HbA_{1c} Change and Diabetic Retinopathy During GLP-1 Receptor Agonist Cardiovascular Outcome Trials: A Meta-analysis and Meta-regression

M. Angelyn Bethel,[1] Rafael Diaz,[2,3] Noelia Castellana,[2,3] Indranil Bhattacharya,[4] Hertzel C. Gerstein,[5] and Mark C. Lakshmanan[1]

Diabetes Care 2021;44:290–296 | https://doi.org/10.2337/dc20-1815

META-ANALYSIS

BACKGROUND

Long-term glycemic control reduces retinopathy risk, but transient worsening can occur with glucose control intensification. Glucagon-like peptide 1 receptor agonists (GLP-1RA) lower glucose, but the long-term impact on retinopathy is unknown. GLP-1RA cardiovascular outcome trials (CVOTs) provide long-term follow-up, allowing examination of retinopathy outcomes.

PURPOSE

To examine the associations between retinopathy, HbA_{1c}, systolic blood pressure (SBP), and weight in GLP-1RA CVOTs.

DATA SOURCES

Systematic review identified six placebo-controlled GLP-1RA CVOTs reporting prespecified retinopathy outcomes.

STUDY SELECTION

Published trial reports were used as the primary data sources.

DATA EXTRACTION

HbA_{1c}, SBP, and weight data throughout follow-up by treatment group were extracted.

DATA SYNTHESIS

Random-effects model meta-analysis showed no association between GLP-1RA treatment and retinopathy (odds ratio [OR] 1.10; 95% CI 0.93, 1.30), with high heterogeneity between studies ($I^2 = 52.2\%$; Q statistic $P = 0.063$). Univariate meta-regression showed an association between retinopathy and average HbA_{1c} reduction during the overall follow-up (slope = 0.77, $P = 0.007$), but no relationship for SBP or weight. Sensitivity analyses for HbA_{1c} showed a relationship at 3 months ($P = 0.006$) and 1 year ($P = 0.002$). A 0.1% (1.09 mmol/mol) increase in HbA_{1c} reduction was associated with 6%, 14%, or 8% increased Ln(OR) for retinopathy at the 3-month, 1-year, and overall follow-up, respectively.

LIMITATIONS

CVOTs were not powered to assess retinopathy outcomes and differed in retinopathy-related criteria and methodology. The median follow-up of 3.4 years is short compared with the onset of retinopathy.

CONCLUSIONS

HbA_{1c} reduction was significantly associated with increased retinopathy risk in meta-regression for GLP-1RA CVOTs. The magnitude of HbA_{1c} reduction was correlated with retinopathy risk in people with diabetes and additional cardiovascular risk factors, but the long-term impact of improved glycemic control on retinopathy was unmeasured in these studies. Retinopathy status should be assessed when intensifying glucose-lowering therapy.

[1]Eli Lilly and Company, Indianapolis, IN
[2]Estudios Clínicos Latino América (ECLA), Rosario, Argentina
[3]Instituto Cardiovascular de Rosario, Rosario, Argentina
[4]Eli Lilly and Company (India) Pvt. Ltd, Haryana, India
[5]Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

Corresponding author: M. Angelyn Bethel, abethel@lilly.com

Received 20 July 2020 and accepted 12 October 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.13100045.

Diabetic retinopathy is a leading cause of vision loss globally and develops in response to prolonged exposure to hyperglycemia (1). Despite clear evidence that near-normalization of blood glucose levels reduces the long-term risk of diabetic retinopathy (2), transient worsening of preexisting retinopathy has also been demonstrated when glucose control is intensified (3–5), typically with insulin or sulfonylurea treatment (2,5). Newer agents, such as glucagon-like peptide 1 receptor agonists (GLP-1RAs), are effective glucose-lowering agents that reach steady state quickly to produce significant glycemic reductions (6), but the effect of glucose lowering by these agents on diabetic retinopathy is poorly understood. Cardiovascular outcome trials (CVOTs) provide the longest available randomized, placebo-controlled follow-up for the GLP-1RAs, with currently completed trials ranging in duration from 1.3 to 5.4 years (7–12). Some CVOTs have shown a point estimate suggestive of increased risk of retinopathy related to treatment; however, none of these trials was designed or powered to provide robust estimates of GLP-1RA effects on retinopathy. Meta-analyses of CVOT data sets have not demonstrated a potential class effect of GLP-1RA treatment, showing instead no significant relationship between GLP-1RA treatment and retinopathy outcomes, and offering only limited insight to discriminate between direct pharmacological drug effects and indirect effects potentially mediating changes in HbA_{1c} or other risk factors. The purpose of this study is to use meta-analysis and meta-regression to investigate the relationship between retinopathy outcomes and changes in glycemic control, systolic blood pressure (SBP), and body weight associated with GLP-1RA treatment.

