Exposure to glucagon-like peptide 1 receptor (GLP-1R) agonists is associated with reduced risk for glaucoma

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Purpose

- GLP-1R agonists regulate blood glucose, weight, and satiety to treat type 2 diabetes mellitus (DM) and induce weight loss.
- Recent work identified neuroinflammation as a shared pathogenic mechanism in animal models of Parkinson's disease and glaucoma.[1,2]
- Treatment with the GLP-1R agonist NLY01 ameliorated neuroinflammation to rescue dopaminergic neurons and retinal ganglion cells in animal models.[1,2]
- **In this study, an insurance claims databased was used to examine whether the use of GLP-1R agonists impacted risk for a new diagnosis of glaucoma.[3]**
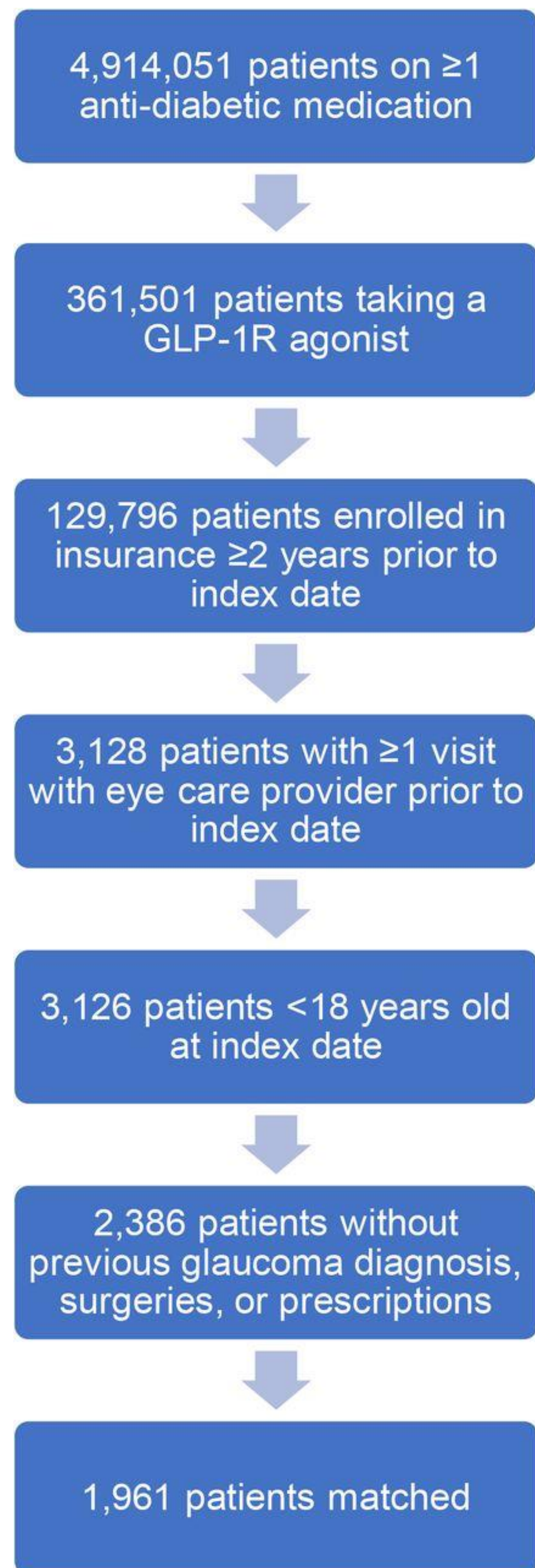
Methods

- De-identified medical claims information from Optum's Clinformatics Data Mart.
- GLP-1R agonist cohort: **All patients ≥ 18 y.o. who initiated a new GLP-1R agonist** (exenatide, liraglutide, albiglutide, dulaglutide, semaglutide, or lixisenatide).
- Matching cohort: **Patients who initiated a new oral diabetic medication, matched to the GLp-1R agonist cohort** 3:1 on age, gender, race, classes of active diabetes medications, and date of new medication initiation.
- Exclusion criteria: < 2 years in the database, < 1 visit to an eye care provider, prior treatment for glaucoma, diagnosis of glaucoma, glaucoma suspect, or OHT (Table 3).
- Diabetes severity was assessed using hemoglobin A1c and the Diabetes Complications Severity Index (DCSI), a validated metric based on six categories of DM complications.
- **Inverse probability of treatment weight (IPTW)**, derived from DCSI, HbA1c, demographic factors, and other systemic health conditions, **was used within a multivariable Cox proportional hazard regression model to determine the association between hazard of developing glaucoma and GLP-1R agonist exposure.**

