Version of Record: https://www.sciencedirect.com/science/article/pii/S1056872722001647
Manuscript_de65669d24846c967eae9f9056c2b2bf

Progression of Retinopathy with Glucagon-Like Peptide-1 Receptor Agonists with Cardiovascular Benefits in Type 2 Diabetes – A Systematic Review and Meta-Analysis

Authors: Yilin Yoshida, PhD[1]; Preeti Joshi, MBBS[2]; Saba Barri, BS[2]; Jia Wang, MS[1]; Amy L. Corder, MLIS[3]; Samantha S. O'Connell, MS[4]; Vivian A. Fonseca, MD[1]

[1]Section of Endocrinology and Metabolism, Deming Department of Medicine, Tulane University School of Medicine, New Orleans, LA
[2]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana
[3]Rudolph Matas Library of the Health Sciences, Tulane University, New Orleans, LA
[4]Tulane University Office of Academic Affairs and Provost

Corresponding authors: Vivian A Fonseca and Yilin Yoshida, Section of Endocrinology, Department of Medicine, Tulane University School of Medicine. 1430 Tulane Ave. New Orleans, LA 70112.

Phone: 504-988-6272

Fax: 504-988-6271

Email: vfonseca@tulane.edu and yyoshida1@tulane.edu

Word count: 2779

Keywords: GLP1-RA, retinopathy, type 2 diabetes, meta-analysis

© 2022 published by Elsevier. This manuscript is made available under the Elsevier user license
https://www.elsevier.com/open-access/userlicense/1.0/

Abstract

Aims: The effect of Glucagon-like peptide 1 receptor agonists (GLP1 RA) on diabetic retinopathy (DR) remains controversial. Previous reviews combined data from randomized clinical trials (RCTs) with or without cardiovascular (CV) benefits and did not address confounders, therefore may have generated misleading results. The study aimed to examine the effect of GLP1RA on DR in type 2 diabetes (T2DM) in RCTs with or without CV benefits and distinguish the effect by major confounders.

Methods: We conducted electronic searches of multiple databases and a manual search using references lists. We included 13 RCTs examining the effect of GLP1 RA on health outcomes/adverse events including DR or DR complications in T2DM. We performed a random-effects model meta-analysis.

Results: GLP1RA was associated with an elevated risk of rapidly worsening DR in four major RCTs with CV benefits in T2DM (OR 1.23, 95% CI 1.05-1.44). The association between GLP1 RA and DR was significant in subgroups of RCTs with length over 52 weeks (1.2, 1.00-1.43), using placebo as a comparator (1.22, 1.05-1.42). In subgroups with patients who had T2DM ≥10 years (1.19, 0.99-1.42) or with subjects enrolled from multiple countries (1.2, 0.99-1.46), the association appeared to be evident but did not reach statistical significance.

Conclusions: GLP1 RA including liraglutide, semaglutide, and dulaglutide are associated with an increased risk of rapidly worsening DR in RCTs with CV benefits. Further data from clinical studies with longer follow-up purposefully designed for DR risk assessment, particularly including patients of established DR are warranted.

Introduction

Glucagon-like peptide 1 receptor agonists (GLP1 RA) are recommended as second-line therapy for adult patients with type 2 diabetes (T2DM), however, their effect on microvascular complications such as diabetic retinopathy (DR) remains controversial. In 2008, FDA recommended that new glucose-lowering medications for diabetes are shown to not increase cardiovascular risk [1]. Since then, several long-term prospective cardiovascular outcomes trials (CVOTs) for different classes of GLP1 RA have been conducted. Among these, semaglutide, liraglutide, and dulaglutide have shown superiority in cardiovascular (CV) outcomes. However, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide (SUSTAIN-6) was among the first to raise a concern of GLP1 RA on the risk of DR [2].

Previous systematic reviews on the association between GLP1RA and DR have generated mixed findings with some reporting a neutral effect on DR [3-5] while others suggested a harmful effect that is attributable to rapid glycemic control [5]. The main issue with the existing reviews is that their examinations have combined GLP1 RA drugs with and without CV benefits [5]. Current clinical guidelines have specified that only drugs with known benefits should be used in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD risk [6,7]. The use of GLP1 RA drugs without CV benefits is less likely in clinical practice for patients with high risk due to the guideline recommendation. Another limitation of previous reviews is that they lack consideration on study characteristics, such as study length, comparator, sample composition, and patients' characteristics, such as duration of T2DM, presence of DR at enrollment, and baseline insulin use. All of these are

confounding factors that could potentially alter the association of GLP1 RA and DR and need to be adjusted for when assessing the combined effect across RCTs [5]. The objective of this study was to examine the effect of GLP1RA on DR in T2DM in RCTs with and without CV benefits separately. In addition, we stratified the analysis by key confounders including the comparator, study length, the inclusion of participants from diverse populations, and patients' baseline characteristics such as diabetes duration, glycemic levels, DR history, or insulin use.

