Efficacy and Safety of Glucagon-like peptide-1 receptor agonists in type 2 diabetes

Systematic review and mixed-treatment comparison analysis

Running Title: GLP-1RAs treatments in diabetes

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PRISMA checklist

ABSTRACT

Aims

To compare efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in subjects with type 2 diabetes

Materials and Methods

We electronically searched, up to June 3rd, 2016, published randomised clinical trials lasting between 24 and 32 weeks and comparing a GLP-1RA (albiglutide, dulaglutide, twice-daily (EBID) and once-weekly exenatide, liraglutide, lixisenatide, semaglutide, and taspoglutide) with placebo or another GLP-1RA. Data on cardiometabolic and safety outcomes were analysed using a mixed-treatment comparison meta-analysis

Results

34 trials (14464 participants) met the inclusion criteria; no published data for semaglutide were available. Compared to placebo, all GLP-1RAs reduced HbA1c and fasting plasma glucose (FPG) (from -0.55% and -0.73mmol/L for lixisenatide to -1.21% and -1.97mmol/L for dulaglutide). There were no differences within short-acting (EBID and lixisenatide) or long-acting (albiglutide, dulaglutide, once-weekly exenatide, liraglutide, and taspoglutide) groups. Compared to EBID, dulaglutide treatment was associated with the greatest HbA1c and FPG reduction (0.51% and 1.04mmol/L), followed by liraglutide (0.45%, 0.93mmol/L) and once-weekly exenatide (0.38% and 0.85mmol/L); similar reductions were found when

these three agents were compared to lixisenatide. Compared to placebo, all GLP-1RAs except albiglutide reduced weight and increased the risk of hypoglycaemia and gastrointestinal (GI) side effects and all agents except dulaglutide and taspoglutide reduced systolic blood pressure. When all GLP-1RAs were compared against each other, no clinically meaningful differences were observed in weight loss, blood pressure reduction or hypoglycaemia risk. Albiglutide had the lowest risk of nausea and diarrhoea and once-weekly exenatide the lowest risk of vomiting.

Conclusions

RCTs demonstrate that all GLP-1RAs improve glycaemic control, reduce body weight, and increase the risk of adverse gastrointestinal symptoms vs placebo. Although there are no differences when short-acting agents are compared against each-other or when long-acting agents are compared against each-other, dulaglutide, liraglutide, and once-weekly exenatide are superior to EBID and lixisenatide at lowering HbA1c and FPG. There are no differences in hypoglycaemia between these three agents whilst once-weekly exenatide has a lowest risk of vomiting. These results, along with patient's preferences and individualised targets, should be considered in selecting a GLP-1RA.

Introduction

Type 2 diabetes (T2DM) is a chronic metabolic disorder characterised by complex pathophysiology of progressive beta cell dysfunction and a varying degree of insulin resistance. As the condition progresses, achieving and maintaining glycaemic control becomes a challenge despite the availability and use of a number of classes of glucose lowering therapies[1]. Current guidelines recommend a patient-centred approach when choosing appropriate glucose lowering treatments, with a primary goal of achieving individualised glycaemic target whilst minimising adverse effects, particularly weight gain and hypoglycaemia [2].

Glucagon like peptide-1 receptor agonists (GLP-1RAs) are a class of therapeutic agent, which provide significant improvement in HbA1c with an added benefit of promoting weight loss and low risk of hypoglycaemia [3-6]. GLP-1 is a gut hormone produced by the small intestine in response to oral ingestion of glucose, which promotes a glucoregulatory effect by increasing insulin and suppressing glucagon secretion [7]. It also facilitates weight loss by delaying gastric emptying and acting centrally on the satiety centre to reduce the food intake [7]. Manipulating the molecular structure of GLP-1 alters its pharmacological properties and produces biological effects that can be exploited clinically. GLP-1RAs are increasingly classified by duration of action into long-acting (albiglutide, dulaglutide, once-weekly exenatide, liraglutide, semaglutide, and taspoglutide) and short-acting (twice-daily exenatide (EBID) and lixisenatide) agents [8].

To date, EBID, lixisenatide, liraglutide, albiglutide, dulaglutide, and once-weekly exenatide are licensed by the US Food and Drug Administration (FDA) to be used in the management

of T2DM. The clinical trials and development of taspoglutide were discontinued in 2010 and therefore it is not available in clinical practice while semaglutide in a once-weekly subcutaneous formulation is in phase III clinical trials.

The American Diabetes Association (ADA)/European Association for the study of Diabetes (EASD) guidelines recommend the use of GLP-1RAs as an adjunctive therapy to lifestyle modification and metformin [9]. However, there are no specific recommendations on which GLP-1RA to choose in clinical practice possibly due to limited availability of head to head studies comparing the efficacy and safety of GLP-1RAs [10]. When direct comparisons are limited, mixed-treatment comparison analysis (also known as network meta-analysis) is regarded as the methodology of choice to compare several treatments [11, 12]. Using this approach and available data, we therefore aimed to compare the clinical profiles of GLP-1RAs.

Methods

Data Sources and Searches

This study was performed following a pre-specified protocol and PRISMA guidelines for conducting and reporting of systematic reviews and meta-analysis [11, 13, 14] (Supplementary Material). We searched PubMed, ISI Web of Science, and the Cochrane Library for randomised clinical trials (RCTs) published from inception to June 3rd, 2016 and comparing a GLP-1RA with placebo or another GLP-1RA (EBID, lixisenatide, liraglutide, albiglutide, dulaglutide, once-weekly exenatide, semaglutide, and taspoglutide) in adults with type 2 diabetes [15]. Only fully published RCTs were included (abstracts were excluded). We sought additional studies by manually scanning reference lists of eligible studies and previous systematic reviews and meta-analysis. Although the clinical trials and the development of taspoglutide were discontinued in 2010, we included taspoglutide RCTs data as they contribute to indirect estimations. No language restrictions were applied. Details on the search strategy are provided in supplementary Figure S1.