Results

- **1,961 new users of GLP-1R agonists (Fig 1) were matched to 4,371 controls.**
- After matching and inverse proportional treatment weighting (IPTW), **all covariates except age were balanced and comparable between cohorts** (standard mean deviation [SMD] <0.1; Table 1).
- Weighted ages of GLP-1R agonist users were ~2 years younger than controls (Table 1).
- During follow-up, **58 new diagnoses (1.33%) of glaucoma or glaucoma suspect were present in unexposed controls compared to 10 new diagnoses (0.51%) in the GLP-1R agonist cohort** (Table 1).
- Cox regression analysis with IPTW revealed a **54% risk reduction (HR; 95% CI: 35-85%, P =0.007; Table 2) of incident glaucoma among users of GLP-1R agonists**.
- Increasing age was also associated with increased glaucoma hazard (Table 2).

Figure 1. Study Inclusion and exclusion criteria.

- 4,914,051 patients on ≥1 anti-diabetic medication
- 361,501 patients taking a GLP-1R agonist
- 129,796 patients enrolled in insurance ≥2 years prior to index date
- 3,128 patients with ≥1 visit with eye care provider prior to index date
- 3,126 patients <18 years old at index date
- 2,386 patients without previous glaucoma diagnosis, surgeries, or prescriptions
- 1,961 patients matched

Abbreviations: SMD: Standard mean deviation; CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; HbA1c: Hemoglobin A1c; DCSI: Diabetes Complications Severity Index; DM: Diabetes Mellitus.

Results (continued)

Table 1. Baseline characteristics.

Variable	Non-user (n=4371)		GLP-1R agonist User (n=1961)		SMD
	Unweighted	Weighted	Unweighted	Weighted	
Race					0.047
Asian	69 (1.58%)	1.55%	33 (1.68%)	1.72%	
Black	542 (12.40%)	12.61%	234 (11.93%)	11.31%	
Hispanic	330 (7.55%)	7.57%	157 (8.01%)	8.23%	
White	3430 (78.47%)	78.27%	1537 (78.38%)	78.74%	
Gender (female)	2271 (51.96%)	51.41%	1028 (52.42%)	55.04%	0.073
Age	55.63 (10.59)	56.09 (12.72)	55.43 (10.43)	54.31 (19.19)	-0.109
Education					0.016
<12th Grade	14 (0.32%)	0.30%	5 (0.25%)	0.30%	
High School Diploma	1321 (30.22%)	30.22%	589 (30.04%)	30.34%	
<bachelor's degree	2380 (54.45%)	54.56%	1079 (55.02%)	54.18%	
Bachelor's degree+	638 (14.60%)	14.61%	286 (14.58%)	14.93%	
Unknown	18 (0.41%)	0.32%	2 (0.10%)	0.25%	
Income					0.016
Unknown	533 (12.19%)	12.28%	246 (12.54%)	12.26%	
<$40K	661 (15.12%)	15.23%	296 (15.09%)	15.62%	
$40K-$49K	260 (5.95%)	5.83%	108 (5.51%)	5.98%	
$50K-$59K	336 (7.69%)	7.38%	132 (6.73%)	7.11%	
$60K-$74K	481 (11.00%)	10.52%	189 (9.64%)	10.48%	
$75K-$99K	708 (16.20%)	16.18%	322 (16.42%)	16.06%	
$100K+	1392 (31.85%)	32.59%	668 (34.06%)	32.49%	
Geographic Division					0.039
Mountain	326 (7.46%)	7.51%	148 (7.55%)	7.77%	
Northeast	314 (7.18%)	6.75%	113 (5.76%)	6.72%	
Pacific	254 (5.81%)	5.41%	88 (4.49%)	5.62%	
South Atlantic	1491 (34.11%)	34.23%	677 (34.52%)	33.98%	
Southern Midwest	695 (15.90%)	17.54%	405 (20.65%)	17.70%	
Unknown	4 (0.09%)	0.06%	0 (0.00%)	0.00%	
Upper Midwest	1287 (29.44%)	28.50%	530 (27.03%)	28.21%	
Diabetic retinopathy	1817 (41.57%)	45.87%	1094 (55.79%)	45.74%	-0.003
Hypertension	3507 (80.23%)	82.61%	1722 (87.81%)	82.23%	-0.010
Hypercholesterolemia	3735 (85.45%)	87.29%	1792 (91.38%)	87.05%	-0.007
Kidney Disease					0.008
No	3105 (71.04%)	66.49%	1104 (56.30%)	66.82%	
CKD	1188 (27.18%)	31.30%	798 (40.69%)	30.94%	
ESRD	78 (1.78%)	2.21%	59 (3.01%)	2.24%	
Smoking	1061 (24.27%)	24.90%	510 (26.01%)	24.94%	0.001
HbA1c level (mean[SD])	7.82 (1.90)	7.92 (2.36)	8.12 (1.80)	7.91 (3.08)	-0.006
# of days of health care usage (mean[SD])	7.39 (6.26)	8.11 (8.64)	9.28 (6.70)	8.22 (10.50)	0.012
DCSI (Mean[SD])	1.66 (1.98)	1.81 (2.51)	2.12 (2.16)	1.83 (3.62)	0.004
# of active DM med classes (mean[SD])	1.66 (0.74)		1.89 (0.82)		
Time prior to censoring/events					
Mean (SD)	266.5 (299.8)		143.9 (195.1)		
Median (Q1-Q3)	151 (91-326)		84 (28-168)		
Number of events (new diagnosis of glaucoma or glaucoma suspect)					
No event	4313 (98.67%)	98.65%	1951 (99.49%)	99.60%	
Had an event	58 (1.33%)	1.35%	10 (0.51%)	0.40%	