RESEARCH DESIGN AND METHODS

Search Strategy and Eligibility Criteria

This meta-analysis was aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). The protocol was registered in The International Prospective Register of Systematic Reviews (PROSPERO) (14).

An updated systematic literature review was performed based on a recent publication in 2019 (15). MEDLINE, Embase, and the Cochrane Library databases were searched without language restrictions, using search terms including "glucagon-like peptide-1 receptor agonist", and "diabetes," and "randomized trials." The full list of search terms is listed in Supplementary Table 1. We included large ($N > 1{,}000$) randomized controlled trials published from January 2018 up to September 2019 that compared the efficacy and safety of GLP-1RA versus placebo in adults with type 2 diabetes. Eligible trials reported both major adverse cardiovascular events (MACE, a composite including myocardial infarction, stroke, and cardiovascular death) and retinopathy as prespecified end points. Definitions of retinopathy were as described by each trial and were not standardized for these analyses. The technical data extraction requirements for the meta-regression required eligible studies to report and display data for changes in HbA_{1c}, SBP, and body weight by treatment group over the duration of follow-up. After full-text screening, new eligible studies were added to those included in the recent systematic review (15). Title and abstract screening and full-text screening were done in duplicate.

Data Extraction and Quality Assessment

Published trial reports and supplementary materials were used as the primary data source. Data extraction was done in duplicate using standardized forms, and conflicts were resolved by R.D. Study characteristics (e.g., year of publication, study design, sample size, and length of follow-up), intervention characteristics, patient characteristics (e.g., age, sex, duration of type 2 diabetes, BMI, and baseline HbA_{1c}), and efficacy and safety data, including the retinopathy event definitions, were recorded. HbA_{1c}, SBP, and body weight data throughout the follow-up periods by treatment group were extracted from published figures using DigitizeIt software (https://www.digitizeit.de/). This software facilitated the extraction of the (x, y) numerical data from the image, considering the specified axes system.

Data Synthesis and Analysis

The odds ratio (OR) and 95% CI for retinopathy outcomes were obtained from each trial along with the available event information to unify the reported effect size. The overall OR and 95% CI were calculated using a random-effects model meta-analysis, in which the reported effect size of every study was weighted by the inverse of its variance and the between-study variance was estimated using the DerSimonian-Laird estimator. The Cochran Q test was used to assess heterogeneity of treatment effect between trials. The null hypothesis evaluated by this test is that all studies share a common effect size. The proportion of the total observed variance that reflects real differences in effect size was evaluated through the I^2 index. Thresholds describing the degree of heterogeneity for the I^2 index are low ($\leq$25%), moderate (26−50%), and high ($>$50%). The P value for statistical significance was set at 0.05.

Changes in HbA_{1c}, SBP, and body weight over the duration of follow-up were analyzed as follows: First, the published figures describing these variables were digitized using DigitzeIt software (https://www.digitizeit.de/). Second, the extracted data were used to calculate the areas under the curve for each of the three variables in response to GLP-1RA or placebo by trapezoidal integration. Third, the relative difference in area under the curve in the GLP-1RA versus the placebo group was calculated for each trial. Fourth, the average reduction was calculated as the average of the differences between groups throughout follow-up weighted by time (years) for each variable and trial. Thus, for each trial we obtained two summary metrics—the relative difference in area under the curve in the GLP-1RA versus the placebo groups and the average reduction calculated as the average of the differences between groups throughout follow-up weighted by time in years. Sensitivity analyses provided both summary metrics at discrete time points of 3 months and 1 year.

