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The Effect of Glucagon-Like Peptide-1 Receptor Agonists on Diabetic Retinopathy at a Tertiary Care Center

Julia H. Joo, MPH,[1,2] *Neha Sharma, MPH,*[2,3] *Jacqueline Shaia, BS,*[2,3] *Anna K. Wu, MD,*[2] *Mario Skugor, MD,*[4] *Rishi P. Singh, MD,*[1,2,5,6] *Aleksandra V. Rachitskaya, MD*[2,5]

Objective: The potential association between diabetic retinopathy (DR) worsening and glucagon-like peptide-1 receptor agonists (GLP-1RA) has affected therapeutic management of diabetic patients but remains controversial. This study compared rates of DR development or progression in patients on GLP-1RA to those on SGLT-2 inhibitors (SGLT-2I).

Design: Retrospective cohort study.

Subjects: Nine hundred eighty-one patients with diabetes mellitus taking GLP-1RA or SGLT-2I, the latter serving as controls, between 2012 and 2023.

Methods: Patients were one-to-one greedy matched by propensity scores on race/ethnicity, age, smoking status, baseline body mass index and hemoglobin A1c %, type of diabetes mellitus, baseline DR status and history of DR procedures, duration of drug use, whether they had taken both drug types, and change in hemoglobin A1c % after 1 year on the drug.

Main Outcome Measures: The primary outcome was clinical DR development or progression (termed "worsening") detected by International Classification of Diseases (ICD), 10th edition codes, confirmed by manual review, on GLP-1RA compared with SGLT-2I after propensity score matching. Secondary outcomes included DR worsening indicated by need for procedures due to complications, and time-to-first DR worsening event.

Results: The study included 692 GLP-1RA users and 289 SGLT-2I users. The mean follow-up periods for GLP-1RA versus SGLT-2I use were 1.54 (standard deviation [SD] 1.82) years and 1.38 (SD 1.56) years, respectively. The rates of clinical worsening were 2.3% and 2.8%, respectively. After propensity score matching, an association was not identified between GLP1-RA and DR worsening neither clinically by ICD-10 codes (odds ratio [OR] = 0.33, 95% confidence interval [CI]: 0.11−1.03) nor by indication for procedures (OR = 0.50, 95% CI 0.13−2.00). Time-to-first DR worsening did not differ between the groups in Kaplan-Meier analysis. The most common type of clinical worsening event for both drug types was vitreous hemorrhage (43.7% and 50% of worsening events in GLP-1RA and SGLT-2I users, respectively). The most common DR procedure indicated was anti-VEGF injections (34% and 35% of GLP-1RA and SGLT-2I events, respectively).

Conclusions: Diabetic retinopathy worsening, either clinically or by procedures, was not associated with GLP-1RA compared with SGLT-2I, both before and after propensity score matching on all analyses, including time-to-first worsening event.

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Diabetic retinopathy (DR) is a common complication of diabetes that affects the vasculature of the eye, with increasing incidence correlated with increased duration of diabetes. The progression and development of DR is associated with several risk factors, including duration of diabetes, poor glycemic control. and poorly controlled hypertension.[1,2] Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a class of medications being used with increased frequency as a second-line treatment in the management of type 2 diabetes mellitus and obesity. The effect of GLP-1RA on DR is controversial. On one hand, it has been shown that GLP-1 receptors are expressed in the human retina and studies have suggested neuroprotective effects of GLP-1RA.[3,4] On the other hand, certain GLP-1RAs have been cited to be associated with an early worsening of DR phenomenon, a paradoxical worsening of DR upon initiation of the therapy. For instance, in the SUSTAIN-6 trial semaglutide showed a higher rates of

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retinopathy complications including "vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation."[5] This resulted in the semaglutide label to include the following warning: "In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with OZEMPIC (3.0%) compared to placebo (1.8%)."[5] The trial demonstrated that the absolute risk increase for DR complications was larger among patients with a history of DR at baseline (OZEMPIC: 8.2%, placebo: 5.2%) than among patients without a known history of DR (OZEMPIC: 0.7%, placebo: 0.4%).[5] The literature on the topic is varied. Some subsequent studies have shown DR development and progression and many others have not.

It has been postulated that it might be dramatic improvement in glycemic control and not the therapeutic per se that has an effect on DR. The association between rapid improvement in glucose control and a transient worsening of DR has been previously reported. It is a phenomenon that was initially seen in insulin users, particularly in those who experienced a dramatic and rapid drop in blood sugar from therapy.[6,7]

The goal of this study was to assess the development or worsening of DR among patients with type 2 diabetes mellitus who initiated treatment with GLP-1RA using observational data from a single center. The study compared this group to those on SGLT-2 inhibitors (SGLT-2I), a comparably effective diabetes medication,[8] as a control. The definition of DR worsening was very inclusive and manual review was performed to verify each case of worsening.

