HbA1c Change and Diabetic Retinopathy During GLP-1 Receptor Agonist Cardiovascular Outcome Trials: A Meta-analysis and Meta-regression

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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, HbA1c, 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

HbA1c, 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 HbA1c reduction during the overall follow-up (slope = 0.77, $P = 0.007$), but no relationship for SBP or weight. Sensitivity analyses for HbA1c showed a relationship at 3 months ($P = 0.006$) and 1 year ($P = 0.002$). A 0.1% (1.09 mmol/mol) increase in HbA1c 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

HbA1c reduction was significantly associated with increased retinopathy risk in meta-regression for GLP-1RA CVOTs. The magnitude of HbA1c 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.
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 glycemeric 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 demonstrated 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 HbA1c, 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 HbA1c), and efficacy and safety data, including the retinopathy event definitions, were recorded. HbA1c, 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 I² index. Thresholds describing the degree of heterogeneity for the I² index are low (≤25%), moderate (26–50%), and high (>50%). The P value for statistical significance was set at 0.05.

Changes in HbA1c, SBP, and body weight over the duration of follow-up were analyzed as follows: First, the published figures describing these variables were digitized using DigitizeIt 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 HbA1c, 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
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 Clinicos 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 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). Investigation 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 1—Key baseline characteristics from each CVOT

|                         | LEADER (2016) | SUSTAIN-6 (2016) | EXSCEL (2017) | HARMONY (2018) | REWIND (2019) | PIONEER-6 (2019) |
|-------------------------|--------------|-----------------|--------------|---------------|--------------|---------------|
|                         | $N = 9,340$ (9) | $N = 3,297$ (8) | $N = 14,752$ (7.30) | $N = 9,463$ (11) | $N = 9,901$ (10) | $N = 3,183$ (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.
| Retinopathy exclusion criterion                                      | Method of ascertainment                                                                 |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| None                                                               | Adverse event reporting at each visit                                                   |
| None                                                               | Fundus photography at scheduled visits (weeks 0, 56, 104 and 143)                       |
| None                                                               | Address adverse event reporting at each visit using Retinopathy adjudication (yes/no)  |
| Diabetic eye disease: laser photocoagulation, cataract extraction,  | Adverse event reporting at each visit                                                   |
| blindness, enucleation, steroid/Avastin injection, scleral buckling |
| or retinal fixation procedure                                      | Address adverse event reporting at each visit using Retinopathy adjudication (yes/no)  |

Table 2—Definitions of retinopathy events from each CVOT
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. 2B).

Similar conclusions were derived when area under the curve reduction metrics for HbA1c, 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 HbA1c, 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 HbA1c 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 HbA1c on the GLP-1RA CVOT meta-analysis. Trials with the smallest impact on HbA1c, 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 HbA1c differences recorded at follow-up of 3 months, 1 year, and overall. However, the median duration of follow-up for retinopathy within the HbA1c 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 HbA1c, 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...
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, HbA1c 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 HbA1c; 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

Figure 2—The association of HbA1c (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 HbA1c (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.
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.

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