Three separate univariate meta-regression analyses were used to estimate the relationship between changes in each of HbA_{1c}, SBP, and body weight and the Ln-transformed OR of retinopathy in people randomly assigned to the GLP-1RA versus placebo comparator. Independent variables were the relative change in the area under the curve or the average reduction, both calculated for each of the three variables at three time points. The exponential of the regression coefficient of each univariate meta-regression was used to estimate of the relative change in the intervention effect with a unit increase in the independent

Table 1—Key baseline characteristics from each CVOT

	LEADER (2016) N = 9,340 (9)	SUSTAIN-6 (2016) N = 3,297 (8)	EXSCEL (2017) N = 14,752 (7,30)	HARMONY (2018) N = 9,463 (11)	REWIND (2019) N = 9,901 (10)	PIONEER-6 (2019) N = 3,183 (12)
Active treatment	Liraglutide 1.8 mg, s.c. daily	Semaglutide 0.5 mg or 1.0 mg s.c. weekly	Exenatide 2 mg s.c. weekly	Albiglutide 30–50 mg s.c. weekly	Dulaglutide 1.5 mg s.c. weekly	Semaglutide 14 mg oral daily
Age, years	64 ± 7	65 ± 7	62 ± 9	64 ± 7	66 ± 7	66 ± 7
Sex, *n* (%)						
Male	6,003 (64)	2,002 (61)	9,149 (62)	6,569 (69)	5,312 (54)	2,176 (68)
Female	3,337 (36)	1,295 (39)	5,603 (38)	2,894 (31)	4,589 (46)	1,007 (32)
Duration of diabetes, years	12.8 ± 8.0	13.9 ± 8.1	13.1 ± 8.3	14.1 ± 8.6	10.6 ± 7.2	14.9 ± 8.5
HbA_{1c}, %	8.7 ± 1.6	8.7 ± 1.5	8.1 ± 1.0	8.7 ± 1.5	7.3 ± 1.1	8.2 ± 1.6
HbA_{1c}, mmol/mol	71.6 ± 17.5	71.6 ± 16.4	65.0 ± 10.9	71.6 ± 16.4	56.3 ± 12.0	66.1 ± 17.5
BMI, kg/m^2	32.5 ± 6.3	32.8 ± 6.2	32.7 ± 6.4	32.3 ± 5.9	32.3 ± 5.7	32.3 ± 6.5
SBP, mmHg	136 ± 18	136 ± 17	135 ± 17	135 ± 17	137 ± 17	136 ± 18
Established CVD, *n* (%)	7,598 (81)	2,735 (83)	10,782 (73)	9,463 (100)	3,114 (31)	2,695 (85)
History of heart failure, *n* (%)	1,667 (18)	777 (24)	2,389 (16)	1,922 (20)	853 (9)	388 (12)
Retinopathy, *n* (%)	N/A	N/A	N/A	1,937 (20)	891 (9)	898 (28)

Data are mean ± SD, unless otherwise noted. N/A, not available.

variable. The *P* value for statistical significance was set at 0.05. Analyses were done using Comprehensive Meta-Analysis software (version 2.0; Biostat, Englewood, NJ), R (version 3.6.0; R Core Team, Vienna, Austria), and the R package metafor (version 2.0-0) (16).

Role of Funding Source

Estudios Clínicos Latino América (ECLA) Foundation (Rosario, Argentina) covered all of the costs related to the data collection, statistical analyses, and writing of the manuscript.

RESULTS

Individual Trial Characteristics

Five randomized GLP-1RA CVOTs were included in a recently published systematic review (15). We performed the electronic search on 10 September 2019, detecting 707 additional publications that underwent screening. After duplicate removal and full-text screening, six randomized trials were included in the meta-analysis: LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), SUSTAIN-6 (Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), EXSCEL (Exenatide Study of Cardiovascular Event Lowering), HARMONY (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus), REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes), and PIONEER 6 (Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) (7–12).

Key trial features and retinopathy event definitions used in each trial are presented in Tables 1 and 2. All trials used subcutaneous injectable GLP-1RAs, except for PIONEER 6, which studied an oral GLP-1RA. These analyses included 49,936 patients (n = 24,943 GLP-1RA, n = 24,993 placebo). The mean age of the population was similar across the trials (range 62−66 years), 31−46% of the populations were women, the mean BMI was similar (32−33 kg/m^2), and the mean duration of diabetes ranged from 10 to 15 years. All patients had a history of established cardiovascular disease in HARMONY, whereas almost 70% did not have a history of established cardiovascular disease in REWIND. Mean HbA_{1c} ranged from 7.3 to 8.7% (56.3–71.6 mmol/mol). Duration of follow-up ranged from a median of 1.3 to 5.4 years. Retinopathy prevalence was reported at baseline in the REWIND, HARMONY, and PIONEER 6 trials, ranging from 9.0 to 28.2% of patients (Table 1). Investigational drug nonadherence ranged from 5.4 to 15.0% per year.