Study Selection

Fully published RCTs in subjects with T2DM lasting between 24 and 32 weeks with data on EBID 10µg, lixisenatide 20µg, liraglutide 1.8mg, albiglutide 50mg, dulaglutide 1.5mg, once-weekly exenatide 2mg, semaglutide 1mg, and taspoglutide 20mg were included if they reported data on HbA1c. RCTs including patients with chronic kidney disease were excluded.

Data extraction and Quality Assessment

Three authors (ZZH, DP, FZ) independently performed the literature search and extracted study data using pre-defined forms. Extracted information included: first author name, trial name/acronym, year of journal publication, background glucose-lowering therapies, GLP-1RA treatments, study duration, sample size, gender, age, diabetes duration, baseline HbA1c. We collected data on arm-specific number of participants, mean difference and standard error (or standard deviation) for continuous data (cardiometabolic outcomes: HbA1c, fasting plasma glucose (FPG), body weight, total, low- and high-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, and heart rate) and on total number of participants and participants with events for dichotomous data (safety outcomes: nausea, vomiting, diarrhoea, all (total) hypoglycaemic events, and injection site reactions). Data were extracted according to the intention to treat principle. When it was not possible to obtain efficacy and safety information from the published report, we retrieved data from ClinicalTrials.gov. In case of disagreement between the three reviewers on the eligibility of an article or on extracted data, consensus was reached by re-evaluation of the article and consultation with an independent reviewer. Study quality was assessed using the Cochrane risk of bias tool [16].

Data Synthesis and Analysis

We performed a mixed-treatment comparison within a frequentist framework based on the method of multivariate meta-analysis [17-19]. We used treatment-specific mean difference from baseline and odds ratio (OR) as effect measure for continuous and dichotomous data, respectively; we added 0.5 when studies reported zero events for safety outcomes. For each

outcome, we graphically summarised the evidence by using a network diagram [20] and performed random-effects network meta-analyses assuming that all treatment contrast have the same heterogeneity variance. We presented results against placebo and comparisons across all GLP-1RAs in graphs and tables. For each outcome, we assessed consistency between direct and indirect evidence by using the 'design by treatment' interaction model [21]. Stata 14.1 (Stata Corp, College Station, TX, USA) was used for all analyses and results are reported with 95% confidence intervals (CIs); a p-value <0.05 was deemed statistically significant.

Results

Study characteristics

We identified 7697 records, of which thirty-four fulfilled the inclusion criteria (Supplementary Figure S1). Included RCTs were published between 2004 and 2016; no published data for semaglutide fulfilling inclusion criteria were available (Table 1) [22-55]; ten were 'head-to-head' comparisons. A total of 14464 participants (47.9% female; range 35.5-63.5) with T2DM were included in our analysis with a mean baseline age of 56.2 (range, 53.0-63.6) years, HbA1c of 8.2% (range, 7.6-9.0), and duration of diabetes of 8.1 (range, 1.5-17.2) years. Background therapies were metformin, sulphonylurea, thiazolidinedione, and insulin alone or any combination of these medications. Overall risk of bias for the individual studies was variable, either low (69.6% for the six domains), high (9.8%) or unclear (20.6%) (Table S1).

Mixed-treatment comparison

Estimates for cardiometabolic outcomes are shown in Figure 1, Table 2 and Table S2, and results for safety outcomes in Figure 2, Table 3 and Table S3. Networks of comparisons are depicted in Figure S2. For both cardiometabolic and safety outcomes, results are first presented for against placebo. Then, when comparing GLP-1RAs with each other, results are first reported comparing short-acting (EBID and lixisenatide) vs long-acting; then comparing short-acting against each other; and lastly long-acting GLP-1RAs agents against each other.

Comparison vs Placebo for cardiometabolic outcomes

Glycaemic control

Compared to placebo, all GLP-1RA treatments improved both HbA1c and FPG. HbA1c reduction ranged from 0.55% to 1.21%, the greatest being with dulaglutide (1.21%; 1.05, 1.36), followed by liraglutide (1.15%; 1.03, 1.27), once-weekly exenatide (1.08%; 0.89, 1.27), taspoglutide (0.99%; 0.85, 1.14), albiglutide (0.94%; 0.64, 1.24), EBID (0.70%; 0.59, 0.81) and lixisenatide (0.55%; 0.42, 0.68) (Figure 1, Table S2). Improvement in FPG followed the same pattern as that of HbA1c, ranging from a maximum of 1.97mmol/L (1.49, 2.44) with dulaglutide to a minimum of 0.73mmol/L (0.38, 1.08) with lixisenatide (Figure 1, Table S2).

Body weight

Data on body weight were available for 14054 participants. Compared to placebo, treatment with GLP-1RAs was associated with significant weight loss, the greatest being with liraglutide (1.96kg; 1.25, 2.67) followed by EBID (1.67kg; 1.05, 2.29), dulaglutide (1.57;

0.66, 2.48), taspoglutide (1.54kg; 0.66, 2.41), once-weekly exenatide (1.49kg; 0.40, 2.58), and lixisenatide (0.78kg; 0.09, 1.48) (Figure 1, Table S2).

