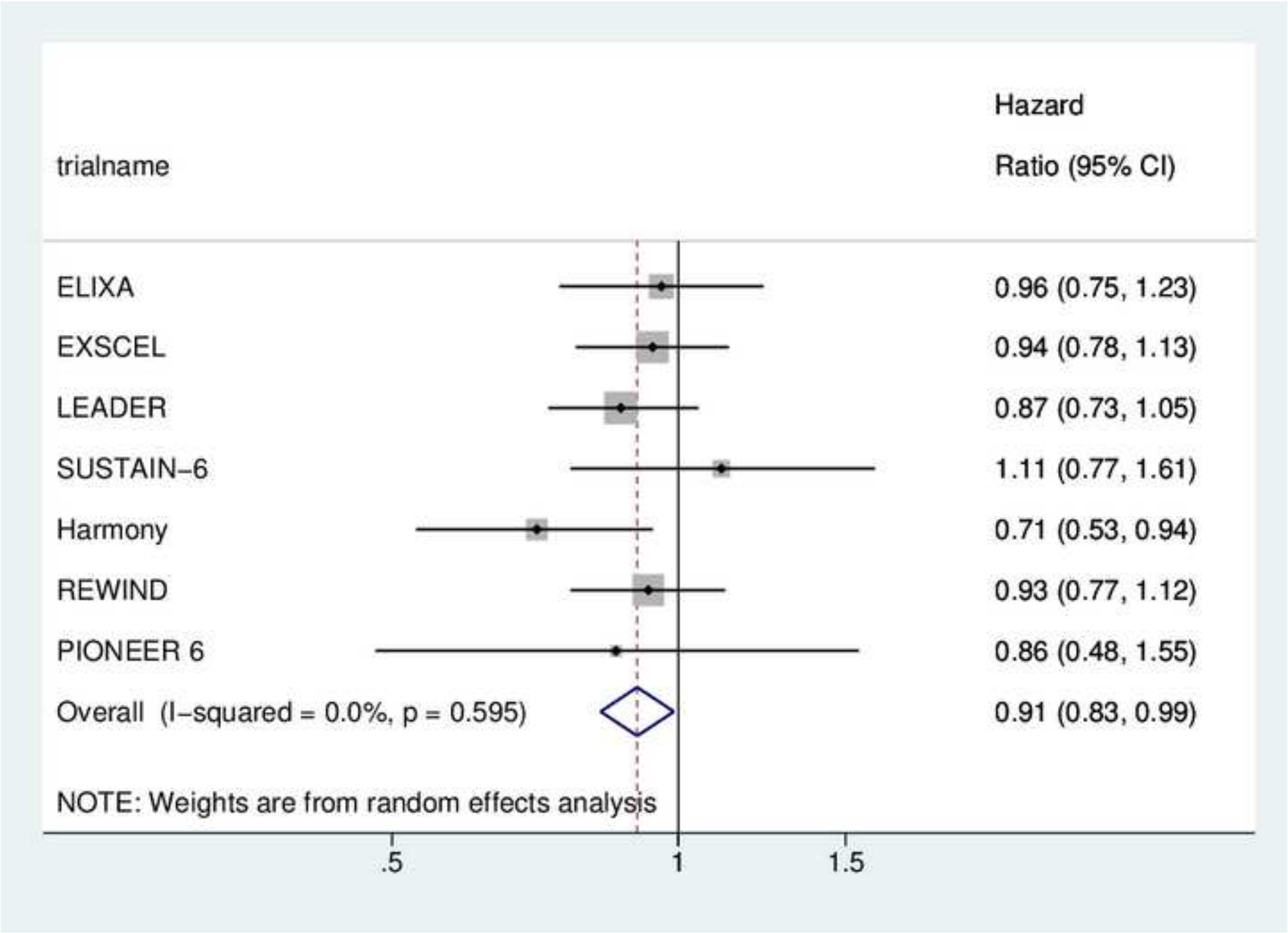

Figure 4 worsening