Meta-analysis: GLP-1RA Treatment and Retinopathy Outcomes

The combined median follow-up time of the six trials for retinopathy outcomes was 3.4 years (41 months). Meta-analysis showed no significant association between GLP-1RA and retinopathy risk (OR 1.10; 95% CI 0.93, 1.30), with high heterogeneity between studies (I^2 = 52.2%; Q statistic P = 0.063) (Fig. 1).

Meta-regression: Association Between Retinopathy and Key Risk Factors for Retinopathy

Mean reduction values in HbA_{1c}, SBP, and body weight weighted by follow-up period for each individual CVOT and area under the curve relative reduction metrics are presented in Supplementary Tables 2–4.

For the overall follow-up period, meta-regression showed a significant association, with the Ln(OR) for retinopathy increasing by 0.77 for every 1% (10.93 mmol/mol) greater average reduction in HbA_{1c} (95% CI 0.21, 1.34; P = 0.007), but no significant relationship for SBP (slope = 0.23 [95% CI 0.004, 0.45]; P = 0.054) or weight (slope = 0.09 [95% CI −0.02, 0.19]; P = 0.095) (Fig. 2). Sensitivity analyses showed that a significant relationship was consistently present at all time points only for HbA_{1c} reduction (3 months: slope = 0.58, [95% CI 0.17, 0.99]; P = 0.006; 1 year: slope = 1.31 [95% CI 0.48, 2.13]; P = 0.002) (Supplementary Fig. 1). Thus, a 0.1% (1.09 mmol/mol) greater HbA_{1c} reduction was associated with 6%, 14%, or 8% increased Ln (OR) at 3 months, 1 year, or overall follow-up, respectively (Fig. 2). Sensitivity

Table 2—Definitions of retinopathy events from each CVOT

	LEADER (2016) *N* = 9,340 (9)	SUSTAIN-6 (2016) *N* = 3,297 (8)	EXSCEL (2017) *N* = 14,752 (7,30)	HARMONY (2018) *N* = 9,463 (11)	REWIND (2019) *N* = 9,901 (10)	PIONEER-6 (2019) *N* = 3,183 (12)
Retinopathy exclusion criterion	None	None	None	None	None	Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days before screening or within the period between screening and randomization
Method of ascertainment	Adverse event reporting at each study visit	Adverse event reporting at each visit + fundoscopy/ fundus photography at scheduled visits (weeks 0, 56, 104 and 143)	Adverse event reporting at each study visit	Adverse event reporting at each study visit	Adverse event reporting at each study visit	Adverse event reporting at each visit + fundoscopy at scheduled visits (weeks −3, 50, and 83)
Retinopathy end point definition	The need for retinal photocoagulation or vitreous hemorrhage or diabetes-related blindness (defined as Snellen visual acuity of ≤20/200 [6/60], or visual field of <20°, in the better eye with best correction possible)	The need for retinal photocoagulation, or treatment with intravitreal agents, or vitreous hemorrhage, or diabetes-related blindness (defined as Snellen visual acuity of ≤20/200 [6/60], or visual field of <20°, in the better eye with best correction possible)	Diabetic eye disease: photocoagulation, cataract extraction, blindness, enucleation, steroid/Avastin injection, scleral buckling or retinal fixation procedure	Laser photocoagulation or antivascular endothelial growth factor treatment or vitrectomy for diabetic retinopathy/eye disease	Photocoagulation, antivascular endothelial growth factor therapy, or vitrectomy	Retinopathy and related complication events were identified through a search of terms in the Medical Dictionary for Regulatory Activities, version 20.1
Retinopathy adjudication (yes/no)	Yes	Yes	No	No	No	No