Methods

We reported our methods and results according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) statement [8] for included RCTs.

Data Sources and Searches

We identified eligible publications through electronic searches of PubMed, Embase.com, and Web of Science Core Collection from database inception to March 12, 2021, without imposing any language restriction. We additionally searched the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov. The key searching terms include 'Type 2 diabetes mellitus', 'glucagon-like peptide 1 receptor agonist' and specific drug agents such as 'semaglutide', 'liraglutide', and 'dulaglutide', 'diabetic retinopathy' and DR related outcomes such as 'blindness', 'eye bleeding', 'laser treatment', 'eye injection', and 'severe vision deterioration, and. The PubMed search incorporated search hedges developed at The University of Texas Health Science Center at Houston for clinical trials, cohort studies, and epidemiologic studies,

which were also adapted to Web of Science and Embase.com syntax [9]. The full list of search terms can be found in **eTable 1 in the supplement**. Search syntax among databases was mapped with the help of the Polyglot Search Translator [10]. We also performed supplementary searches using references lists of eligible articles and relevant systematic reviews and other review articles we encountered.

Data Selection

One researcher (AC) exported database search records to EndNote, and then uploaded those records to Covidence, where duplicates were removed. Articles were screened using Covidence, and they were deemed eligible if they were peer-reviewed RCTs with parallel or cross-over design studies containing methodology and result sections that studied the effect of GLP1RA and DR in T2DM. Articles were excluded if they lack information on predefined outcomes or intervention of interest, studies testing off-market drugs (e.g., albiglutide), or not strongly recommended by ADA for use among patients with T2DM and with risk of ASCVD or with severe loss of kidney function (ELIXA [lixisenatide] and EXSCEL [exenatide]) [6]. A complete study selection process is shown in Figure 1.

Figure 1. PRISMA diagram

Data extraction and Quality Assessment

Data from eligible articles were extracted independently by four researchers using Qualtrics (PJ, SB, SO, JW). A coding manual was used to maintain reliable practices. For studies with more than one publication, we kept the records from the publication with the most complete result reporting. The coding manual specified study

characteristics (i.e., intervention agent, dosage, route, comparator, sample size, attrition rate, intervention length), patient characteristics at baseline (i.e., demographics, T2DM duration, clinical measurements [A1c, weight, blood pressure, and medications]). Discrepancies were resolved by two senior authors (YY, VAF) before the final data entry.

The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) [11] was used to appraise the quality of RCTs by four researchers (SO, PJ, SB, and JW). The overall risk of bias was considered as high in the presence of high bias in any domain, low if all domains were at low risk of bias, and of some concern in any other case. Any discrepancies between assessors were discussed until consensus was reached.

We appraised the risk of selective reporting or publication bias by visual inspection of funnel plot symmetry of the standard error of each trial plotted against its estimated effect. This assumes that trials with larger sample sizes were less subject to publication bias.

Analysis

We examined the relationship between GLP1RA and DR outcomes by calculating the odds ratio (OR) and 95% confidence intervals (CI). Definitions of DR were described by each study and not standardized in this analysis**.** In general, the outcome included incident DR or DR complications such as the need for ophthalmologic concern or intervention—retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or diabetes-related blindness **(eTable 2 in the supplement).** We obtained OR and 95% CI from each study directly along with the available event information to unify the reported effect size. The pooled OR and 95 CI were calculated using a

random-effects model meta-analysis. We used the random-effects model to maintain the generalizability of the results. the heterogeneity of each model was assessed using Cochran's Q and I^2 statistics [12]. We considered heterogeneity to be greater than expected by chance alone if either Cochran's Q showed $P<0.05$ or the I^2 statistics was ≥75% [12]. Our primary analyses included, the combined estimate of OR from trials with or without CV benefits. We also performed a series of secondary analyses distinguishing the effect of GLP1 RA on DR by the comparator (placebo vs DM drugs), length of the study (<52 vs ≥52 weeks), diabetes duration of participants (<10 years vs ≥10 years), studies with or without the inclusion of international participants, baseline mean HbA1c (≤8% vs >8%), with or without baseline DR, and with or without baseline insulin use. All quantitative analyses were performed using Stata 16.1.

Patient and Public Involvement

This is a systematic review based on published results from previous clinical trials. It did not have patient or public involvement.