Methods

Study Population

This study was approved as exempt human subject research from the Cleveland Clinic Institutional Review Board (IRB #22-463). Study-related procedures were performed in accordance with good clinical practice (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use E6), applicable United States Food and Drug Administration regulations, the Health Insurance Portability and Accountability Act, and the Declaration of Helsinki.

Adult patients seen at the Cleveland Clinic Cole Eye Institute with a documented diagnosis of diabetes mellitus and initiated on GLP-1RA (semaglutide, dulaglutide, and exenatide) or SGLT-2I (empagliflozin, canagliflozin, and dapagliflozin) from January 2012 through February 2023 were included in the study. If a patient took both drug types over the study period, the drug class initiated first was chosen as the treatment group under the analysis. Patients with concurrent nondiabetic ocular pathologies (e.g., age-related macular degeneration and retinal vein occlusion) that could impact retinal findings of interest, patients with proliferative DR (PDR) at time of study initiation, or patients who underwent prior retinal surgery were excluded from the cohort.

Diabetic retinopathy development or early worsening (henceforth referred to as "worsening") criteria included development of (1) any DR from no DR at baseline using International Classification of Diseases, 10th Edition (ICD-10) codes, (2) progression to PDR using ICD-10 codes, (3) development of macular edema using ICD-10 codes, (4) development of vitreous hemorrhage or tractional retinal detachment using ICD-10 codes, or (5) worsening necessitating procedural intervention (i.e., administration of anti-VEGF injections, pars plana vitrectomy [PPV], or panretinal photocoagulation [PRP] to manage the disease). Worsening events were only included in analysis if they occurred $\geq$30 days after initiation of the medication. Any case of DR worsening was counted as an event throughout the entire duration that the patient was on either class of medication. Every case of ICD-10 worsening matching any of criteria 1-4 listed earlier was individually reviewed by 2 members of the study team (J.H.J. and N.S.) and a retina specialist (A.V.R.). Manual review included checking individual charts for clear documentation of worsening on examination findings from a retina specialist and documented interpretation of imaging (e.g., fundus photography, fluorescein angiography, B-scans, and OCT) when available. Among the worsening events manually reviewed, 77% of cases had imaging available from the clinic visit. Of those who had imaging, 89.4% had OCT images available, 7.0% had fundus photos, 3.5% had fluorescein angiography, 3.5% had OCT-angiography, and 7.0% had B-scans available to review. The sum of percentages surpasses 100% because $>$1 modality was available for some patients. Events were not reviewed for improvements.

Demographic information such as age, race/ethnicity, and smoking status was collected. Values for body mass index (BMI), hemoglobin A1c (HbA1C) %, DR, and ICD-10 visit codes were collected at baseline and after initiation of either drug. "Baseline" for each group was defined as the date of the most recent ophthalmology visit within 1 year before initiating GLP-1RA or SGLT-2. Types and number of treatments for DR (e.g., anti-VEGF injection, PRP, and PPV) in each eye and changes in eye-related ICD-10 codes from baseline were recorded for the duration that the patient was on either drug or until study end.

Statistical Analysis

The primary outcome was the odds ratio (OR) of DR worsening by ICD-10 codes on GLP-1RA compared with SGLT-2I after linear propensity score matching. The linear propensity model is a transformation of the propensity scores calculated by logistic regression to the logit scale, which avoids problems with propensity score estimates near 0 or 1.[9,10] Propensity score analyses were conducted for each of the outlined early worsening criteria. Before matching, overlap between the GLP-1RA and SGLT-2I groups were evaluated and presented in Fig S1A (available at www.ophthalmologyscience.org).

Patients were 1:1 greedy matched using linear propensity scores calculated from a logistic regression model that was fit based on the drug type (GLP-RA or SGLT-2I) and included the covariates: race/ethnicity, age, smoking status, baseline BMI and HbA1C %, type of diabetes mellitus, baseline DR severity, whether they had ever undergone DR procedures at baseline (i.e., anti-VEGF injections, PPV, or PRP), duration of drug use, whether they had taken both GLP-1RA and SGLT-2I, and change in HbA1C after 1 year on the drug (Fig S1B, available at www.ophthalmologyscience.org).