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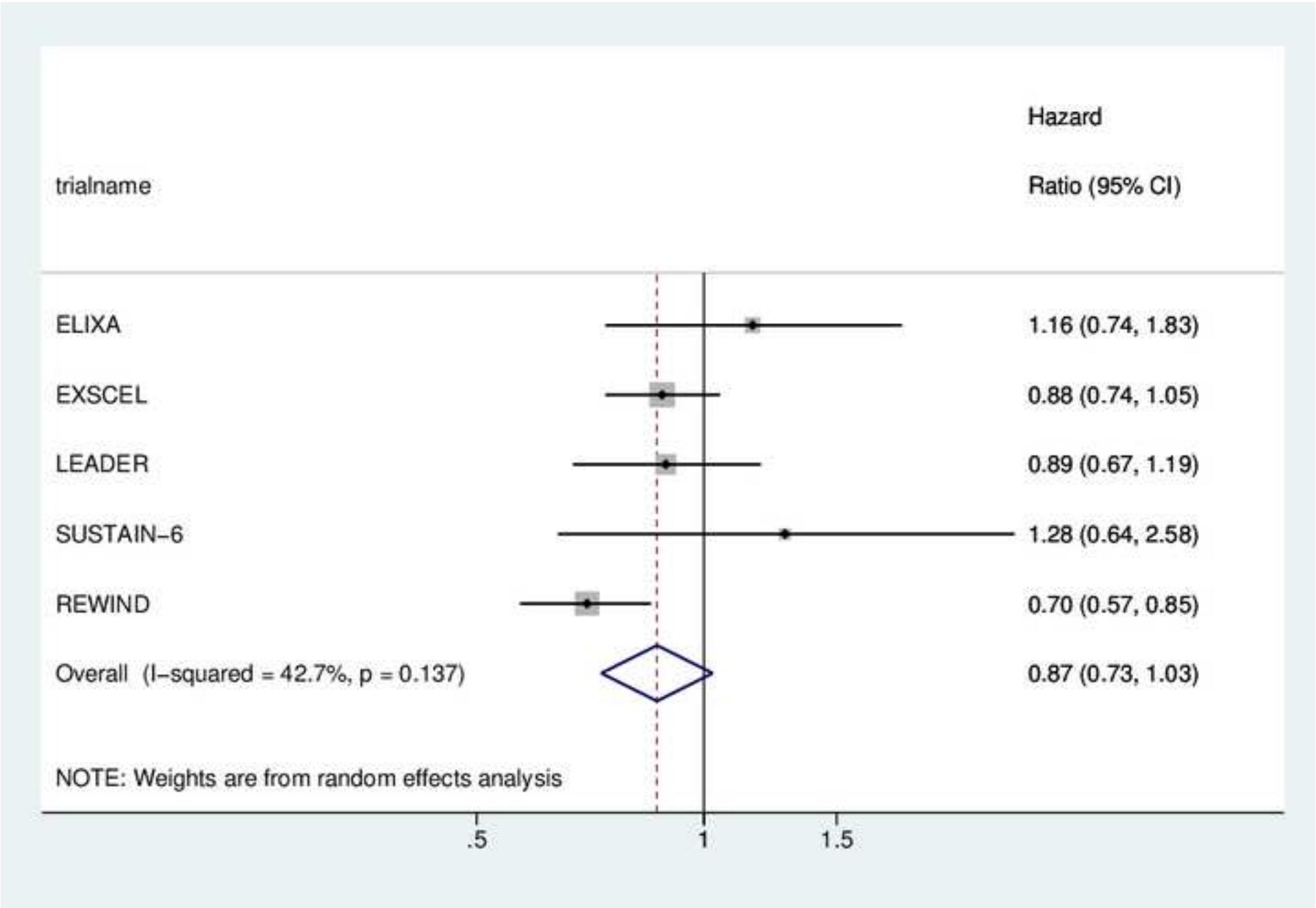