Blood pressure and lipid profile

Data for other cardiometabolic outcomes ranged from 4955 subjects for triglycerides to 7375 subjects for systolic blood pressure (SBP). Compared to placebo, treatment with liraglutide, once-weekly exenatide, EBID and dulaglutide resulted in significant reduction in SBP of 4.04mmHg (2.90, 5.19), 3.64mmHg (2.13, 5.15), 3.43mmHg (2.17, 4.69) and 3.35mmHg (2.10, 4.61), respectively; and in diastolic blood pressure (DBP) of 1.80 mmHg (1.00, 2.60) for EBID, 1.16mmHg (0.17, 2.15) for once-weekly exenatide, 0.92mmHg (0.13, 1.71) for liraglutide (Figure 1, Table S2).

With the exception of lixisenatide, treatment with all GLP-1RAs significantly raised heart rate (HR) compared to placebo, ranging from a minimum of 1.07bpm (0.00, 2.15) with EBID to a maximum of 3.28bpm (2.45, 4.11) with liraglutide (Figure 1, Table S2).

Compared to placebo, dulaglutide and liraglutide lowered triglycerides while albiglutide, dulaglutide, once-weekly exenatide, and liraglutide lowered both total cholesterol and LDL-C (Figure 1, Table S2). No clinically meaningful changes in HDL-C level were noted.

Comparison among GLP-1RAs for cardiometabolic outcomes

Glycaemic control

Compared to EBID, treatment with dulaglutide, liraglutide, once-weekly exenatide and taspoglutide showed greater HbA1c reduction, with differences of 0.51% (95% CI: 0.34,

0.68), 0.45% (0.31, 0.59), 0.38% (0.21, 0.55), and 0.30% (0.13, 0.46) respectively while albiglutide showed no difference. Corresponding FPG reductions were 1.04mmol/L (0.54, 1.53) for dulaglutide, 0.93mmol/L (0.56, 1.31) for liraglutide, 0.85mmol/L (0.41,1.28) for once-weekly exenatide, and 0.75mmol/L (0.32,1.18) for taspoglutide; no significant difference was found between albiglutide and EBID (Table 2).

When compared to lixisenatide, HbA1c differences were 0.66% (0.46, 0.86) with dulaglutide, 0.60% (0.43, 0.77) with liraglutide, 0.53% (0.31, 0.75) with once-weekly exenatide, 0.45% (0.26, 0.64) with taspoglutide, and 0.39% (0.07, 0.72) with albiglutide. Corresponding FPG reductions were 1.23mmol/L (0.65, 1.81) for dulaglutide, 1.13mmol/L (0.66, 1.60) for liraglutide, 1.05mmol/L (0.47, 1.63) for once-weekly exenatide, and 0.95mmol/L (0.45, 1.45) for taspoglutide; there was no significant difference between albiglutide and lixisenatide (Table 2).

Amongst all GLP-1RAs comparisons, the largest reductions in HbA1c (0.66%; 0.46, 0.86) and FPG (1.23mmol/L; 0.31, 1.87) were observed with dulaglutide vs lixisenatide. Within short-acting agents, no significant differences were noted for both HbA1c and FPG; similarly, no differences were observed for the same outcomes when long-acting agents were compared against each other.

Body weight

Among all possible comparisons of GLP-1RAs, the only differences noted were reduction of 0.89kg (0.01, 1.76) with EBID vs lixisenatide and 1.17kg (0.19, 2.15) with liraglutide vs lixisenatide (Table 2).

Blood pressure and lipid profile

For SBP, among all possible GLP-1RAs comparisons the only difference was between liraglutide and taspoglutide (2.40mmHg; 0.21, 4.59 reduction in favour of liraglutide). Regarding DBP, EBID lowered it to a significantly greater extent than taspoglutide (1.41mmHg; 0.03, 2.78), dulaglutide (1.07mmHg; 0.15, 1.99) and liraglutide (0.88mmHg; 0.94, 1.72) while no differences were noted for DBP among long-acting GLP-1RAs (Table 2). Compared to EBID, HR was 2.21bmp (1.05, 3.37), 2.18 bpm (0.92, 3.44), and 1.51bpm (0.41, 2.61) higher with liraglutide, once-weekly exenatide, and dulaglutide, respectively (Table 2). Corresponding values vs lixisenatide were 3.48 (1.96, 5.01) increase for liraglutide, 3.45 (1.36, 5.55) for once-weekly exenatide, and 2.79 (1.25, 4.32) for dulaglutide. Among all GLP-1RAs, the treatment with liraglutide resulted in the greatest increase in heart rate of 3.48bpm (1.96, 5.01) compared to lixisenatide. Within short-acting agents, no significant differences were noted for HR; similarly, no differences were observed when long-acting agents were compared against each other.

Only marginal differences were found for the lipid profile among all GLP-1RAs (Table 2).

The network meta-analytical comparisons between lixisenatide and other GLP-1RAs for SBP, DBP, and lipid parameters was not possible from available published RCTs. Statistical inconsistencies of the networks were not significant for all cardiometabolic outcomes.

Comparison vs Placebo for Safety outcomes

Hypoglycaemia

Total hypoglycaemic events were reported in 12761 subjects; all GLP-1RAs except albiglutide significantly increased the risk of hypoglycaemia compared to placebo from a minimum OR of 1.59 (1.10, 2.31) for lixisenatide to a maximum OR of 3.74 (1.51, 2.24) for taspoglutide (Figure 2, Table S3); results were consistent after excluding studies reporting background sulphonylurea and insulin therapy (Table S3).