The primary outcome was clinical DR worsening. Secondary outcomes included the subtypes of DR worsening criteria listed earlier, including the categories of worsening by ICD-10 code changes and the need for DR procedures due to worsening. Greedy one-to-one matching with replacement was utilized for all matches due to improved Love plots (Fig S1B, available at www.ophthalmologyscience.org), and improved Rubin's 1 and 2 rules compared with unmatched values (Table S1, available at www.ophthalmologyscience.org). Rubin's first rule evaluates the absolute value of the standardized difference of the linear propensity score, comparing the intervention group with the control group, should be close to 0, ideally below 10%, and in

any case <50%. Rubin's second rule evaluates the ratio of the variance of the linear propensity score in the intervention group to the variance of the linear propensity score in the control group. The ratio should be close to 1.[10,11] Matching on replacement allowed maximization of the intervention group. By matching the controls to the intervention more than once, the risk of selection bias was limited in our intervention group. Ninety-five percent confidence intervals (CIs) were calculated to compare drug types and risk of early worsening. Kaplan Meier curves were used for time-to-event analyses. R (v4.1.1; R Core Team) was used to perform the analyses.

Data Preparation

To prepare for propensity score matching, a complete case analysis was conducted for the HbA1C change after 1 year, race, smoking status, and BMI at 1-year variables due to the minimal amount of missing data. Afterwards, simple imputation was conducted for the starting BMI variable (n = 33) and starting HbA1C variable (n = 72). Single imputation was performed using Multivariate Imputation by Chained Equations with the "mice" package in R. Before matching, Rubin's first rule was 42.78 and Rubin's second rule was 1.14 (Table S1, available at www.ophthalmologyscience.org). After completing greedy 1:1 matching with replacement, Rubin's first and second rules improved to 0.53 and 1.03, respectively. These improved values along with the Love Plot (Fig S1, available at www.ophthalmologyscience.org) improved the matching greatly.

Results

Population Characteristics of GLP-1RA and SGLT-2I Users

Out of 1191 patients who had taken either SGLT-2I or GLP1-RA between 2012 and 2023, 981 met the inclusion criteria (Table 1). Of this total, 692 patients had taken GLP-1RA and 289 had taken SGLT-2I. The demographic and clinical characteristics were comparable between the 2 groups. The average age of GLP-1RA users was 66 years and 65 years for SGLT-2I users. The majority of patients in both groups were never smokers (54% and 55% for GLP-RA and SGLT-2I, respectively). The majority of patients were White (59% and 64%), followed by African American (29% and 26%).

At baseline, 11% of GLP-1RA users and 8% of SGLT-2I users had no DR. Average drug duration was 1.54 (standard deviation [SD] = 1.82) years and 1.38 (SD = 1.56) years for GLP-1RA and SGLT-2I, respectively. Less than 10% of patients had taken both drug types during the study period. As expected, the baseline BMI for GLP-1RA users was slightly higher than that of the control, 37 (SD = 8) kg/m^2 compared to 34 (SD = 7) kg/m^2. Most patients in both groups were treatment naive to intravitreous injections (GLP-1RA: 74.1%; SGLT-2I: 78.5%) and other interventions for DR, such as PRP or PPV (GLP-1RA: 78.8%; SGLT-2I: 83.7%).

Average baseline HbA1C was calculated to be 8.53% (SD = 1.81%) in GLP-1RA users and 8.61% (SD = 1.72%) in SGLT-2I users. The change in HbA1C on either drug after 1 year was not significantly different between the groups ($P > 0.9$). The GLP-1RA users experienced a 0.38% (SD = 1.63%) decrease and SGLT-2I users had 0.34% (SD = 1.67%) decrease in HbA1C level, but the difference within each group was not significant (Table 1).

Of 78 cases that were initially flagged as worsening by ICD-10 code, 24 were confirmed to be true worsening cases. Overall, 16 cases (2.3%) of DR worsening in GLP-1RA users and 8 cases (2.8%) of documented worsening in SGLT-2I users were identified (Table 1). The rates of worsening were not significantly different between the groups ($P = 0.7$).

Characterization of DR Clinical and Procedural Worsening

The types of clinical worsening or types of procedures indicated for worsening were characterized in Table 2. Most of the clinical worsening cases were seen in patients who already had PDR and subsequently developed a vitreous hemorrhage on a GLP-1RA (n = 7, 43.8% of worsening events) or SGLT-2I (n = 4, 50% of worsening events). The next most frequent types of events were development of macular edema (n = 6 across both medications, 25% of total events) or PDR development (n = 3 across both medications, 12.5% of total events). Two-step nonproliferative DR worsening and development of any DR from no DR at baseline were infrequently seen in GLP-1RA users (n = 2) and were not observed in SGLT-2I users (Table 2).