Results

We identified 20,943 records from five electronic databases initially and manually identified 86 papers from previous reference lists (**Figure 1**). After removing 7,437 duplicate records, 13,592 records remained for title/abstract review. A total of 369 full texts were assessed, among which we further excluded 212 articles lacking relevant outcomes or intervention reporting, 102 with irrelevant study type (non-intervention or observational analysis), 23 RCT registrations, 15 without full text, 2 HARMONY trials on albiglutide [13,14] which has been off-market since 2018. We further excluded two ELIXA

(Lixisenatide) [15] and EXSCEL (Exenatide) [16] that are less strongly recommended by the current ADA guidelines due to their lack of evidence of CVD benefits. A total of 13 RCTs were included in the final analysis [2,17-28].

Study characteristics were summarized in **eTable 3 in supplement**. Among included 13 RCTs, 10 centered on the effects of semaglutide (6 oral [22-25,28,29], 4 injection [2,17,19,27]), 2 on liraglutide (injection) [20,26], and 1 on dulaglutide (injection) [18]. Five RCTs compared GLP1 RA agents with a placebo [2,18,20,28,29], and 8 with other anti-diabetic medications[17,19,22-25,27 26]. The mean sample size for RCTs was 2519 (range 308 to 9901). The mean attrition rate was 4%. The mean follow-up period was 20 months (range 7.5 to 46 months). Six studies included T2DM patients with pre-existing CVD[2,18-20,27,29]. The average age for participants in included RCTs was 60 years (range 55-66 years), and more than half were men (59%). The average length of diabetes for participants at baseline was 10.5 years (range 6.5-12.8 years) with mean HbA1c was 8.2% (range 7.4% to 8.8%), and mean BMI was 31 (range 26 to 33). At baseline, 4 RCTs have reported including small portion of patients with pre-existing DR [2,18,22,25] (ranged 2% to 28%), and 6 including patients with insulin treatment [2,18,20,26,28,29] (insurance use at baseline ranged 32% to 100%).

Risk of bias: Overall, six out of 13 RCTs were deemed to be at high risk of bias, and 2 with some concerns. The source of bias was mainly from a lack of information for intervention assignment and intervention adherence (**eFigure 1.a and b, eTable 4 in supplement**).

Publication bias: Among RCTs, the funnel plot demonstrated that the distribution of effect sizes for individual studies was approximately symmetrical around the pooled OR

for trials estimating the effect of GLP1RA on DR in T2DM. Notably, only two studies were imputed using the trim and fill method (**eFigure 2 in supplement**). The Egger test detected non-significant asymmetry with a p-value of 0.568.

Quantitative results:

We found GLP1RA was significantly associated with an elevated risk of DR progression in four major RCTs that have shown CV benefits in diabetes (OR 1.23, 95% CI 1.05-1.44) (**Figure 2**). In RCTs with study length over 52 weeks (OR 1.2, 95% CI 1.00-1.43) (**Figure 3**), and using placebo as a comparator (OR 1.22, 95% CI 1.05-1.42) (**Figure 4)**, GLP1 RA was significantly associated with risk of DR. In RCTs with patients had long diabetes history (≥10 years) or with subjects enrolled from multiple countries, the risk of DR associated with GLP1 RA appeared to be elevated but without statistical significance (OR 1.19, 95% CI 0.99-1.42) **(eFigure 3 in supplement)** and (OR 1,2, 95% CI 0.99-1.46) **(eFigure 4 in supplement),** respectively. Subgroup analyses among RCTs with baseline DR and sensitivity analysis of RCTs with baseline HbA1c>8% did not show significant association **(eFigure 5 and eFigure 6 in supplement).** Heterogeneity in the results in each analysis was low.

Discussion

From four GLP1RA RCTs that have been deemed to have CV benefits in patients with T2DM with a relatively longer follow-up (mean 38 months vs mean 13 months in others), we found GLP1 RA was significantly associated with risk of DR. This finding underscores the concern of the adverse retinal effect that was previously raised for

subcutaneous semaglutide (SUSTAIN 6). Our result suggests this adverse effect may not be agent- or administration route-specific as liraglutide (LEADER), dulaglutide (REWIND) and oral semglutide (PIONEER 6) all showed a concerning trend towards harm.