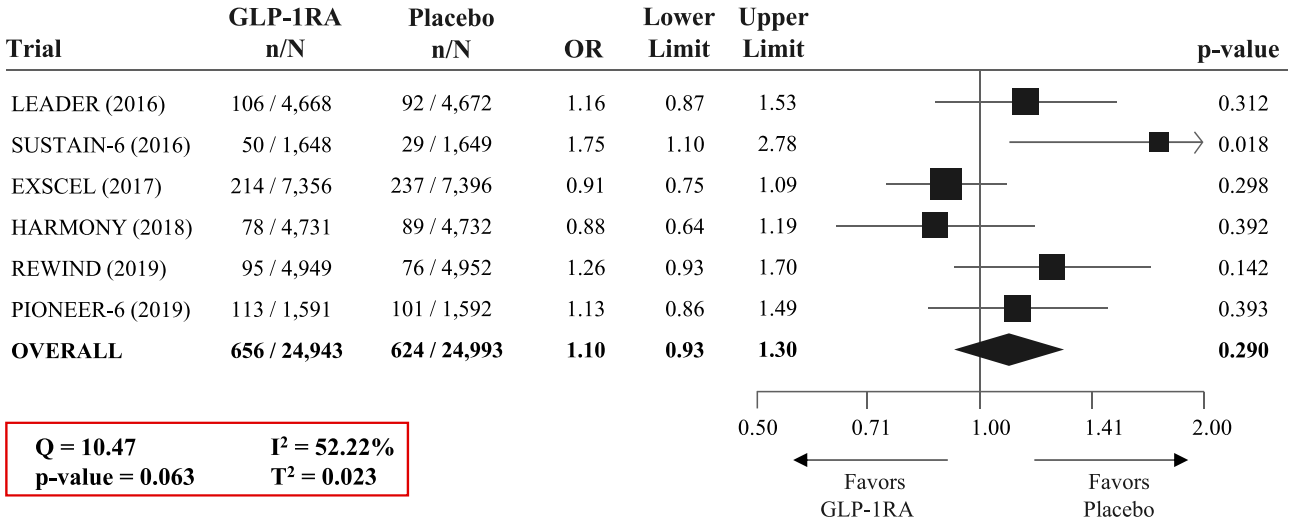

Figure 1—Meta-analysis of retinopathy outcomes in GLP-1RA CVOTs. Data were assessed using the random-effects model.

analyses for SBP and body weight at 3 months and 1 year are presented in Supplementary Figs. 2 and 3. A significant relationship with SBP reduction was only present at 1 year, at which time a 1-mmHg greater SBP reduction was associated with 27% increased Ln(OR) for retinopathy (slope = 0.24 [95% CI 0.03, 0.44]; $P = 0.025$) (Supplementary Fig. 2*B*).

Similar conclusions were derived when area under the curve reduction metrics for HbA_{1c}, body weight, and SBP in each CVOT were replaced by relative reduction metrics (data not shown).

CONCLUSIONS

This analysis uses the tools of meta-analysis and meta-regression to explore the relationship between retinopathy outcomes and GLP-1RA treatment, changes in HbA_{1c}, SBP, and body weight. While meta-analysis did not demonstrate an association between GLP-1RA treatment and retinopathy outcomes, meta-regression showed a significant association between HbA_{1c} reduction and retinopathy, regardless of the follow-up time period. No consistent relationship was observed with SBP or body weight over the different follow-up time periods over a median follow-up of 3.4 years.

The association between initiation of intensive glucose control and worsening of preexisting retinopathy is well known. It was first described in patients with type 1 diabetes who were treated with continuous subcutaneous insulin infusion rather than the conventional short- to intermediate-acting injectable insulin (4,17–19), but has also been documented in other studies in both type 1 and type 2 diabetes (2,5,20,21). These early studies documented worsening with sequential retinal photographs, which is a highly sensitive method to detect incidence and progression of retinopathy. The time course of this early worsening is variable, ranging from 3 months to >3 years after treatment intensification (3). In contrast, the time course for improved retinopathy outcomes attributable to intensive glucose control is longer, ranging from ~3 years in the DCCT (5) to >5 years in a meta-analysis of intensive versus conventional treatment trials in type 2 diabetes (22).

Similar trends can be seen among the trials included in this meta-regression of HbA_{1c} on the GLP-1RA CVOT meta-analysis. Trials with the smallest impact on HbA_{1c}, for example within the first 3 months, were EXSCEL, HARMONY Outcomes, and PIONEER-6. These trials also had the lowest OR for retinopathy. The outlier for retinopathy outcomes, SUSTAIN-6, also had the largest HbA_{1c} differences recorded at follow-up of 3 months, 1 year, and overall. However, the median duration of follow-up for retinopathy within the HbA_{1c} meta-regression (3.4 years) is unlikely to have been of sufficient length to evaluate the potential long-term impact on retinopathy.

Neither SBP nor weight changes were significantly associated with overall retinopathy outcomes in the meta-regression, consistent with existing literature showing inconsistent or only epidemiological relationships between these risk factors and the incidence or progression of retinopathy (23,24). However, the magnitudes of SBP and weight changes demonstrated in the meta-regression are relatively small, and as with HbA_{1c}, the follow-up is perhaps too short to evaluate any potential impact on retinopathy outcomes.