A similar subanalysis was conducted for DR procedural worsening events. Of the procedures indicated for DR worsening, anti-VEGF injections were most common (34% and 35% of procedures in GLP-1RA and SGLT-2I users, respectively), followed by PRP, then PPV. None of the subtypes of worsening were significantly different between GLP-1RA and controls, assessed by Wilcoxon rank sum test (Table 2).

Generation of a Propensity Model and Comparison of DR Worsening Between GLP-1RA and SGLT-2I

A linear propensity model was generated using relevant baseline clinical and demographic variables to address the primary outcome of clinical DR worsening on GLP-1RA. No significant difference in DR worsening was identified between GLP-1RA and SGLT-2I users either before (OR = 0.72, 95% CI 0.31−1.68) or after propensity score matching (OR = 0.33, 95% CI 0.11−1.03) (Fig 1). The odds of clinical worsening were further evaluated by categories of worsening. The majority of worsening cases were due to vitreous hemorrhage. The odds of vitreous hemorrhage or vitreous hemorrhage and retinal detachments were not statistically different between GLP-1RA users and controls (OR = 2.50, 95% CI 0.49−12.89 and OR = 1.50, 95% CI 0.25−8.98, respectively). Statistical analysis for the other DR worsening subtype outcomes was not possible because there were no DR worsening events in the 1:1 greedy matched cohorts. Therefore, an unmatched univariate analysis was performed for these subtypes of worsening, which showed no significant OR ($P > 0.05$) (Fig 1).

Table 1. Patient Demographics and Characteristics

Characteristic	GLP-1RA, N = 692*	SGLT-2I, N = 289*	*P* value†
Age	65.76 (11.62)	65.52 (10.64)	0.5
Smoking status			0.2
Current smoker	38 (5.5%)	24 (8.3%)	
Former	279 (40%)	105 (36%)	
Never smoker	375 (54%)	160 (55%)	
Race/Ethnicity			0.2
African American	198 (29%)	75 (26%)	
White	406 (59%)	186 (64%)	
Hispanic	51 (7.4%)	13 (4.5%)	
Other	37 (5.3%)	15 (5.2%)	
Took both drug categories	43 (6.2%)	23 (8.0%)	0.3
Baseline HbA1C	8.53 (1.81)	8.61 (1.72)	0.4
Baseline BMI	36.71 (7.89)	34.35 (7.03)	<0.001
Baseline DR severity			
No DR	75 (10.8%)	23 (8.0%)	
Mild NPDR	303 (44%)	136 (47%)	
Moderate NPDR	113 (16%)	49 (17%)	
Severe NPDR	49 (7.1%)	23 (8.0%)	
PDR	152 (22%)	58 (20%)	
Baseline intravitreal injections	179 (25.9%)	62 (21.5%)	0.5
Baseline PRP, PPV	147 (21.2%)	47 (16.3%)	0.2
T1DM	53 (7.7%)	23 (8.0%)	0.9
T2DM	639 (92%)	266 (92%)	0.9
Drug duration (years)	1.54 (1.82)	1.38 (1.57)	0.4
1-year change in HbA1C	−0.38 (1.63)	−0.34 (1.67)	>0.9
Worsening by ICD-10 code	16 (2.3%)	8 (2.8%)	0.7

BMI = body mass index; DR = diabetic retinopathy; GLP-1RA = glucagon-like peptide-1 agonists; HbA1C = hemoglobin A1c; ICD = International Classification of Diseases; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; PPV = pars plana vitrectomy; PRP = panretinal photocoagulation; SGLT-2I = SGLT-2 inhibitors; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
*n (%); mean (standard deviation).
†Wilcoxon rank sum test was used for quantitative variables; Pearson chi-square test was used for multicategorical variables; Fisher exact test was used for categorical variables with exactly 2 groups.

The need for procedures for DR worsening events was also evaluated before and after propensity score matching. Overall, the odds of DR worsening by procedures were unaffected by GLP-1RA use after matching (OR = 0.5, 95% CI 0.13−2.00). Glucagon-like peptide-1 agonists use was not significantly associated with greater risk of anti-VEGF injections (OR = 1.02, 95% CI 0.81, 1.29), PRP (OR = 1.10, 95% CI 0.81, 1.48), and PPV (OR = 1.09, 95% CI 0.68, 1.75) (Fig 1).