Figure 1 tif

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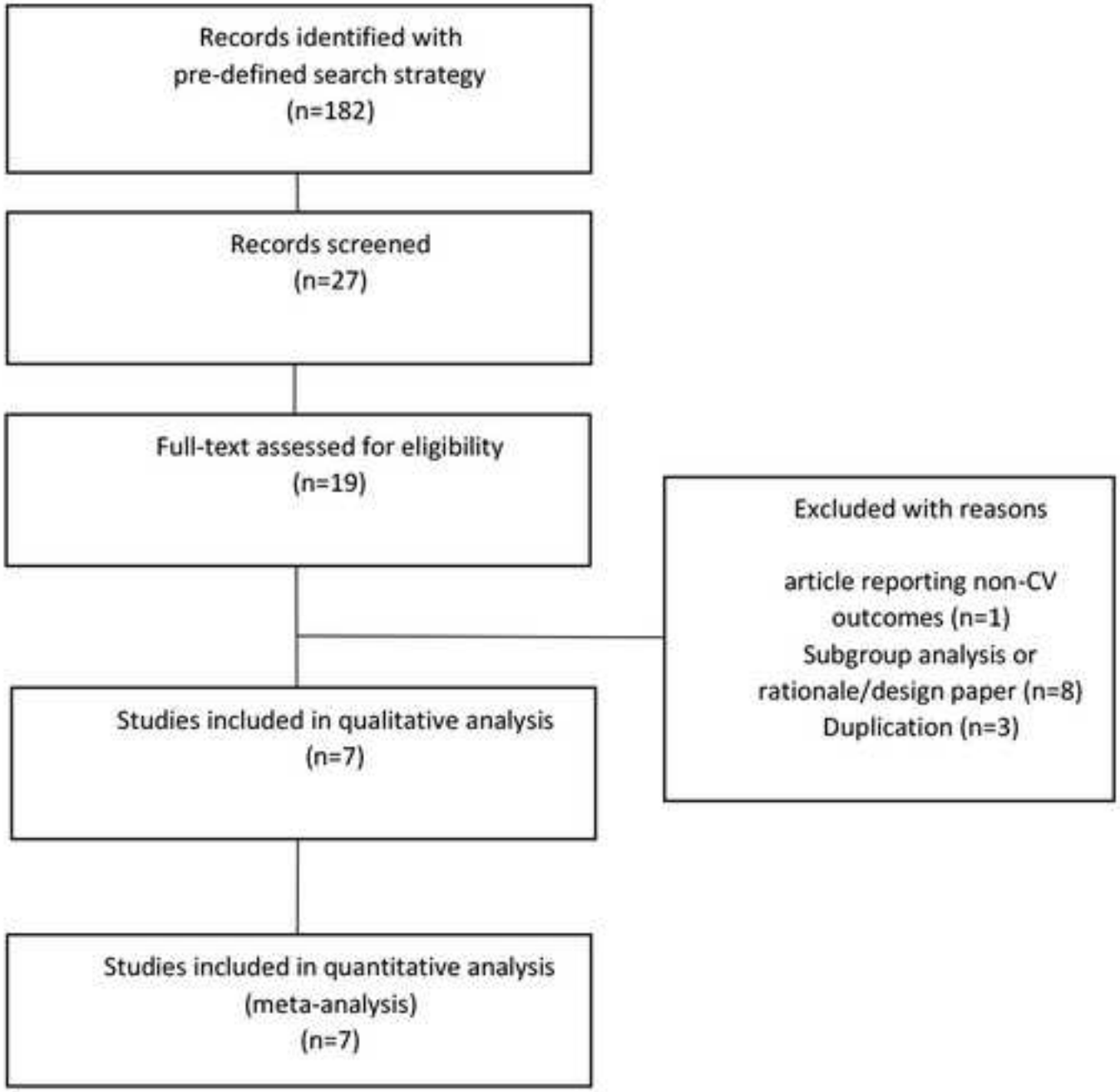