Gastrointestinal side-effects

Data on treatment-associated nausea, vomiting and diarrhoea were available in 12258, 11835, and 12064 subjects, respectively. Compared to placebo, all GLP-1RAs had significantly higher risk of nausea (except albiglutide), vomiting, and diarrhoea (except taspoglutide and lixisenatide). The highest risks were with taspoglutide for nausea (OR 8.28; 4.16, 16.13) and vomiting (10.33; 4.42, 24.15) and with albiglutide for diarrhoea (3.25; 1.59, 6.64) (Table S3).

Other side effects

Imprecise estimates were found in the injection site reactions analyses, possibly due to heterogeneous outcomes definitions across studies. Compared to placebo, available data suggested an increased risk with lixisenatide and, particularly, taspoglutide (Table S3).

Comparison among GLP-1RAs for safety outcomes

Hypoglycaemia

Among all GLP-1RAs comparisons, the risk of hypo was not significantly different (Table 3). Statistical inconsistency was found for hypoglycaemia only in the main analysis (p=0.044;

analysis excluding background sulphonylurea and insulin, p=0.118).

Gastrointestinal side-effects

Both EBID and lixisenatide increased the risk of nausea compared to albiglutide (OR 3.35 and 3.07, respectively) and once-weekly exenatide (OR 2.38 and 2.17, respectively) (Table 3). No difference was found between EBID and lixisenatide. Among long-acting agents, taspoglutide (OR 3.67), dulaglutide (OR 2.94), and liraglutide (OR 2.64) increased the risk of nausea compared to once-weekly exenatide; a similarly pattern was found when these three drugs were compared to albiglutide. The largest differences amongst all comparisons was between taspoglutide vs albiglutide (OR 5.20; 1.71, 15.80).

The risk of vomiting was lower comparing once-weekly exenatide vs EBID (OR 0.52) and higher comparing taspoglutide vs lixisenatide (OR 2.66). No difference was found between EBID and lixisenatide. Among long-acting agents, taspoglutide (OR 4.64), dulaglutide (2.70), and liraglutide (OR 2.39) had an increased risk of vomiting compared to once-weekly exenatide and taspoglutide vs albiglutide (OR 3.83). The largest differences amongst all comparisons was between taspoglutide vs once-weekly exenatide (OR 4.64; 1.68. 12.77).

The risk of diarrhoea was lower with EBID vs liraglutide (OR 0.67) and with lixisenatide vs liraglutide (OR 0.45), dulaglutide (OR 0.42) and albiglutide (OR 0.40; 0.19, 0.87); no significant differences were within short-acting and within long-acting agents (Table 3). The largest differences amongst all comparisons was between albiglutide and lixisenatide (OR 2.50; 1.15, 5.26).

Discussion

GLP-1RAs are a class of therapeutic agents available for the management of hyperglycaemia in people with type 2 diabetes. ADA/EASD treatment algorithm recommends the use of GLP-1RAs as a second line therapy when glucose control on metformin alone is inadequate [9]. However, no specific recommendations are made as to which GLP-1RAs should be chosen. In individual RCTs, GLP-1RAs have been shown to improve glycaemic control with weight loss compared to other conventional glucose lowering agents. However, there is limited evidence from 'head-to-head' studies comparing the efficacy and safety of GLP-1RAs. As a result, decision-makers have to rely mainly on anecdotal evidence and clinical judgement in choosing a particular agent among all available GLP-RAs. To help clarify the evidence, we have conducted a systematic review and mixed-treatment comparison meta-analysis aiming to compare GLP-1RAs across a wide range of clinically relevant outcomes. These results could provide unified hierarchies of evidence for GLP-1RAs in the holistic management of hyperglycaemia in T2DM.

We presented efficacy and treatment-related adverse event results against placebo and compared GLP-1RAs against each other to aid decision makers in selecting the appropriate agent. When compared to placebo, all GLP-1RAs significantly improved both HbA1c and FPG, the greatest reduction being with dulaglutide (1.2% and 1.97 mmol/L, respectively). Compared to short-acting agents (EBID and lixisenatide), our results showed that the long-acting agents dulaglutide, liraglutide, and once-weekly exenatide all resulted in significantly greater HbA1c reduction. Treatment with dulaglutide was associated with the greatest HbA1c reduction of 0.51% followed by liraglutide (0.45%) and once-weekly exenatide (0.38%) vs

EBID; the pattern of reduction for these three drugs was similar when compared against lixisenatide. Likewise, there was a significant reduction in FPG with dulaglutide, liraglutide, and once-weekly exenatide compared to EBID or lixisenatide. However, short-acting agents (EBID and lixisenatide) were similar in terms of HbA1c and FPG lowering efficacy when compared with each other; similarly, there were no differences for the same outcomes across long-acting agents.

Previous studies have shown that GLP-1RAs are effective in reducing body weight and blood pressure compared to placebo [56, 57]. Our results are in line with these observations as they show a reduction of body weight and particularly of systolic blood pressure when compared to placebo; however, we did not find clinically meaningful differences across all GLP-1RAs for these two outcomes. Regarding lipid profiles, differences between each GLP-1RAs vs placebo and across all GLP-1RAs were clinically marginal.

Notably, available data showed that twice-daily and once-weekly exenatide, liraglutide, and dulaglutide significantly raised heart rate vs placebo from a minimum of 1.1bpm for EBID to a maximum of 3.3bpm for liraglutide. The highest difference was found between liraglutide and lixisenatide (3.5bpm) although no differences were noted within short-acting agents or within long-acting agents.