Next, the time to the first worsening event for those who experienced DR worsening between GLP-1RA and SGLT-2I users was compared. Survival curves using both

Table 2. Subtypes of Clinical and Procedural DR Worsening

Subtype of Worsening	GLP-1RA, N = 692*	SGLT-2I, N = 289*	*P* value†
Worsening by ICD-10 code	16 (2.3%)	8 (2.8%)	0.7
Any DR from no DR	2 (0.3%)	0 (0%)	>0.9
Two-step NPDR worsening	2 (0.3%)	0 (0%)	>0.9
DME development	3 (0.4%)	3 (1.0%)	0.4
PDR development	2 (0.3%)	1 (0.3%)	>0.9
VH or TRD from baseline PDR	7 (1.0%)	4 (1.4%)	0.7
Anti-VEGF injection	236 (34%)	100 (35%)	0.9
PPV	38 (5.5%)	13 (4.5%)	0.5
PRP	109 (16%)	42 (15%)	0.6

DME = diabetic macular edema; DR = diabetic retinopathy; GLP-1RA = glucagon-like peptide-1 agonists; HbA1C = hemoglobin A1c; ICD = International Classification of Diseases; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; PPV = pars plana vitrectomy; PRP = panretinal photocoagulation; SGLT-2I = SGLT-2 inhibitors; TRD = tractional retinal detachment; VH = vitreous hemorrhage.
*n (%).
†Pearson chi-square test; Fisher exact test.

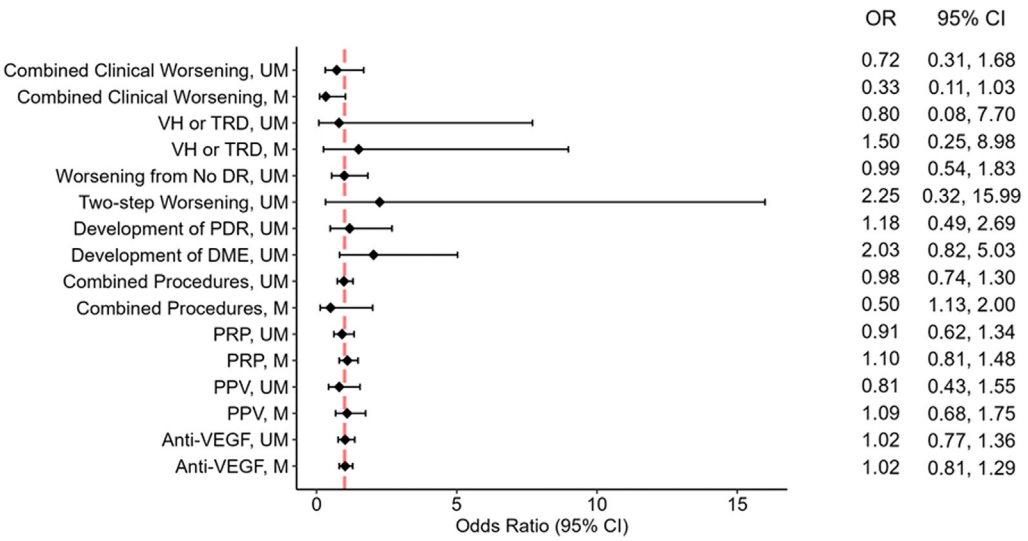

Figure 1. Propensity score matched and unmatched odds of DR progression on GLP-1RA versus SGLT-2I. A forest plot shows the odds of DR worsening on GLP-1RA compared with SGLT-2I for various indications of progressing disease, both clinically and by need for procedures. No significant association between GLP-1RA use and any worsening outcome was identified, both before and after propensity score matching. CI = confidence interval; DME = diabetic macular edema; DR = diabetic retinopathy; GLP-1RA = glucagon-like peptide-1 agonists; M = matched by propensity score; OR = odds ratio; PDR = proliferative diabetic retinopathy; PPV = pars plana vitrectomy; PRP = panretinal photocoagulation; SGLT-2I = SGLT-2 inhibitors; TRD = tractional retinal detachment; UM = unmatched; VH = vitreous hemorrhage.

unmatched and propensity score matched data showed no significant difference between the drug types in time to worsening events ($P = 0.44$ and $P = 0.1$, respectively) (Fig 2). In both groups, both before and after matching, the majority of worsening events occurred after 1000 days of starting the respective drug.

Discussion

While metformin remains the first-line therapy for most diabetic patients,[12] GLP-1RAs have become increasingly popular because of their superior efficacy in reducing HbA1C %,[13,14] cardiovascular and cardiorenal benefits,[8,15] and indication for obesity.[16] In particular, it might be indicated in a patient with a contraindication or intolerance to metformin, with a HbA1C >1.5% over target, or in patients who do not reach their target HbA1C in 3 months, particularly in patients with atherosclerosis, heart failure, or chronic kidney disease.[17] The introduction of GLP-1R agonists into health care and their increasing popularity has led to increased interest evaluating different consequences of this class of drugs, including potential development or worsening of DR.