Figure 2 tiff

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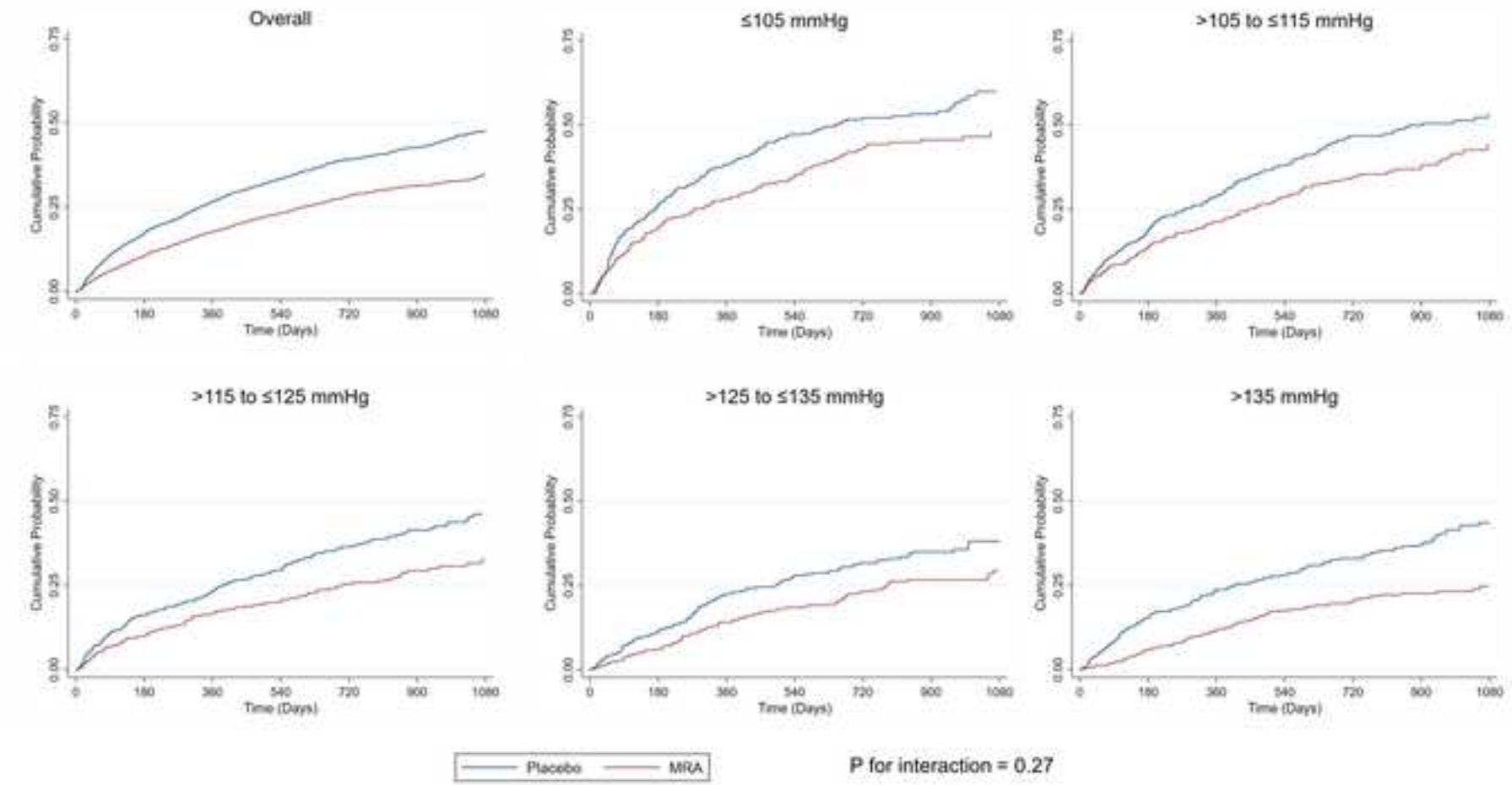