In addition to a relatively short follow-up time compared with the time course of improvements in retinopathy, this meta-regression analysis is further limited by several factors. Even though 49,936 participants contributed data to the CVOT analyses, the information is analyzed as six unique observations (one data point from each trial) rather than as patient-level data. This is smaller than the minimum of 10 recommended by the Cochrane Collaboration Handbook (25) for a meta-regression, potentially limiting assessments of heterogeneity within the data.

It is also important to remember none of the included CVOTs were designed or powered to assess retinopathy outcomes. The baseline prevalence of retinopathy was not reported in all trials, and only PIONEER-6 excluded patients with existing retinopathy, defined as proliferative retinopathy or maculopathy requiring acute treatment. The methods of ascertainment differ, and within-trial retinopathy event definitions range from a categorical yes/no retinopathy question included in EXSCEL to capture of retinal procedures in most other studies. Only SUSTAIN-6 and PIONEER-6 evaluated retinopathy outcomes with fundus

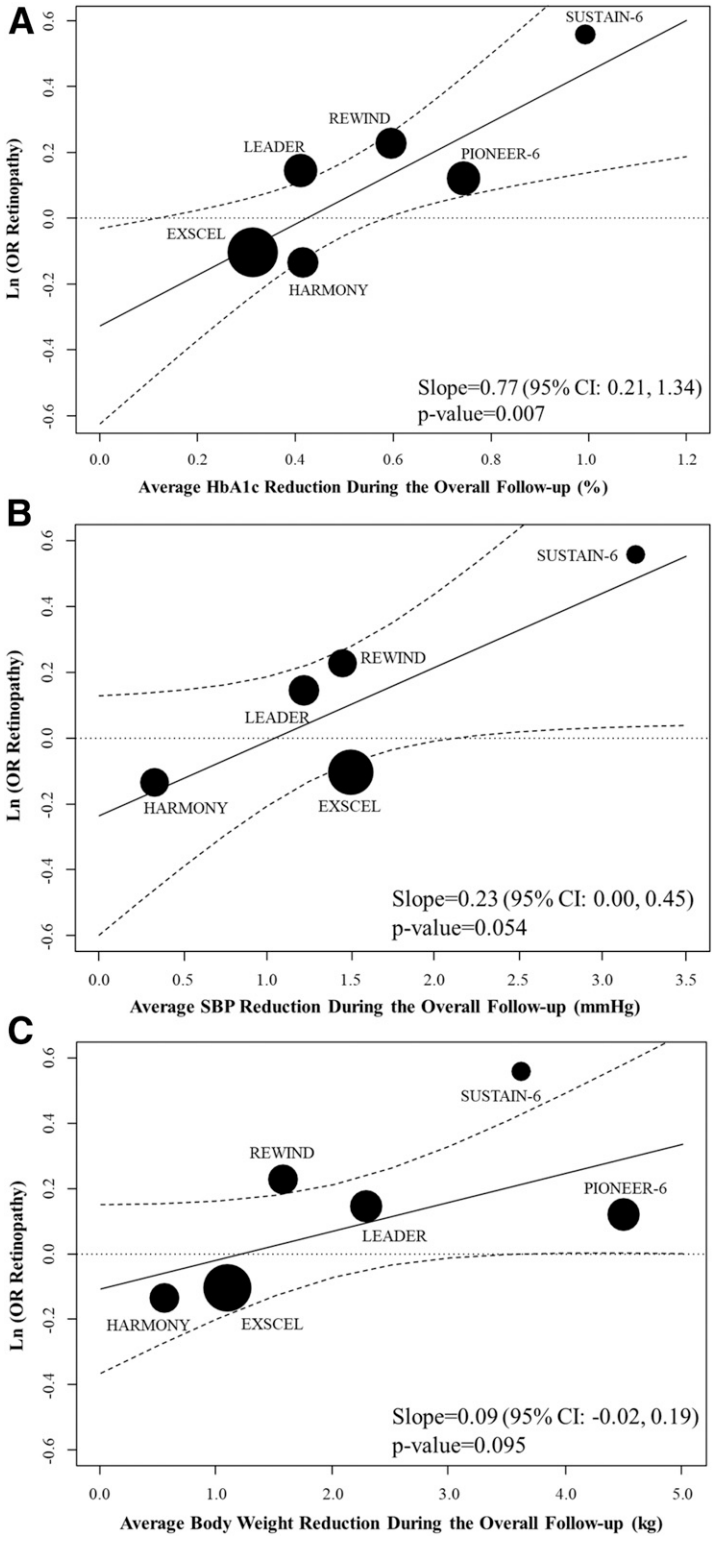

Figure 2—The association of HbA_{1c} (*A*), SBP (*B*), and body weight reduction (*C*) vs. retinopathy Ln(OR) at the overall follow-up period. Data are meta-regression estimations and the 95% CI (represented by the dotted lines). The average of the differences of HbA_{1c} (*A*), SBP (*B*), and body weight (*C*) between the two treatment groups (GLP-1RA or placebo) weighted by follow-up (years) are presented. The area of each circle is proportional to the study's variance.

photography or dilated fundoscopy as scheduled assessments within the trial. Adjudication of retinopathy events was not used in all of included CVOTs. These limitations are probably most important when considering the findings of the meta-regression in the context of dedicated retinopathy studies, which typically use retinal photographs or dilated fundoscopic examinations to provide more detailed assessment of retinopathy progression, for example by using a five-stage diabetic retinopathy severity score (26) to more objectively quantify retinal changes.

The ongoing FOCUS trial (ClinicalTrial.gov identifier: NCT03811561) will examine long-term effects of semaglutide compared with placebo on diabetic retinopathy using validated and standard ophthalmic assessments (27). The study will enroll 1,500 patients with type 2 diabetes, HbA_{1c} between 7 and 10% (53–86 mmol/mol), and Early Treatment Diabetic Retinopathy Study (ETDRS) level of 10–75 evaluated by fundus photography and confirmed by a central reading center, with follow-up planned for 5 years.