The association between GLP1RA and DR is biologically plausible as these drugs may have direct effects on the retina, due to the expression of GLP1 receptors in human retinal cells [30,31]. Another major explanation for this GLP1 RA-related DR is the rapid lowering of HbA1c. In fact, the divergence of DR events between the two arms occurred relatively early in both the LEADER and the SUSTAIN studies [2,20], hence supporting this hypothesis. Additionally, in a meta-regression published recently, HbA1c reduction was significantly associated with increased DR risk for GLP1 RA among GLP1 RA CV outcome trials [5]. Early worsening of DR is a well-described phenomenon in diabetes and has been reported in patients receiving diverse antidiabetic treatments including insulin [2,32-34]. However, this phenomenon has been seen more commonly in type 1 diabetes and was not reported in clinical trials of very intensive glycemic control in T2DM, where the rate of glucose decline was just as rapid [35-38]. Indeed, in the ACCORD trial, the opposite was observed with slowing of progression of DR by intensive treatment of glycemia in its participants who were very similar to the participants in CVOTs [36].

Several mechanisms potentially explain the worsening of DR following rapid and large reduction of blood glucose, including osmotic force theory where the rapid reductions in blood glucose affect osmotic pressure and the extracellular and intravascular areas [39], the synergistic hypothesis where there is the synergistic action of drug agents and

vascular endothelial growth factor (VEGF) on blood vessels in retina, which triggers vascular proliferation and then, worsening DR [39], and also VEGF upregulation that results from tight glycemic control in a hypoxic environment [40,41]. However, unlike insulin where gradual improvement in HbA1c is possible, it is challenging for GLP1 RA to achieve the same goal as its improvement in glycemic control can be rapid and profound [42].

Our results varied by the comparator, T2DM duration, study follow-up, and composition and size of the sample (international trial vs single-country trial). First, when compared to placebo, there was a small but significant elevated risk of DR. However, in RCTs compared with other antidiabetic drugs, the association was not evident. One possible explanation for this divergent finding is the overlap of placebo comparing subgroup with the major 4 RCTs, which all had longer follow-up and larger sample size, therefore were more powered to show the effect. Additionally, previous studies have shown when the duration of diabetes is long, even relatively good control of glycemia is eventually associated with the development of DR [33,43], indicating other factors that mediate DR in addition to glycemia, including increased serum lipids[44,45]. Elevated serum lipid levels are a common complication of diabetes and are known to cause endothelial dysfunction due to a reduced bioavailability of nitric oxide. This endothelial dysfunction was suggested to play a role in retinal exudate formation in DR [46]. Among studies that had 52 weeks or longer follow-up, the association between GLP1 RA and DR was significant. Even though the general sufficient time to evaluate DR development is 5 years [47], by excluding those with very short follow-up (<52 weeks), our analysis already can demonstrate a small but significant positive association, suggesting the importance of

the length of follow-up when looking at DR with GLP1 RA. Additionally, excluding trials with only single country participants (3 Japanese RCTs) that were smaller in sample size and less powered to show adverse events, such as DR, the association of GLP1 RA and DR was also significant.

Limitations: Our study has several limitations. The major RCTs included in this study were designed primarily to test CVD outcomes rather than DR. The clinical rationale for DR-related outcomes was not determined in advance, therefore subject to underreporting. The ascertainment of DR also varied across studies. Nevertheless, the seriousness of a threat of visual loss is important to recognize. Among 4 major RCTs that our primary result was generated from, two (SUSTAIN 6 and PIONEER 6) used fundus photography or dilated fundoscopy as scheduled assessment for DR, and another two (LEADER and REWIND) used retinal procedures to capture DR events. Another limitation is the short follow-up of included RCTs. Except for REWIND, all other trials had a median follow-up of fewer than 5 years, which may be insufficient to capture incident DR or to show a nonlinear progression of DR [47]. Further, the majority of studies did not systematically assess DR at baseline except for PIONEER 6, which excluded those with proliferative DR, potentially decreasing the risk of progression, and thus making any progression clinically important. We were not able to capture the complete information pertaining to underlying DR or the severity of DR in each study sample, which may have precluded a significant finding in this subgroup analysis.

Further, the nature of our study does not lend itself to an evaluation of the underlying mechanisms of the DR progression. It has been postulated that the DR progression is related to the more rapid improvement in glycemic control in the more powerful drug

class [2,32-34]. While this phenomenon has been described in type 1 diabetes [48] it has not been observed in trials of aggressive glucose-lowering in T2DM [49,50], despite systematic evaluation of DR in these trials. Thus, the possibility of a direct effect of the most powerful GLP1 RA drugs on the vasculature remains plausible.Finally, without detailed individual level data, we were not able to perform sex- or ethnic-stratified analyses.