Table 2. Multivariable Cox regression with IPTW.

Variable	Category	Hazard Ratio (95% CI)	P-value
GLP-1R agonist			0.007
	User	0.54 (0.35, 0.85)	
	Non-user	Ref.	
Age		1.03 (1.01, 1.05)	<0.001

Abbreviations: IPTW: Inverse probability of treatment weighting; ICD-9: International Classification of Disease, Ninth Edition; ICD-10: International Classification of Disease and Related Health Problems, Tenth Revision; CPT: Current Procedural Terminology.

Table 3. ICD-9/ICD-10/CPT codes used in the study.

Diagnosis	ICD-9 Code	ICD-10 Code
Anatomic narrow angle	365.02	H40.03
Steroid responder	365.03	H40.04
Angle closure, no damage	365.06	H40.06
Pigmentary glaucoma	365.13	H40.13
Capsular glaucoma	365.14	H40.14
Angle closure glaucoma	365.2	H40.2
Glaucoma 2/2 trauma	365.4	H40.3
Glaucoma 2/2 inflammation	365.5	H40.4
Glaucoma 2/2 other eye disorders	365.6	H40.5
Corticosteroid-induced glaucoma	365.3	
Other specified forms of glaucoma	365.8	
Glaucoma 2/2 drugs		H40.6
Other glaucoma - aqueous misdirection/hypersecretion		H40.8
Glaucoma, unspecified		H40.9

Conclusions and Next Steps

- Results showed a **significant reduction in hazard for a new diagnosis of glaucoma or glaucoma suspect in DM patients exposed to GLP-1R agonists.**
- Findings provide preliminary impetus for clinicians to preferentially use GLP-1R agonists in treating diabetic patients at high risk for glaucoma.
- **In combination with our recent work,[1] results argue strongly that GLP-1R agonisms is an urgently needed novel therapy for glaucoma.**
- Ongoing experiments using induced and inherited models of glaucoma will identify the cell type(s) mediating GLP-1R agonists' RGC protection and the relative contribution of infiltrating versus resident myeloid cells in the early inflammatory response to IOP elevation.

References

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DISCLOSURES: Patent Pending (Penn Center for Innovation); SRA (Neuraly, Inc.).