In conclusion, our data suggest that the strongest relationship between GLP-1RA treatment and early worsening of retinopathy after drug initiation is via their impact on HbA_{1c}; however, without dedicated trials designed to evaluate the impact on retinopathy, a direct mechanism attributable to one or more drugs in this class cannot be excluded. In this respect, care for those initiating GLP-1RA treatment should not differ from care provided for patients initiating any type of intensive glucose-lowering therapy. Early detection and treatment of retinopathy remains the standard of care. Screening for retinopathy in patients with type 2 diabetes is recommended from the time of diagnosis and typically annually thereafter, depending on the level of glycemic control and retinopathy status (28). Those with severe, proliferative retinopathy should undergo treatment for retinopathy before or in conjunction with the initiation of intensive glucose-lowering therapy. Progression of diabetic retinopathy due to intensified glycemic control is typically transient and reversible over a longer period of time (29). Even with the potential for initial progression of retinopathy, intensive glycemic treatment reduces risk for the onset and progression of diabetic retinopathy over time compared with conventional treatment (29). Current recommendations that GLP-1RAs be used early in the treatment of type 2 diabetes acknowledge their effective glucose-lowering effects and associated

potential for weight loss and low risk of hypoglycemia. As with any potent glucose-lowering agent, clinicians should consider retinopathy status at the time of treatment initiation and follow guidelines for monitoring in patients with established retinopathy.

Acknowledgments. The authors would like to thank Chrisanthi A. Karanikas (Eli Lilly and Company) for her writing and editorial assistance.
Funding. Estudios Clínicos Latino América (ECLA) Foundation (Rosario, Argentina) covered all the costs related to the data collection, statistical analyses, and writing of the manuscript.
Duality of Interest. M.A.B., I.B., and M.C.L. are employees and shareholders of Eli Lilly and Company. M.A.B. was previously employed as the Deputy Director of the Diabetes Trials Unit at the University of Oxford and a member of the leadership for the EXSCEL trial. R.D. reports research grants from Sanofi, DalCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Cirius, Montreal Health Innovations Coordinating Center, and Lepetit, and personal fees, as a member of the Executive Steering Committee, from Amgen and Cirius, and speaker fees from Eli Lilly and Company. H.C.G. has been an advisory board member for Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, Merck, Novo Nordisk, and Sanofi, has received consulting fees from Sanofi, and has been a grant recipient from Eli Lilly & Company, Novo Nordisk, Sanofi, AstraZeneca, and Merck. R.D. and M.C.L. were members of the Steering Committee for the REWIND trial. H.C.G. chaired the Steering Committee and was the principal investigator for the REWIND trial. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. N.C. was responsible for the statistical analysis. M.C.L. wrote the first draft of the manuscript. All authors participated in interpretation of the data and critical review of the manuscript. M.A.B., R.D., N.C., I.B., H.C.G., and M.C.L. had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Prior Presentation. Parts of this study were presented in poster form at the 80th Scientific Sessions of the American Diabetes Association, 12–16 June 2020.