Strengths: This study provides a systematic and thorough assessment of the effect of GLP1 RA on DR. We synthesized findings from GLP1 RA classes that are recommended by ADA and contained measurements of DR events. To differentiate effect from major confounding factors, we performed a series of subgroup analyses that were not addressed in previous reviews. Despite heterogeneity in sample composition, outcome, comparator, and confounding control, the summarized findings provide some insights on DR associated with GLP1 RA.

Conclusion

Our meta-analysis based on the 4 major RCTs demonstrates that the use of GLP1 RA drugs which have CV benefits including Liraglutide, semaglutide (both subcutaneous and oral), and dulaglutide, may be associated with an increased risk of progression of DR. However, given the primary purpose of these trials were not for DR, and that they lack systematic DR measurement throughout, further data from large-scale, well-designed clinical studies with systematic evaluation of DR are warranted. Until then these drugs should be used with caution in patients with known DR or high risk for DR who have not been fully evaluated.

Acknowledgment

The authors thank the support from the Tulane Meta-Analysis Systematic Review Support (MARS) Program.

Author contributions

VAF and YY designed the study, resolved discrepancies during data screening and extraction, and interpreted results. YY completed the study protocol and drafted the manuscript. PJ, SB, JW, AC and SO took part in data searching, screening, extraction, and finding synthesis. SO provided technical support throughout the meta-analysis. All authors provided critical comments to the study and reviewed and edited the manuscript. YY is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

YY is supported by a grant (NIH K12HD043451) from the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholar. YY is also supported in part by U54 GM104940 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds the Louisiana Clinical and Translational Science Center.

Disclaimer

The funders played no role in study design, conduct, data collection, analysis and interpretation and did not assist in preparation or review of this manuscript.

Patient consent for publication

Not required

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Conflicts of interest: none

Research Ethnics Approval for Humans: This study does not involve human participants. This is a meta-analysis based on aggregated data from published clinical trials. Consent to participate had been obtained from participants in each original trial. This review paper does not meet the definition of human subjects research, therefore, does not need IRB approval.

Research Ethnics Approvals for Animals: not applicable

Patient and Public Involvement: not applicable

References

1. Food and Drug Administration. Diabetes mellitus-evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. . In: Administration FaD, ed. Rockvielle, MD2008.
2. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
3. Tang H, Li G, Zhao Y, et al. Comparisons of diabetic retinopathy events associated with glucose-lowering drugs in patients with type 2 diabetes mellitus: A network meta-analysis. *Diabetes Obes Metab.* 2018;20(5):1262-1279.
4. Avgerinos I, Karagiannis T, Malandris K, et al. Glucagon-like peptide-1 receptor agonists and microvascular outcomes in type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab.* 2019;21(1):188-193.
5. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA1c Change and Diabetic Retinopathy During GLP-1 Receptor Agonist Cardiovascular Outcome Trials: A Meta-analysis and Meta-regression. *Diabetes Care.* 2021;44(1):290-296.
6. Association AD. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2021. *Diabetes Care.* 2020;44(Supplement_1):S111-S124.
7. Association AD. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2021. *Diabetes Care.* 2021;44(Supplement 1):S125-S150.
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7):e1000100.
9. LibGuides: Search Filters for Various Databases: PubMed. University of Texas School of Public Health. Updated Jul 12, 2021. . 2021. https://libguides.sph.uth.tmc.edu/search_filters/pubmed_filters Accessed Mar. 12, 2021.
10. Clark JM, Sanders S, Carter M, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. *J Med Libr Assoc.* 2020;108(2):195-207.
11. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
12. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-1558.
13. Green JB, Hernandez AF, D'Agostino RB, et al. Harmony Outcomes: A randomized, double-blind, placebo-controlled trial of the effect of albiglutide on major cardiovascular events in patients with type 2 diabetes mellitus-Rationale, design, and baseline characteristics. *Am Heart J.* 2018;203:30-38.
14. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet.* 2018;392(10157):1519-1529.
15. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med.* 2015;373(23):2247-2257.
16. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2017;377(13):1228-1239.

17. Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol.* 2017;5(5):341-354.
18. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019;394(10193):121-130.
19. Kaku K, Yamada Y, Watada H, et al. Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: A randomized trial. *Diabetes Obes Metab.* 2018;20(5):1202-1212.
20. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-322.
21. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7(7):515-527.
22. Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7(7):528-539.
23. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet.* 2019;394(10192):39-50.
24. Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care.* 2019;42(12):2272-2281.
25. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA.* 2019;321(15):1466-1480.
26. Seino Y, Kaneko S, Fukuda S, et al. Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: A 36-week, randomized, double-blind, parallel-group trial. *J Diabetes Investig.* 2016;7(4):565-573.
27. Seino Y, Terauchi Y, Osonoi T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. *Diabetes Obes Metab.* 2018;20(2):378-388.
28. Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. *Diabetes Care.* 2019;42(12):2262-2271.
29. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2019;381(9):841-851.
30. Hernández C, Bogdanov P, Corraliza L, et al. Topical Administration of GLP-1 Receptor Agonists Prevents Retinal Neurodegeneration in Experimental Diabetes. *Diabetes.* 2015;65(1):172-187.
31. Solomon SD, Chew E, Duh EJ, et al. Diabetic Retinopathy: A Position Statement by the American Diabetes Association. *Diabetes Care.* 2017;40(3):412-418.
32. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):837-853.
33. Hooymans JM, Ballegooie EV, Schweitzer NM, Doorebos H, Reitsma WD, Slutter WJ. Worsening of diabetic retinopathy with strict control of blood sugar. *Lancet.* 1982;2(8295):438.

34. Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes.* 1985;34 Suppl 3:74-79.
35. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine.* 2008;358(24):2560-2572.
36. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. *Diabetes Care.* 2016;39(7):1089-1100.
37. Chew EY, Davis MD, Danis RP, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology.* 2014;121(12):2443-2451.
38. Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. *New England Journal of Medicine.* 2009;360(2):129-139.
39. Jingi AM, Tankeu AT, Ateba NA, Noubiap JJ. Mechanism of worsening diabetic retinopathy with rapid lowering of blood glucose: the synergistic hypothesis. *BMC Endocr Disord.* 2017;17(1):63.
40. Hernandez C, Zapata MA, Losada E, et al. Effect of intensive insulin therapy on macular biometrics, plasma VEGF and its soluble receptor in newly diagnosed diabetic patients. *Diabetes Metab Res Rev.* 2010;26(5):386-392.
41. Kennedy A, Frank RN. The influence of glucose concentration and hypoxia on VEGF secretion by cultured retinal cells. *Curr Eye Res.* 2011;36(2):168-177.
42. Bain SC, Klufas MA, Ho A, Matthews DR. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: A review. *Diabetes Obes Metab.* 2019;21(3):454-466.
43. Rasmussen KL, Laugesen CS, Ringholm L, Vestgaard M, Damm P, Mathiesen ER. Progression of diabetic retinopathy during pregnancy in women with type 2 diabetes. *Diabetologia.* 2010;53(6):1076-1083.
44. Rodriguez-Fontal M, Kerrison JB, Alfaro DV, Jablon EP. Metabolic control and diabetic retinopathy. *Curr Diabetes Rev.* 2009;5(1):3-7.
45. Vilsboll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab.* 2018;20(4):889-897.
46. Cetin EN, Bulgu Y, Ozdemir S, et al. Association of serum lipid levels with diabetic retinopathy. *Int J Ophthalmol.* 2013;6(3):346-349.
47. Simo R, Hernandez C. GLP-1R as a Target for the Treatment of Diabetic Retinopathy: Friend or Foe? *Diabetes.* 2017;66(6):1453-1460.
48. Aiello LP, Group DER. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care.* 2014;37(1):17-23.
49. Azad N, Agrawal L, Bahn G, et al. Eye Outcomes in Veteran Affairs Diabetes Trial (VADT) After 17 Years. *Diabetes Care.* 2021.
50. Chew EY, Davis MD, Danis RP, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology.* 2014;121(12):2443-2451.