Figure 3 tiff

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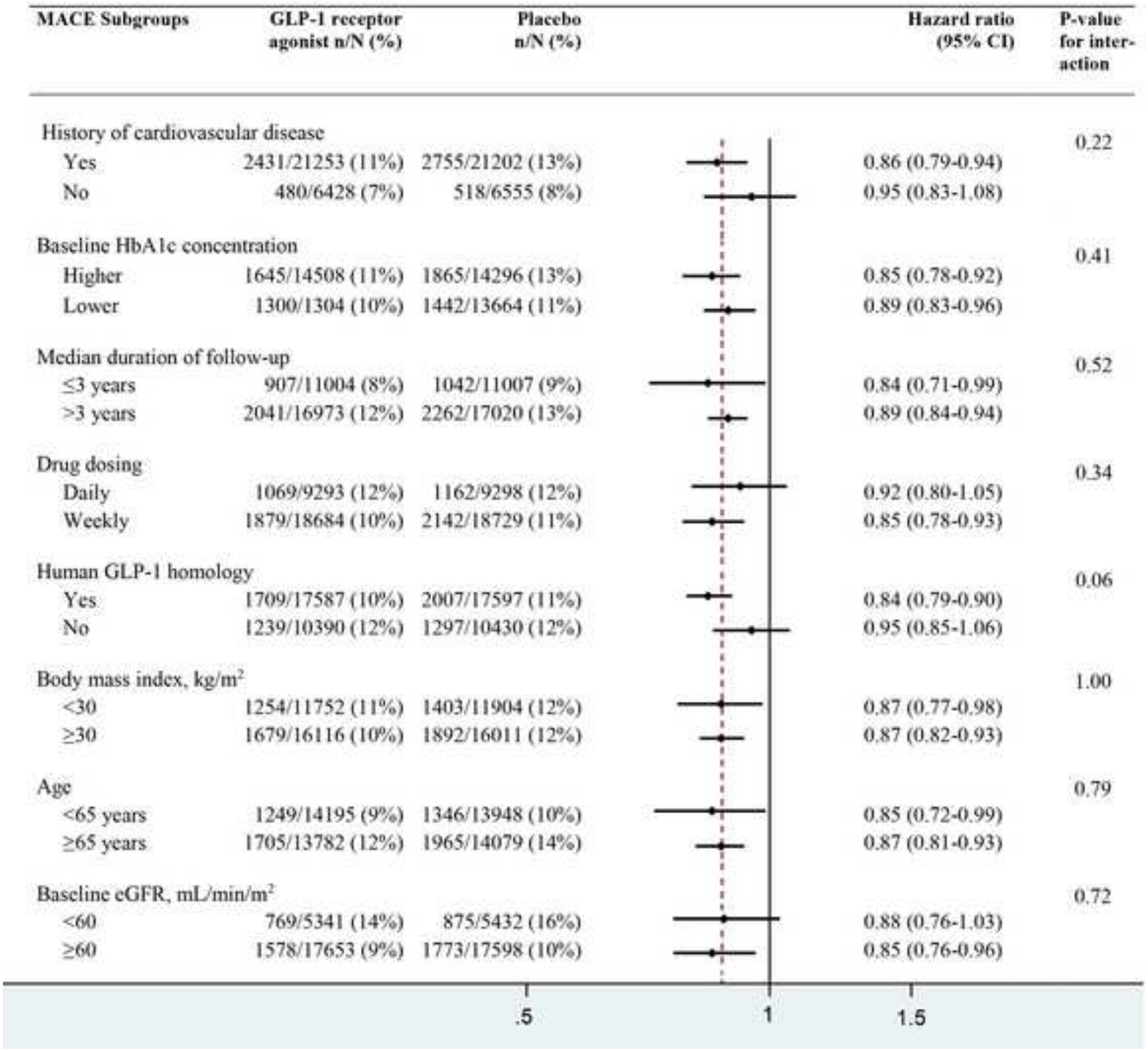

Figure 4

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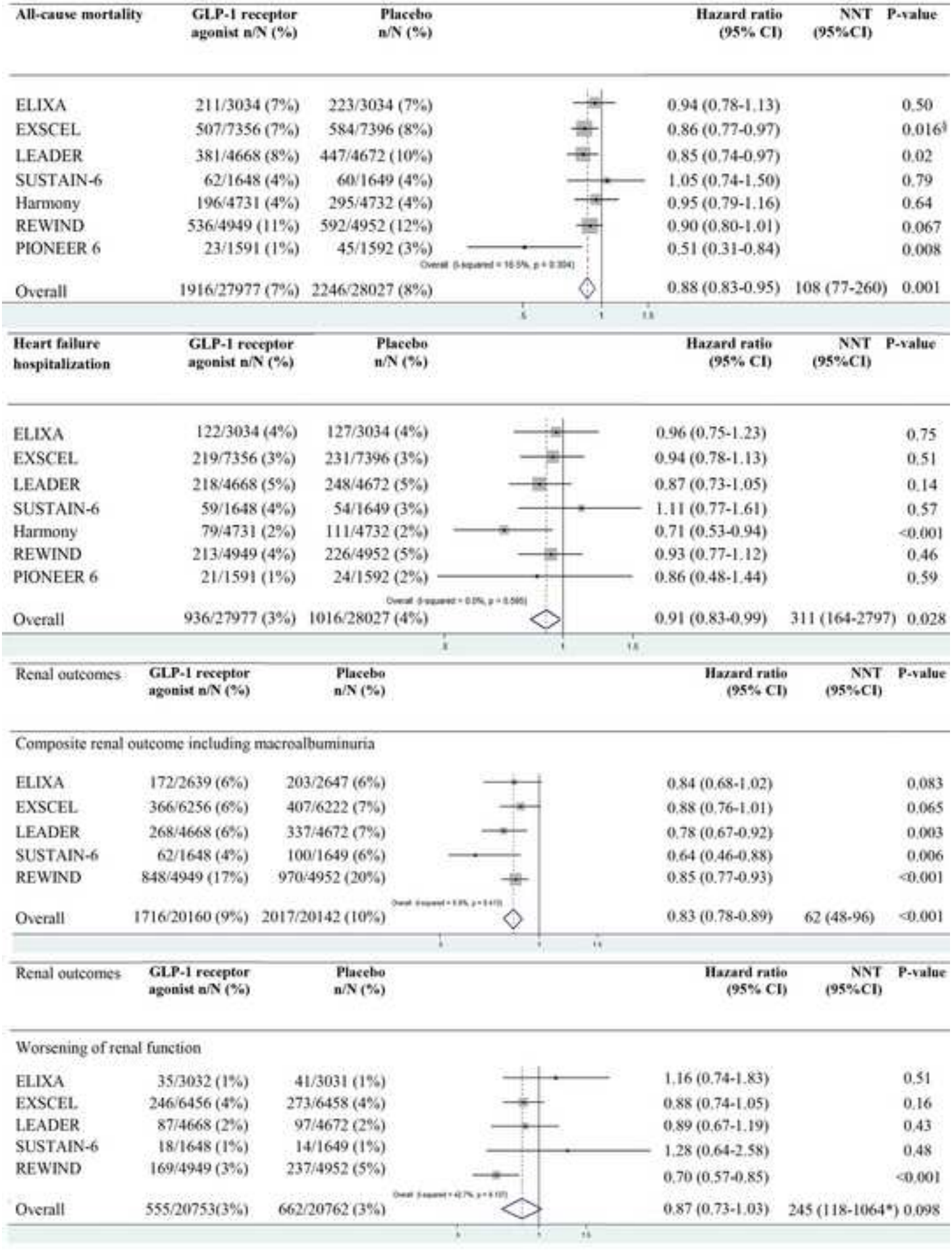