Compared to placebo, taspoglutide was associated with the highest (4-times) and lixisenatide with the lowest (1.6-times) risk of hypoglycaemia. However, no difference were noted among all GLP-1RAs when compared against each other. Treatment-associated gastrointestinal symptoms are well-recognised adverse effects of GLP-1RAs and are demonstrated to be higher when compared to placebo or other common glucose lowering therapies [58]. While

our results have confirmed an increased risk of gastrointestinal side effects compared to placebo, we also noted important differences among GLP-1RAs for nausea, vomiting and diarrhoea. Albiglutide had the lowest risk of nausea (5-times lower than taspoglutide) and diarrhoea (2.5-times lower than lixisenatide) and once-weekly exenatide of vomiting (5-times lower than taspoglutide).

Overall, our findings showed that treatments with the long acting GLP-1RAs dulaglutide, liraglutide, and once-weekly exenatide resulted in greater glycaemic efficacy but not clinically meaningful differences in blood pressure, body weight, lipid profile, or risk of hypoglycaemia when compared to short-acting agents. Across theses three long-acting agents, however, once-weekly exenatide had the lowest risk of nausea and vomiting.

To the best of our knowledge, this is the first attempt to systematically compare all available GLP-1RAs combining several clinically-meaningful efficacy and safety outcomes simultaneously and comprehensively. We have pooled data from published RCTs with a mixed-treatment comparison meta-analytical approach aiming to fulfil the gap in providing decision-makers with evidence to choose the appropriate agents considering specific advantages and disadvantages of each agent. We therefore collated data for multiple outcomes relevant to clinical practice (i.e., HbA1c, FPG, body weight, blood pressure, lipid profile, hypoglycaemia, and common gastrointestinal side-effects). However, we should also acknowledge some shortcomings of this study. First, it should be noted that postprandial glucose, along with FPG, contributes to the overall glycaemic control [59]. Although several studies suggest short acting GLP-1RAs, lixisenatide and EBID, exert a greater effect of on postprandial glucose [60-62], we could not assess the comparative efficacy of GLP-1RAs on

this outcome given its variable definition and very limited availability of these data across all GLP-1RAs studies. Similarly, injection site reactions are common to these treatments. Direct comparisons would suggest more injection site reactions with once-weekly exenatide, albiglutide, and taspoglutide compared to exenatide and liraglutide due to the differences in formulation and delivery technology [42-45, 54] but data were inconsistently reported in the included RCTs limiting the possibility to combine and compare them analytically. Second, some characteristics (population included, duration of follow-up, background therapies and quality of studies) differ across included RCTs. Differences in background therapies are particularly relevant as cardiometabolic effects of GLP-1RAs may differ when these agents are added to metformin, insulin, thiazolidinedione, or sulphonylurea. Third, the search was based only on published papers. Although the risk of publication bias should be lower for RCTs compared to other study types, yet it is possible that some studies have been conducted and not registered and/or reported (e.g. fully published SUSTAIN studies for semaglutide fulfilling inclusion criteria were not reported at the time of literature search). Fourth, we used "intermediate" surrogate biomarkers of vascular disease; future long-term head-to-head RCTs would clarify whether these differences translate to different 'hard' outcomes. As of September 30th 2016, three placebo-controlled studies assessing cardiovascular outcomes have been published. Short acting GLP-1RA lixisenatide showed neutral effect on major adverse cardiovascular events (cardiovascular death, nonfatal MI or nonfatal stroke) while the long-acting GLP-1RAs, liraglutide and semaglutide, demonstrated 13% and 26% relative risk reduction in the LEADER and SUSTAIN-6 study, respectively [63-65]. Other ongoing studies EXSCEL (once-weekly exenatide) and REWIND (dulaglutide) are awaiting to be

reported. Fifth, although a number of potential sensitivity analyses are possible, we assessed the risk of hypoglycaemia excluding studies with background SU and insulin as we deemed it more clinically relevant. Lastly, this meta-analysis shares the same drawbacks common to other network analyses [66].

In conclusion, although there are no differences when short-acting agents are compared against each-other and when long-acting agents are compared against each-other, available data indicate dulaglutide, liraglutide, and once-weekly exenatide are superior to EBID and lixisenatide at lowering HbA1c and FPG. There are no differences in hypoglycaemia between these three agents whilst once-weekly exenatide has a lowest risk of nausea and vomiting. The choice among these agents should be tailored taking into account their differences in safety and efficacy along with patient's targets and needs.

AUTHOR CONTRIBUTION

ZZH, FZ, MJD study idea and design

ZZH, DP, FZ literature search and data extraction

FZ data analysis

ZZH, DP, FZ, DW, KK, MJD study critical revision and manuscript draft

All authors provided final approval of the version to publish. ZZH is the study guarantor.

Statistical codes and datasets are available from the corresponding Author (ZZH).

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CONFLICT OF INTEREST

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. KK has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly. DRW has received grant in support of investigator initiated studies and honoraria from Sanofi-Aventis and Novo Nordisk. All other Authors have no conflict of interests to disclose.