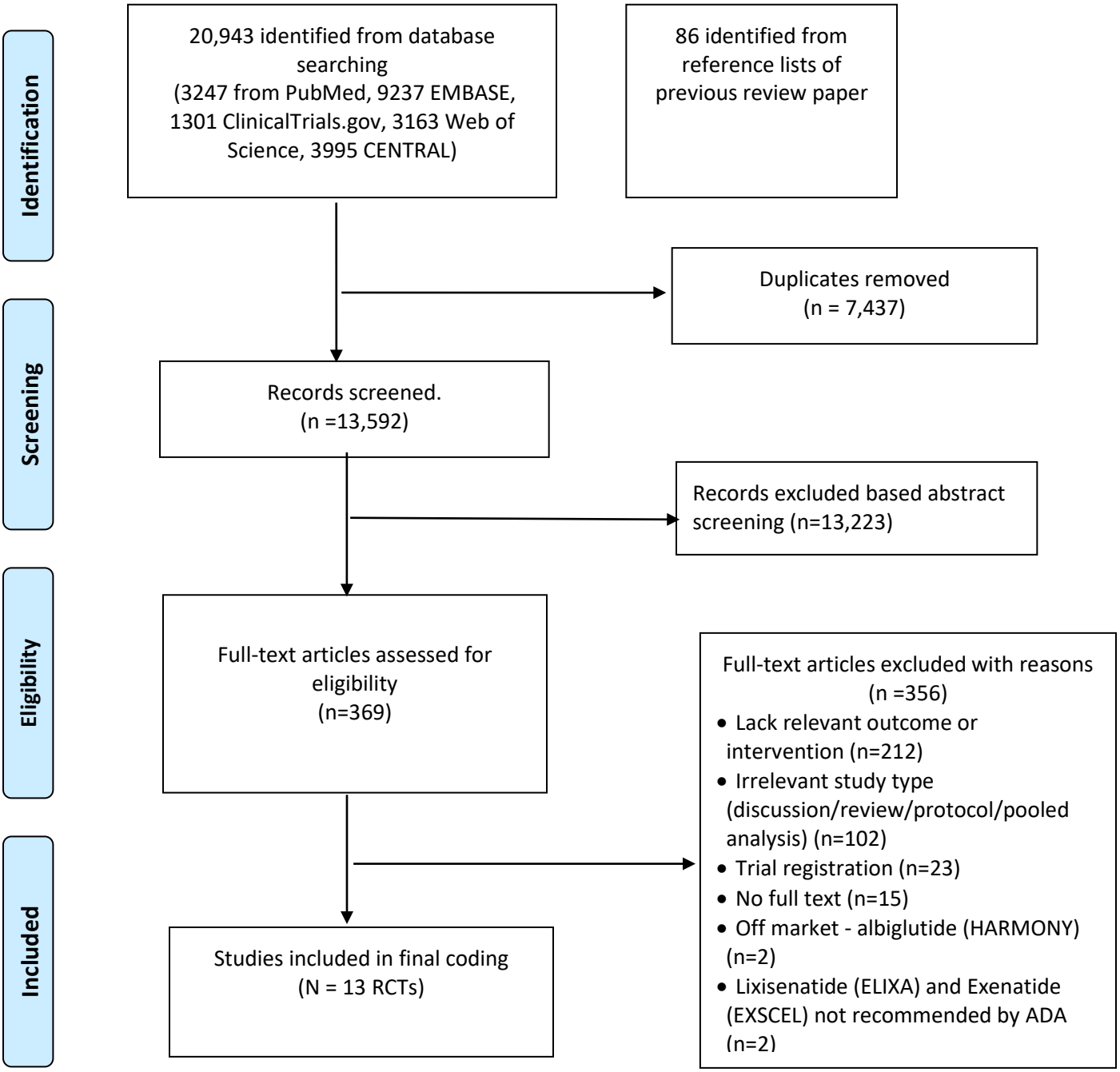
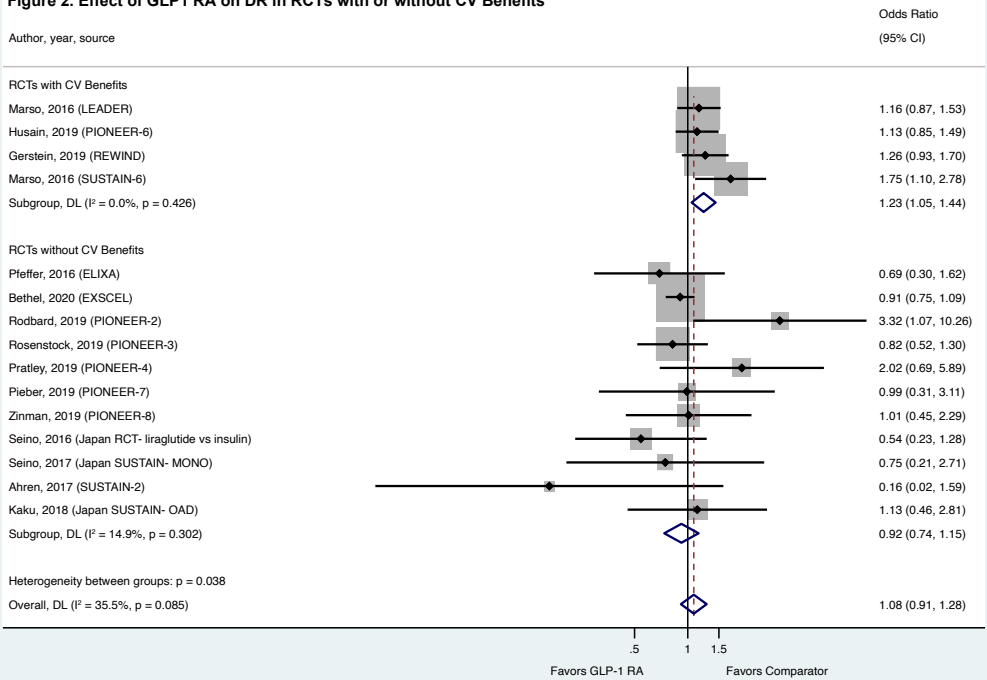