References

1. Yau JW, Rogers SL, Kawasaki R, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556–564
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
3. 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;21:454–466
4. van Ballegooie E, Hooymans JM, Timmerman Z, et al. Rapid deterioration of diabetic retinopathy during treatment with continuous subcutaneous insulin infusion. Diabetes Care 1984;7:236–242
5. DCCT. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:874–886
6. 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
7. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–1239
8. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
9. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
10. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130
11. Hernandez AF, Green JB, Janmohamed S, et al.; Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–1529
12. Husain M, Birkenfeld AL, Donsmark M, et al.; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841–851
13. U.S. Department of Health and Human Services Food and Drug Administration. Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry. Federal Register, 25 February 2020. Accessed 25 February 2020. Available from https://www.fda.gov/media/135936/download
14. Bethel MA, Diaz R, Castellana N, Gerstein HC, Bhattacharya I, Lakshmanan MC. The Relationship between HbA1c Change and Clinical Diabetic Retinopathy During GLP-1 Receptor Agonist Cardiovascular Outcomes Trials. PROSPERO 2020 CRD42020176410. Accessed 30 October 2020. Available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020176410
15. Giugliano D, Maiorino MI, Bellastella G, Chiodini P, Esposito K. Glycemic control, preexisting cardiovascular disease, and risk of major cardiovascular events in patients with type 2 diabetes mellitus: systematic review with meta-analysis of cardiovascular outcome trials and intensive glucose control trials. J Am Heart Assoc 2019;8:e012356
16. Giugliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. Cardiovascular outcome trials and major cardiovascular events: does glucose matter? A systematic review with meta-analysis. J Endocrinol Invest 2019;42:1165–1169
17. Hooymans JM, Ballegooie EV, Schweitzer NM, Doorebos H, Reitsma WD, Slutter WJ. Worsening of diabetic retinopathy with strict control of blood sugar. Lancet 1982;2:438
18. 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
19. Dahl-Jørgensen K. Near-normoglycemia and late diabetic complications. The Oslo Study. Acta Endocrinol Suppl (Copenh) 1987;284:1–38
20. Shurter A, Genter P, Ouyang D, Ipp E. Euglycemic progression: worsening of diabetic retinopathy in poorly controlled type 2 diabetes in minorities. Diabetes Res Clin Pract 2013;100:362–367
21. The Kroc Collaborative Study Group. Diabetic retinopathy after two years of intensified insulin treatment. Follow-up of the Kroc Collaborative Study. JAMA 1988;260:37–41
22. Zoungas S, Arima H, Gerstein HC, et al.; Collaborators on Trials of Lowering Glucose (CONTROL) Group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431–437
23. Zhu W, Wu Y, Meng YF, Xing Q, Tao JJ, Lu J. Association of obesity and risk of diabetic retinopathy in diabetes patients: a meta-analysis of prospective cohort studies. Medicine (Baltimore) 2018;97:e11807
24. Do DV, Wang X, Vedula SS, et al. Blood pressure control for diabetic retinopathy. Cochrane Database Syst Rev 2015;1:CD006127
25. Deeks JJ, Higgins JPT, Altman DG; the Cochrane Statistical Methods Group. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.1, 2020. Chapter 10: Analysing data and undertaking meta-analyses. Specify characteristics in advance. Accessed 1 May 2020. Available from https://training.cochrane.org/handbook/current/chapter-10#section-10-11-4
26. Wilkinson CP, Ferris FL III, Klein RE, et al.; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–1682
27. Novo Nordisk A/S. A research study to look at how semaglutide compared to placebo affects diabetic eye disease in people with type 2 diabetes (FOCUS); [about 9 screens]. In: ClinicalTrials.gov. Bethesda, MD, National Library of Medicine (US), 2000. NLM Identifier: NCT03811561. Accessed 11 September 2020. Available from https://clinicaltrials.gov/ct2/show/NCT03811561
28. American Diabetes Association. Introduction: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S1–S2
29. Aiello LP; DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014;37:17–23
30. Bethel MA, Mentz RJ, Merrill P, et al. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: insights from the EXSCEL trial. Diabetes Care 2020;43:446–452