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References

[1] Wysham CH. New perspectives in type 2 diabetes, cardiovascular risk, and treatment goals. Postgrad Med. 2010; **122**: 52-60

[2] Inzucchi SE, Bergenstal RM, Buse JB*, et al.* Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015; **58**: 429-442

[3] Madsbad S. Exenatide and liraglutide: different approaches to develop GLP-1 receptor agonists (incretin mimetics) - preclinical and clinical results. Best Practice and Research: Clinical Endocrinology and Metabolism. 2009; **23**: 463-477

[4] Monami M, Dicembrini I, Marchionni N, Rotella CM, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. Experimental diabetes research. 2012; **2012**: 672658

[5] Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ. 2012; **344**: d7771

[6] Sun F, Chai S, Li L*, et al.* Effects of Glucagon-Like Peptide-1 Receptor Agonists on Weight Loss in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis. Journal of Diabetes Research. 2015; **2015**: 157201

[7] Ahren B. Gut peptides and type 2 diabetes mellitus treatment. Curr Diab Rep. 2003; **3**: 365-372

[8] Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nature reviews Endocrinology. 2012; **8**: 728-742

[9] Inzucchi SE, Bergenstal RM, Buse JB*, et al.* Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012; **55**: 1577-1596

[10] Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and Harms of Once-Weekly Glucagon-like Peptide-1 Receptor Agonist Treatments: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2016; **164**: 102-113

[11] Hoaglin DC, Hawkins N, Jansen JP*, et al.* Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2
Value in Health. 2011; **14**: 429-437

[12] Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes, obesity & metabolism. 2016; **18**: 783-794

[13] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009; **62**: 1006-1012

[14] Hutton B, Salanti G, Caldwell DM*, et al.* The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and ExplanationsPRISMA Extension for Network Meta-analysis. Annals of Internal Medicine. 2015; **162**: 777-784

[15] Hawkins N, Scott DA, Woods B. How Far Do You Go? Efficient Searching for Indirect Evidence. Medical Decision Making. 2009:
[16] Higgins JP, Altman DG, Gotzsche PC*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; **343**: d5928
[17] White IR. Multivariate random-effects meta-regression: Updates to mvmeta. Stata Journal. 2011; **11**: 255-270
[18] White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Research Synthesis Methods. 2012; **3**: 111-125
[19] White IR. Network meta-analysis. Stata Journal. 2015; **15**: 951-985
[20] Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PloS one. 2013; **8**: e76654
[21] Jackson D, Barrett JK, Rice S, White IR, Higgins JP. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med. 2014; **33**: 3639-3654
[22] Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004; **27**: 2628-2635
[23] DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005; **28**: 1092-1100
[24] Kendall DM, Riddle MC, Rosenstock J*, et al.* Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005; **28**: 1083-1091
[25] Apovian CM, Bergenstal RM, Cuddihy RM*, et al.* Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. The American journal of medicine. 2010; **123**: 468 e469-417
[26] Liutkus J, Rosas Guzman J, PNorwood P*, et al.* A placebo-controlled trial of exenatide twice daily added to thiazolidinediones alone or combination with metformin. Diabetes, obesity and metabolism. 2010; **12** 1058-1065
[27] Ji L, Onishi Y, Ahn CW*, et al.* Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. Journal of Diabetes Investigation. 2013; **4**: 53-61
[28] Marre M, Shaw J, Brandle M*, et al.* Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabetic medicine : a journal of the British Diabetic Association. 2009; **26**: 268-278
[29] Nauck M, Frid A, Hermansen K*, et al.* Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009; **32**: 84-90
[30] Zinman B, Gerich J, Buse JB*, et al.* Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009; **32**: 1224-1230

[31] Russell-Jones D, Vaag A, Schmitz O*, et al.* Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009; **52**: 2046-2055
[32] Buse JB, Rosenstock J, Sesti G*, et al.* Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009; **374**: 39-47
[33] Lind M, Hirsch IB, Tuomilehto J*, et al.* Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). BMJ. 2015; **351**:
[34] Ahmann A, Rodbard HW, Rosenstock J*, et al.* Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. Diabetes, obesity & metabolism. 2015; **17**: 1056-1064
[35] Riddle MC, Forst T, Aronson R*, et al.* Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care. 2013; **36**: 2497-2503
[36] Bolli GB, Munteanu M, Dotsenko S*, et al.* Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabetic medicine : a journal of the British Diabetic Association. 2014; **31**: 176-184
[37] Riddle MC, Aronson R, Home P*, et al.* Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013; **36**: 2489-2496
[38] Seino Y, Min KW, Niemoeller E, Takami A. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes, obesity & metabolism. 2012; **14**: 910-917
[39] Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes, obesity & metabolism. 2013; **15**: 1000-1007
[40] Rosenstock J, Hanefeld M, Shamanna P*, et al.* Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). J Diabetes Complications. 2014; **28**: 386-392
[41] Rosenstock J, Raccah D, Koranyi L*, et al.* Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013; **36**: 2945-2951
[42] Drucker DJ, Buse JB, Taylor K*, et al.* Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. The Lancet. 2008; **372**: 1240-1250

[43] Blevins T, Pullman J, Malloy J*, et al.* DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. The Journal of clinical endocrinology and metabolism. 2011; **96**: 1301-1310
[44] Buse JB, Nauck M, Forst T*, et al.* Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013; **381**: 117-124
[45] Pratley RE, Nauck MA, Barnett AH*, et al.* Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. The lancet Diabetes & endocrinology. 2014; **2**: 289-297
[46] Wysham C, Blevins T, Arakaki R*, et al.* Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care. 2014; **37**: 2159-2167
[47] Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care. 2014; **37**: 2149-2158
[48] Dungan KM, Povedano ST, Forst T*, et al.* Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014; **384**: 1349-1357
[49] Dungan KM, Weitgasser R, Perez Manghi F*, et al.* A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes, obesity & metabolism. 2016; **18**: 475-482
[50] Raz I, Fonseca V, Kipnes M*, et al.* Efficacy and safety of taspoglutide monotherapy in drug-naive type 2 diabetic patients after 24 weeks of treatment: results of a randomized, double-blind, placebo-controlled phase 3 study (T-emerge 1). Diabetes Care. 2012; **35**: 485-487
[51] Henry RR, Mudaliar S, Kanitra L, Woloschak M, Balena R. Efficacy and safety of taspoglutide in patients with type 2 diabetes inadequately controlled with metformin plus pioglitazone over 24 weeks: T-emerge 3 trial. Journal of Clinical Endocrinology and Metabolism. 2012; **97**: 2370-2379
[52] Bergenstal RM, Forti A, Chiasson JL, Woloschak M, Boldrin M, Balena R. Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-emerge 4 trial). Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders. 2012; **3**: 13
[53] Hollander P, Lasko B, Barnett AH*, et al.* Effects of taspoglutide on glycemic control and body weight in obese patients with type 2 diabetes (T-emerge 7 study). Obesity. 2013; **21**: 238-247
[54] Rosenstock J, Balas B, Charbonnel B*, et al.* The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes: the T-emerge 2 trial. Diabetes Care. 2013; **36**: 498-504
[55] Moretto TJ, Milton DR, Ridge TD*, et al.* Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a