Figure data for submission

3-component MACE	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	P-value
ELIXA	400/3034 (13%)	392/3034 (13%)	1.02 (0.89-1.17)		0.78
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91 (0.83-1.00)		0.061
LEADER	608/4668 (13%)	694/4672 (15%)	0.87 (0.78-0.97)		0.015
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0.74 (0.58-0.95)		0.016
Harmony	338/4731 (7%)	428/4732 (9%)	0.78 (0.68-0.90)		<0.001
REWIND	594/4949 (12%)	663/4952 (13%)	0.88 (0.79-0.99)		0.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0.79 (0.57-1.11)		0.17
Overall	2948/27977 (11%)	3304/28027 (12%)	0.88 (0.82-0.94)	75 (50-151)	<0.001

Cardiovascular death	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	P-value
ELIXA	156/3034 (5%)	158/3034 (5%)	0.98 (0.78-1.22)		0.85
EXSCEL	340/7356 (5%)	383/7396 (5%)	0.88 (0.76-1.02)		0.096
LEADER	219/4668 (5%)	278/4672 (6%)	0.78 (0.66-0.93)		0.007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0.98 (0.65-1.48)		0.92
Harmony	122/4731 (3%)	130/4732 (3%)	0.93 (0.73-1.19)		0.58
REWIND	317/4949 (6%)	346/4952 (7%)	0.91 (0.78-1.06)		0.18
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0.49 (0.27-0.92)		0.021
Overall	1277/27977 (5%)	1471/28027 (5%)	0.88 (0.81-0.96)	163 (103-489)	0.003

Fatal – and non-fatal MI	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	P-value
ELIXA	270/3034 (9%)	261/3034 (9%)	1.03 (0.87-1.22)		0.71
EXSCEL	483/7356 (7%)	493/7396 (7%)	0.97 (0.85-1.10)		0.62
LEADER	292/4668 (6%)	339/4672 (7%)	0.86 (0.73-1.00)		0.046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0.81 (0.57-1.16)		0.26
Harmony	181/4731 (4%)	240/4732 (5%)	0.75 (0.61-0.90)		0.003
REWIND	223/4949 (5%)	231/4952 (5%)	0.96 (0.79-1.15)		0.63
PIONEER 6	37/1591 (2%)	31/1592 (2%)	1.18 (0.73-1.90)		0.49
Overall	1540/27977 (6%)	1662/28027 (6%)	0.91 (0.84-1.00)	193 (109-na)	0.043