While GLP-1RAs offer excellent glycemic control and associated cardiovascular benefits, the SUSTAIN 6 cardiovascular outcome trial (CVOT) was the first to show an association between GLP-1RA use and DR complications. The preceding SUSTAIN 1 to 5 trials with semaglutide did not show this relationship.[18–20] In SUSTAIN 6, 3.0% of semaglutide users developed DR complications, including vitreous hemorrhages, DR-related blindness, and need for PRP or intravitreal agents.[5] Many of the patients who experienced worsening had preexisting retinopathy at baseline, particularly PDR. Further inspection of the protocol in this study showed that fundus dilation was not a requirement of the eye examination,[5] which represents a significant limitation in accurate detection of DR development and progression. Subsequent CVOTs for semaglutide such as PIONEER and SUSTAIN 7 developed more stringent inclusion criteria for assessing DR complications by excluding patients with PDR or maculopathy and requiring fundus dilation for eye examinations, as detailed in their published protocols.[21,22] Patients in these later studies also had better management of their glycemic index, as the average HbA1C was lower than in SUSTAIN 6 (e.g., HbA1C of 8.2% in SUSTAIN 7 compared with 8.7% in SUSTAIN 6). Rates of DR complications were found to be comparable between semaglutide and placebo[21] and relatively low in semaglutide and liraglutide users in these studies.[22]

Several systemic reviews and meta-analyses of the CVOTs for GLP-1R agonists show an emerging pattern of dramatic changes in HbA1C level associated with DR worsening. For instance, a meta-analysis of multiple CVOTs from Bethel et al found that HbA1C reduction was significantly associated with increased retinopathy risk in meta-regression for GLP-1RA and the magnitude of HbA1C reduction was correlated with retinopathy risk in people with diabetes and additional cardiovascular risk factors.[23] Retinopathy complications were defined differently in each trial included in the meta-analysis, but most studies included the need for PRP, PPV for vitreous hemorrhage, intravitreal injections, and blindness, similar to the endpoints used in the SUSTAIN 6 trial. The 6 CVOTs may have also been limited in accurately assessing DR, as the study protocols did not uniformly require dilation for fundoscopies, baseline prevalence of retinopathy was not