Figure 1. PRISMA flow diagram

Figure 2. Effect of GLP1 RA on DR in RCTs with or without CV Benefits



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 3. Effect of GLP1 RA on DR by Study Length

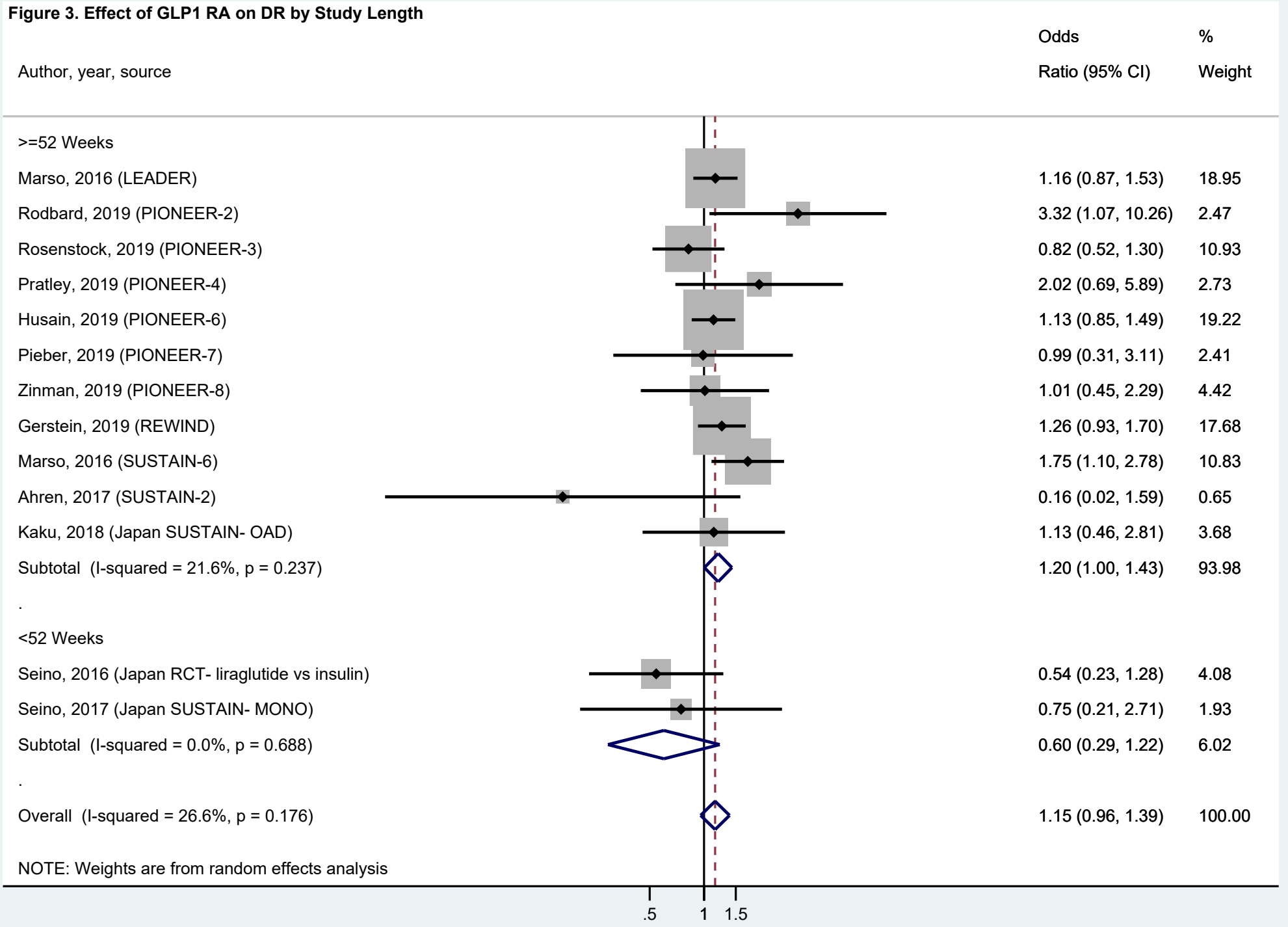


Figure 4. Effect of GLP1 RA on DR by Comparator