Fatal and non-fatal stroke	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	P-value
ELIXA	67/3034 (2%)	60/3034 (2%)	1.12 (0.79-1.58)		0.54
EXSCEL	187/7356 (3%)	218/7396 (3%)	0.85 (0.70-1.03)		0.095
LEADER	173/4668 (4%)	199/4672 (4%)	0.86 (0.71-1.06)		0.16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0.65 (0.41-1.03)		0.066
Harmony	94/4731 (2%)	108/4732 (2%)	0.86 (0.66-1.14)		0.30
REWIND	158/4949 (3%)	205/4952 (4%)	0.76 (0.62-0.94)		0.01
PIONEER 6	12/1591 (1%)	16/1592 (1%)	0.74 (0.35-1.57)		0.43
Overall	721/27977 (3%)	852/28027 (3%)	0.84 (0.76-0.93)	209 (139-477)	<0.001

Heart failure hospitalization	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95%CI)	P-value
ELIXA	122/3034 (4%)	127/3034 (4%)	0.96 (0.75-1.23)		0.75
EXSCEL	219/7356 (3%)	231/7396 (3%)	0.94 (0.78-1.13)		0.51
LEADER	218/4668 (5%)	248/4672 (5%)	0.87 (0.73-1.05)		0.14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1.11 (0.77-1.61)		0.57
Harmony	79/4731 (2%)	111/4732 (2%)	0.71 (0.53-0.94)		<0.01
REWIND	213/4949 (4%)	226/4952 (5%)	0.93 (0.77-1.12)		0.46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0.86 (0.48-1.44)		0.59
Overall	931/27977 (3%)	1021/28027 (4%)	0.91 (0.83-0.99)	311 (164-2797)	0.028

All-cause mortality	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	P-value
ELIXA	211/3034 (7%)	223/3034 (7%)	0.94 (0.78-1.13)		0.50
EXSCEL	507/7356 (7%)	584/7396 (8%)	0.86 (0.77-0.97)		0.016[§]
LEADER	381/4668 (8%)	447/4672 (10%)	0.85 (0.74-0.97)		0.02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1.05 (0.74-1.50)		0.79
Harmony	196/4731 (4%)	295/4732 (4%)	0.95 (0.79-1.16)		0.64
REWIND	536/4949 (11%)	592/4952 (12%)	0.90 (0.80-1.01)		0.067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0.51 (0.31-0.84)		0.008
Overall	1916/27977 (7%)	2246/28027 (8%)	0.88 (0.83-0.95)	108 (77-260)	0.001

MACE Subgroups	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	P-value for inter-action
History of cardiovascular disease				0.22
Yes	2431/21253 (11%)	2755/21202 (13%)	0.86 (0.79-0.94)	
No	480/6428 (7%)	518/6555 (8%)	0.95 (0.83-1.08)	
Baseline HbA1c concentration				0.41
Higher	1645/14508 (11%)	1865/14296 (13%)	0.85 (0.78-0.92)	
Lower	1300/13004 (10%)	1442/13664 (11%)	0.89 (0.83-0.96)	
Median duration of follow-up				0.52
≤3 years	907/11004 (8%)	1042/11007 (9%)	0.84 (0.71-0.99)	
>3 years	2041/16973 (12%)	2262/17020 (13%)	0.89 (0.84-0.94)	
Drug dosing				0.34
Daily	1069/9293 (12%)	1162/9298 (12%)	0.92 (0.80-1.05)	
Weekly	1879/18684 (10%)	2142/18729 (11%)	0.85 (0.78-0.93)	
Human GLP-1 homology				0.06
Yes	1709/17587 (10%)	2007/17597 (11%)	0.84 (0.79-0.90)	
No	1239/10390 (12%)	1297/10430 (12%)	0.95 (0.85-1.06)	
Body mass index, kg/m^2				1.00
<30*	1254/11752 (11%)	1403/11904 (12%)	0.87 (0.77-0.98)	
≥30	1679/16116 (10%)	1892/16011 (12%)	0.87 (0.82-0.93)	
Age				0.79
<65 years	1249/14195 (9%)	1346/13948 (10%)	0.85 (0.72-0.99)	
≥65 years	1705/13782 (12%)	1965/14079 (14%)	0.87 (0.81-0.93)	
Baseline eGFR, $mL/min/m^2$				0.72
<60	769/5341 (14%)	875/5432 (16%)	0.88 (0.76-1.03)	
≥60	1578/17653 (9%)	1773/17598 (10%)	0.85 (0.76-0.96)	
Overall	2948/27977 (11%)	3304/28027 (12%)	0.88 (0.82-0.94)	