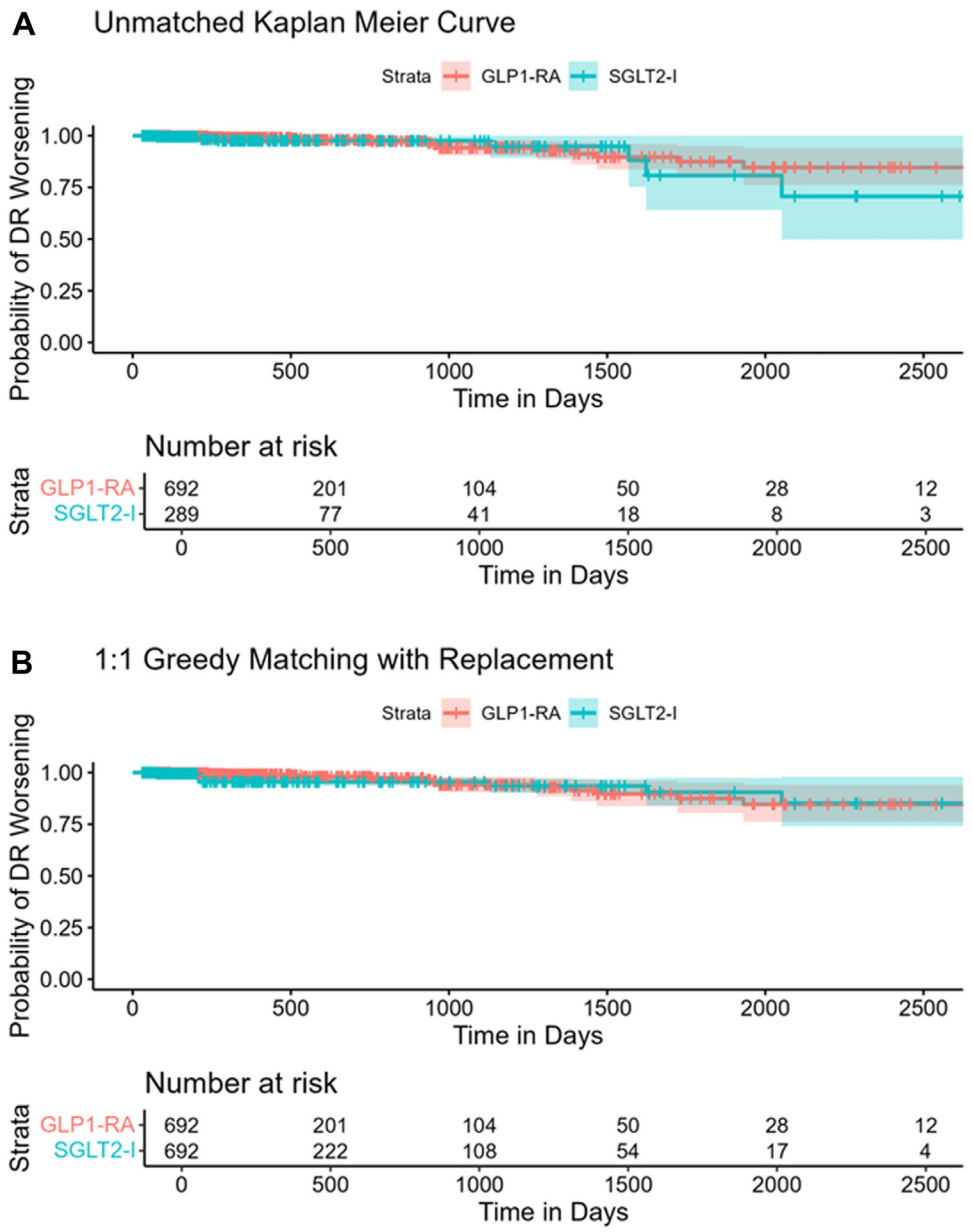

Figure 2. Matched and unmatched time to first DR worsening event. Kaplan Meier curves were generated on the dataset both (**A**) before and (**B**) after propensity score matching for the time-to-first DR worsening event on either GLP-1RA or SGLT-2I. No significant difference was found in either analysis. DR = diabetic retinopathy; GLP-1RA = glucagon-like peptide-1 agonists; SGLT-2I = SGLT-2 inhibitors.

reported across all trials, and baseline HbA1C levels vastly differed between the studies.[5,15,21,24–26] Additionally, Vilsboll et al performed a post hoc mediation analysis of the SUSTAIN 6 trial data, including initial change in HbA1C % as a covariate. They found that the increase in DR complications seen with semaglutide versus placebo may be associated with the large and rapid decline in HbA1C during the first 16 weeks of treatment.[27]

While the phenomenon of early DR worsening has been observed since the 1990's in insulin users,[28] who often also experience rapid glycemic control within treatment initiation, the pathophysiology of this mechanism is poorly understood. One theory postulates that tight glycemic control leads to VEGF upregulation, which is associated with vascular permeability.[29,30] Another study found that reduced blood glucose levels led to a decrease in vitreous glucose concentration, which exacerbated retina injury in rats.[31]

Subgroup analysis in meta-analysis has shown other factors that may increase likelihood of DR complications. Yoshida and colleagues conducted a systemic review and meta-analysis to examine the effect of GLP1-RA on DR in type 2 diabetes mellitus in randomized control trials with or without cardiovascular benefits, adjusted for major confounders, and found the association between GLP1-RA and DR worsening to be significant in the subgroup of patients

who had been on a GLP-1RA for ≥52 weeks.[32] While early worsening has been commonly observed within 3 months and up to 3 years on insulin,[33–35] this study implied that this time frame may not necessarily be the same for GLP-1RA.

Large database studies studying the effect of GLP-1RA outside the restrictive context of randomized control trials have also shown conflicting results on the association with DR worsening. For instance, Wai et al evaluated the effect of GLP-1RA and SGLT-2I on DR complications using TriNetX, a large, deidentified database consisting of patient data from >54 health care organizations across the United States. They found that patients taking GLP-1RA demonstrated increased conversion rates to PDR but underwent similar rates of PPV compared with patients on SGLT-2I.[36] Conversely, in a retrospective cohort study of 10 763 patients from the U.K. Clinical Practice Research Datalink, Douros and colleagues found decreased risk of DR in GLP-1RA users compared with patients on ≥2 oral antidiabetic medications.[37] Furthermore, in observational and Mendelian randomization studies in 2390 diabetic patients from several Swedish Registers, Zheng et al buttressed the clinical finding of an inverse relationship between GLP-1RA use and DR with evidence of protective SNPs in the *GLP1R* gene.[38] While the benefit of reporting aggregate data assessing macroscopic trends and results is evident, large databases rely on accurate diagnostic coding in the electronic medical record, which is often a challenge for accurate DR staging.[39–41]