randomized, double-blind, placebo-controlled, parallel-group study. Clinical therapeutics. 2008; **30**: 1448-1460
[56] Potts JE, Gray LJ, Brady EM, Khunti K, Davies MJ, Bodicoat DH. The Effect of Glucagon-Like Peptide 1 Receptor Agonists on Weight Loss in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison Meta-Analysis. PloS one. 2015; **10**: e0126769
[57] Sun F, Wu S, Guo S*, et al.* Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes research and clinical practice. 2015; **110**: 26-37
[58] Sun F, Chai S, Yu K*, et al.* Gastrointestinal Adverse Events of Glucagon-Like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis Diabetes Technology & Therapeutics. 2015; **17**: 35-42
[59] Zaccardi F, Pitocco D, Ghirlanda G. Glycemic risk factors of diabetic vascular complications: the role of glycemic variability. Diabetes/Metabolism Research and Reviews. 2009; **25**: 199-207
[60] Arnolds S, Dellweg S, Clair J*, et al.* Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin: a proof-of-concept study. Diabetes Care. 2010; **33**: 1509-1515
[61] Kapitza C, Forst T, Coester HV, Poitiers F, Ruus P, Hincelin-Mery A. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. Diabetes, obesity & metabolism. 2013; **15**: 642-649
[62] Meier JJ, Rosenstock J, Hincelin-Mery A*, et al.* Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial. Diabetes Care. 2015; **38**: 1263-1273
[63] Pfeffer MA, Claggett B, Diaz R*, et al.* Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. The New England journal of medicine. 2015; **373**: 2247-2257
[64] Marso SP, Daniels GH, Brown-Frandsen K*, et al.* Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine. 2016; **375**: 311-322
[65] Marso SP, Bain SC, Consoli A*, et al.* Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine. 2016; **0**: null
[66] Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med. 2013; **159**: 130-137

Figure Legends

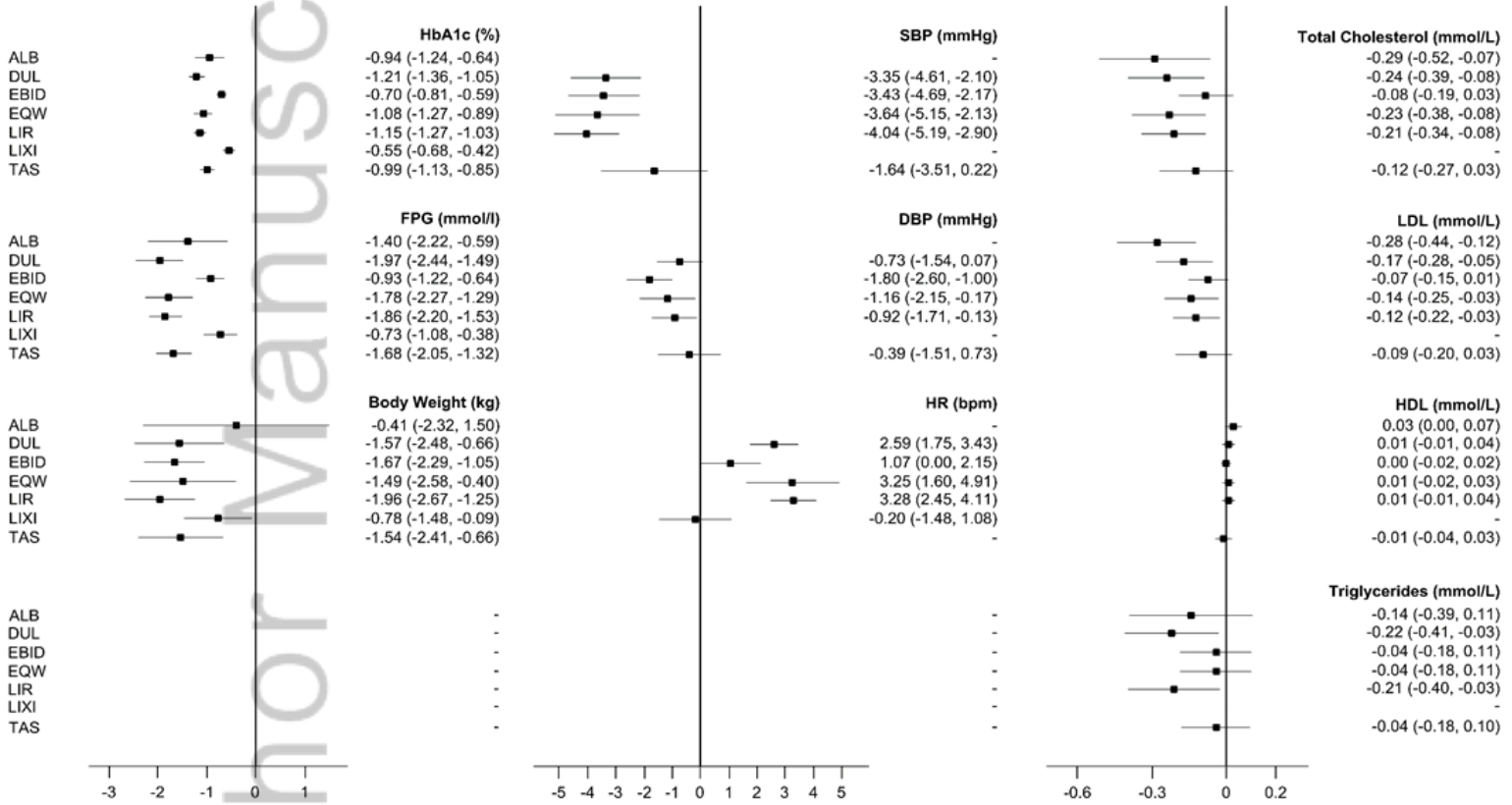
Figure 1: Differences vs placebo for cardiometabolic outcomes