Renal outcomes	**GLP-1 receptor agonist n/N (%)**	**Placebo n/N (%)**	**Hazard ratio (95% CI)**	**NNT (95% CI)**	**P-value**
Composite renal outcome including macroalbuminuria					
ELIXA	172/2639 (6%)	203/2647 (6%)	0.84 (0.68-1.02)		0.083
EXSCEL	366/6256 (6%)	407/6222 (7%)	0.88 (0.76-1.01)		0.065
LEADER	268/4668 (6%)	337/4672 (7%)	0.78 (0.67-0.92)		0.003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0.64 (0.46-0.88)		0.006
REWIND	848/4949 (17%)	970/4952 (20%)	0.85 (0.77-0.93)		<0.001
Overall	1716/20160 (9%)	2017/20142 (10%)	0.83 (0.78-0.89)	62 (48-96)	<0.001
Worsening of renal function					
ELIXA	35/3032 (1%)	41/3031 (1%)	1.16 (0.74-1.83)		0.513
EXSCEL	246/6456 (4%)	273/6458 (4%)	0.88 (0.74-1.05)		0.164
LEADER	87/4668 (2%)	97/4672 (2%)	0.89 (0.67-1.19)		0.43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1.28 (0.64-2.58)		0.48
REWIND	169/4949 (3%)	237/4952 (5%)	0.70 (0.57-0.85)		<0.001
Overall	555/20753(3%)	662/20762 (3%)	0.87 (0.73-1.03)	245 (118-1064*)	0.098

Severe hypoglycaemia	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
ELIXA	14/3034 (<1%)	24/3034 (1%)	0.58 (0.30-1.13)	0.11
EXSCEL	247/7356 (3%)	219/7396 (3%)	1.14 (0.95-1.37)	0.17
LEADER	114/4668 (2%)	153/4672 (3%)	0.74 (0.58-0.95)	0.016
SUSTAIN-6	369/1648 (22%)	350/1649 (21%)	1.07 (0.91-1.26)	0.42
Harmony	31/4731 (1%)	55/4732 (1%)	0.56 (0.36-0.87)	0.009
REWIND	64/4949 (1%)	74/4952 (2%)	0.86 (0.62-1.21)	0.38
PIONEER 6	23/1591 (1%)	13/1592 (1%)	1.78 (0.90-3.53)	0.32
Overall			0.90 (0.73-1.12)	0.34

Pancreatitis	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
ELIXA	5/3034 (<1%)	8/3034 (<1%)	0.62 (0.20-1.91)	0.41
EXSCEL	26/7356 (<1%)	22/7396 (<1%)	1.19 (0.67-2.10)	0.55
LEADER	18/4668 (<1%)	23/4672 (<1%)	0.78 (0.42-1.45)	0.44
SUSTAIN-6	9/1648 (1%)	12/1649 (1%)	0.75 (0.32-1.78)	0.51
Harmony	10/4731 (<1%)	7/4732 (<1%)	1.43 (0.54-3.75)	0.46
REWIND	23/4949 (1%)	13/4952 (<1%)	1.77 (0.90-3.51)	0.11
PIONEER 6	1/1591 (<1%)	3/1592 (<1%)	0.25 (0.03-2.24)	0.20
Overall			1.03 (0.74-1.42)	0.86

Pancreatic cancer	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
ELIXA	3/3034 (<1%)	9/3034 (<1%)	0.33 (0.09-1.23)	0.50
EXSCEL	15/7356 (<1%)	16/7396 (<1%)	0.94 (0.47-1.91	0.87
LEADER	13/4668 (<1%)	5/4672 (<1%)	2.61 (0.93-7.32)	0.069
SUSTAIN-6	1/1648 (<1%)	4/1649 (<1%)	0.25 (0.03-2.24)	0.22
Harmony	6/4731 (<1%)	5/4715 (<1%)	0.95 (0.79-1.16)	0.64
REWIND	19/4949 (<1%)	12/4952 (<1%)	1.59 (0.77-3.27)	0.22
PIONEER 6	na	na	na	na
Overall			1.03 (0.67-1.58)	0.90

Appendix

Click here to download Necessary Additional Data: GLP-1 RA meta-analysis appendix 15 July.docx