In contrast, a strength of the current study is derived from the compilation and granular analysis of patient data collected from an academic institution. As mentioned earlier, this study did not a find statistically significant worsening measures associated with GLP-1RA use across the different criteria used to categorize early worsening events. To account for inconsistencies between true disease state and documented ICD coding, the study team manually reviewed all cases of DR worsening indicated by changes in ICD-10 codes. This included assessing documentation of the retinal examination, image interpretation (e.g., OCT, fundus photography, and B-scan) when available, and a retina specialist's assessment and plan to ensure that only "true" cases of worsening were included in the analyses. Images taken on the day of the clinic visit when worsening was noted were available for 77% of worsening cases. This quality review process decreased the number of worsening cases by over twofold (6.0%−2.3% and 7.4%−2.8% worsening in GLP-1RA and SGLT-2I users, respectively). Cases involving transitions of care between providers, especially from optometry or general ophthalmology to retina specialists, led to notable changes in ICD coding between providers. Unspecified laterality of DR coding in some visits also frequently resulted in false positives during our initial round of detection of ICD-10 code worsening by a coded algorithm. Finally, manual inspection also revealed that the ease of copying forward ICD codes from the previous encounter in the electronic medical record may have facilitated incorrect coding. These findings highlight the challenge of accurately detecting clinical DR progression and the caution required in relying on diagnosis codes, particularly in large databases in which manual quality control is not feasible. Thus, the manual review of worsening cases is a unique strength of this study.

Previous reports of DR worsening on GLP-1RA have found the rates of worsening to be low, usually ≤15%.[2,5] While this single-center study did not identify a significant association between GLP-1RA and early worsening of DR in any analyses, the data set may have been limited in power to detect this relatively uncommon event. In an earlier data set pulled from the electronic medical record for this study before adding the inclusion criteria of having ICD-10 codes entered by an ophthalmologist, the sample was twice as large and revealed greater odds of worsening in GLP-1RA users. However, this difference disappeared after taking greater measures to ensure the accuracy of worsening events, which decreased the sample size nearly twofold, which highlights the importance of manual review of the cases of worsening. Another limitation of this study is the small representation of semaglutide among GLP-1RA users, making up 5.2% of the group (Table S2). While other GLP-1RA drug types have shown greater DR events compared with placebo in some large trials,[5,15,25] semaglutide is the only GLP-1RA that has been significantly associated with DR worsening.[32] Additionally, the study period during which patients were on either drug were limited (1.54 ± 1.82 years on GLP-1RA, 1.38 ± 1.57 years on SGLT-2I), and this relatively short time period of observation could have limited our ability to detect worsening events multiple years after starting the medications. Lastly, the HbA1C changes seen on either drug were not very large (<0.5% median decrease) and were comparable between the drugs. If a dramatic decrease in blood glucose is truly the mechanism that drives paradoxical DR progression,[2,42,43] this would be consistent with the null findings in this study.

This study highlights the need for granular prospective cohort studies to investigate this question, particularly in the main GLP-1RA implicated in early worsening, semaglutide.[5,44] These studies should also be transparent both in the protocol of how DR was detected and diagnosed in patients (i.e., dilation status and availability of fundus imaging) as well as how DR development or progression was defined for the study. The FOCUS trial, currently enrolling patients, is one such study studying the effects of semaglutide compared with placebo on DR progression. The consistent lack of significant associations between drug type and various outcomes despite propensity score matching further supported the finding that GLP-1RA does not significantly increase the odds of DR development or progression, or if such an association exists, it is likely to be associated with certain subtypes of patients that this study was underpowered to analyze. In the meantime, because of the potential severe ramifications of DR worsening on GLP-1RA, ophthalmologists should continue to closely monitor patients taking this class of medication to detect and document potential signs of worsening, particularly in patients with preexisting retinopathy who experience a rapid drop in HbA1C level.

Footnotes and Disclosures

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[1] Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio.

[2] Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

[3] Case Western Reserve University School of Medicine, Cleveland, Ohio.

[4] Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, Ohio.

[5] Cleveland Clinic Cole Eye Institute, Cleveland, Ohio.

[6] Cleveland Clinic Martin Hospitals, Cleveland Clinic Florida, Stuart, Florida.

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Author Contributions:

Conception and design: Joo, Sharma, Wu, Skugor, Rachitskaya

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Abbreviations and Acronyms:
BMI = body mass index; **CI** = confidence interval; **CVOT** = cardiovascular outcome trial; **DR** = diabetic retinopathy; **GLP-1RA** = glucagon-like peptide-1 agonists; **HbA1C** = hemoglobin A1c; **ICD** = International Classification of Diseases; **OR** = odds ratio; **PDR** = proliferative diabetic retinopathy; **PPV** = pars plana vitrectomy; **PRP** = panretinal photocoagulation; **SD** = standard deviation; **SGLT-2I** = SGLT-2 inhibitors.

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Correspondence:
Aleksandra V. Rachitskaya, MD, Cleveland Clinic i32, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, Ohio 44195. E-mail: rachita@ccf.org.

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