Differences estimated with network meta-analysis vs Placebo.

HbA1c, glycated haemoglobin; **FPG**, fasting plasma glucose; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **HR**, heart rate
ALB, albiglutide; **DUL**, dulaglutide; **EBID**, twice-daily exenatide; **EQW**, once-weekly exenatide; **LIR**, liraglutide; **LIXI**, lixisenatide; **TAS**, taspoglutide

Figure 2: Differences vs placebo for safety outcomes

Differences estimated with network meta-analysis vs Placebo.
ALB, albiglutide; **DUL**, dulaglutide; **EBID**, twice-daily exenatide; **EQW**, once-weekly exenatide; **LIR**, liraglutide; **LIXI**, lixisenatide; **TAS**, taspoglutide.



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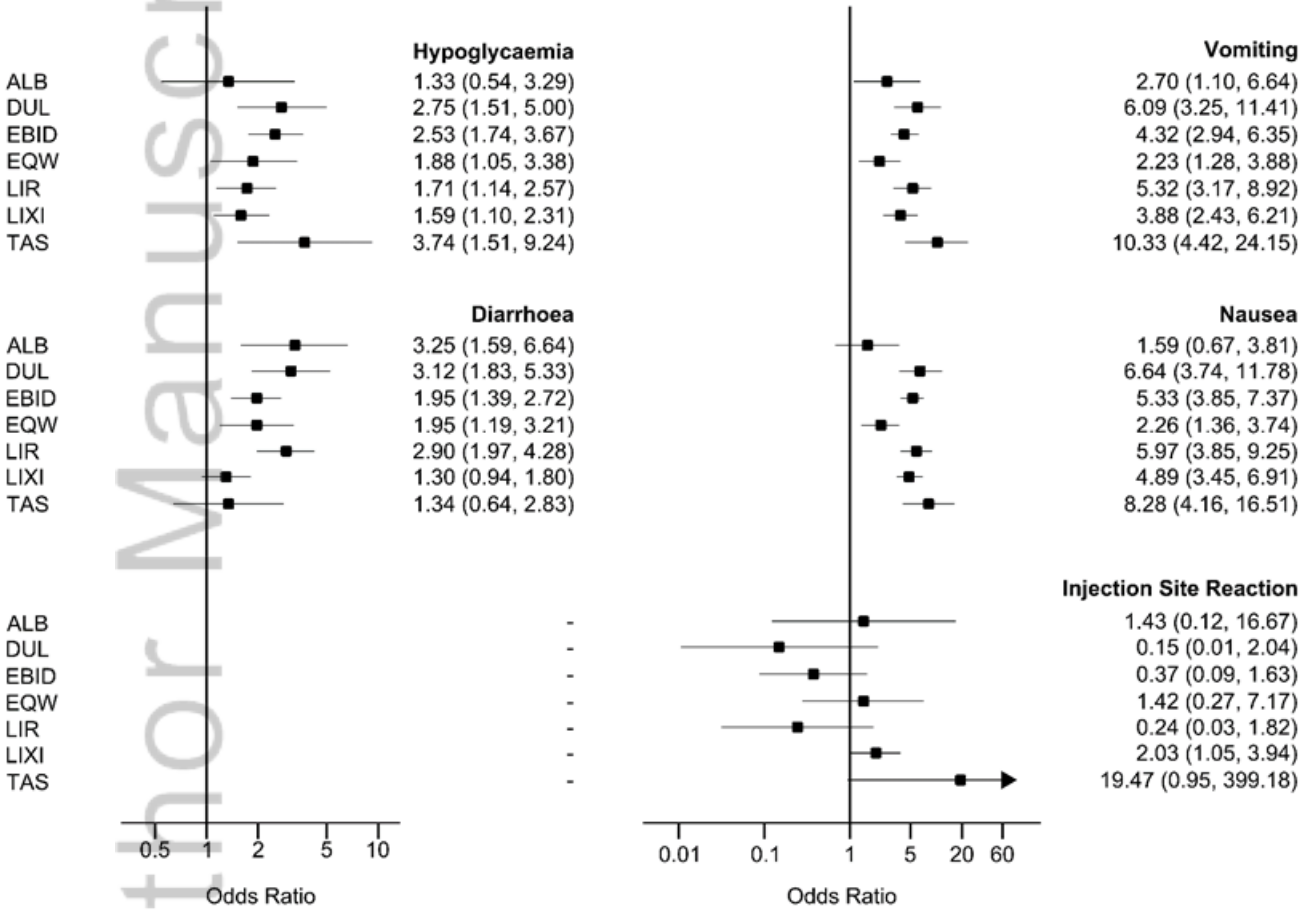

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