

# Liraglutide and Insulin Prescriptions Associated with Increased Likelihood of Rare Vision Loss

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## Key findings:

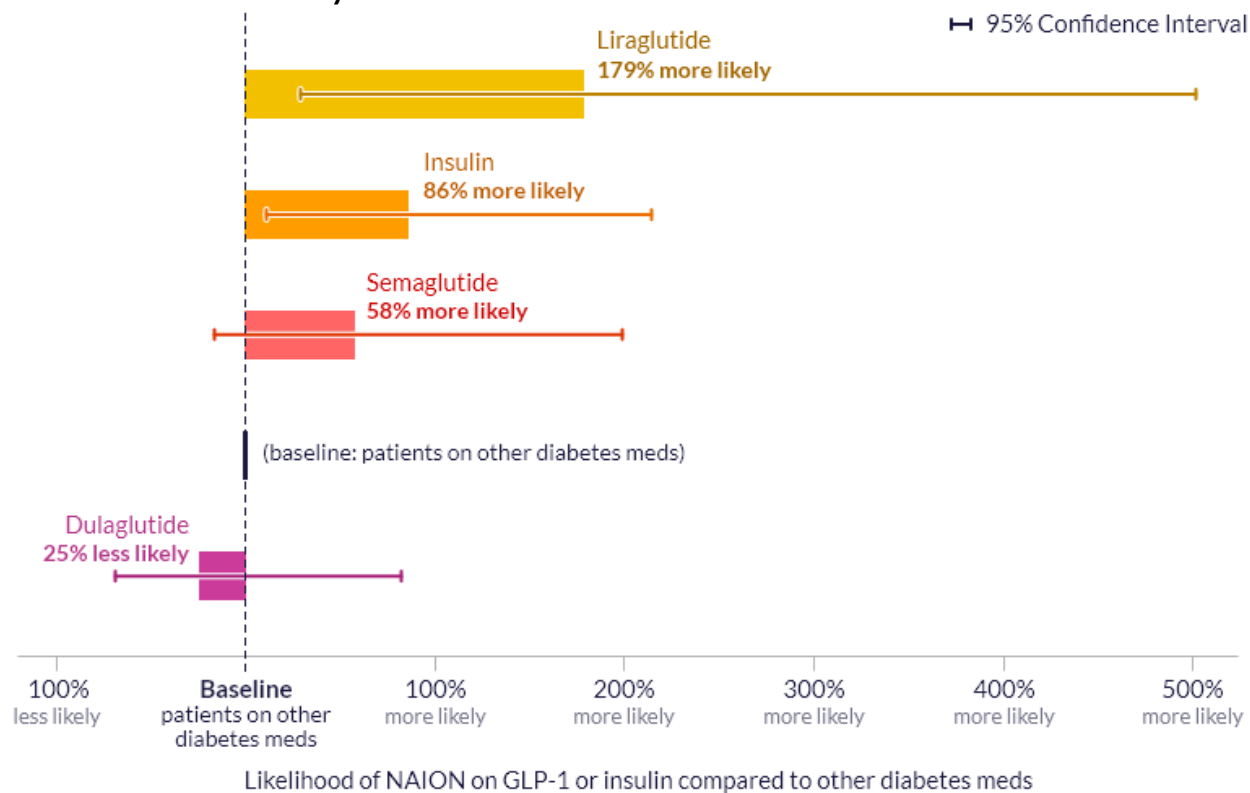
- Patients with type 2 diabetes who are prescribed liraglutide have a 179% higher likelihood of developing non-arteritic anterior ischemic optic neuropathy (NAION), while those prescribed insulin have an 86% greater likelihood compared to patients who were prescribed other diabetes medications. No significant association was found between semaglutide or dulaglutide and NAION.
- Overall, NAION is rare, affecting only three per 100,000 patients with diabetes.

Non-arteritic anterior ischemic optic neuropathy (NAION) is a rare but serious condition that causes sudden, acute, and painless vision loss due to reduced blood flow to the optic nerve. NAION is most common among patients with diabetes, hypertension, hyperlipidemia, or sleep apnea.<sup>1</sup> GLP-1 medications are widely used for the treatment of type 2 diabetes and, more recently, weight loss. However, there have been some concerns about the potential adverse effects of GLP-1s, including NAION.<sup>2</sup>

We aimed to understand the relationship between GLP-1 medications and the likelihood of NAION among patients with type 2 diabetes. We studied 2,446,482 patients with diabetes who were prescribed a diabetes management medication or a GLP-1 for at least 90 days continuously. We compared the patients prescribed a GLP-1 medication with those who were prescribed insulin or other diabetes medications and no history of GLP-1 usage. We adjusted for patient age, sex, BMI, HbA1c, smoking status, and history of cardiovascular disease, chronic kidney disease, hyperlipidemia, hypertension, sleep apnea, and PDE5 inhibitor use.

We found that patients who were prescribed liraglutide had a 179% greater likelihood of being diagnosed with NAION than patients prescribed other diabetes medications, while those prescribed insulin had an 86% greater likelihood, as seen in Figure 1. No statistically significant association was found between semaglutide or dulaglutide and NAION.

## Likelihood of NAION by Diabetes Medication



N=2,446,482 patients

"Likelihood of NAION by Diabetes Medication," 2024. EpicResearch.org

Figure 1. The likelihood of a diabetic patient being diagnosed with NAION by medication.

Despite the increased likelihood of NAION with liraglutide and insulin, it remains a rare condition. Only three per 100,000 patients with diabetes in the study were diagnosed with NAION. As such, the confidence intervals for each treatment studied are wide, and the exact impact on the likelihood of NAION is hard to estimate. Furthermore, the increased likelihood of NAION among patients treated with insulin suggests that differences in diabetes progression or control may also affect likelihood of NAION.

*These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 270 million patient records from 1,500 hospitals and more than 35,500 clinics from all 50 states, Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.*

## References

1. NAION: Diagnosis and Management. American Academy of Ophthalmology. Published August 1, 2022. <https://www.aao.org/eyenet/article/naion-diagnosis-and-management>. Accessed August 12, 2024.
2. Hathaway JT, Shah MP, Hathaway DB, et al. Risk of nonarteritic anterior ischemic optic neuropathy in patients prescribed semaglutide. JAMA Ophthalmol. Published online 2024. doi:10.1001/jamaophthalmol.2024.2296

## Data definitions

Term	Definition
Study period	1/1/2010 – 7/1/2024
Study population	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Patient is 18 years or older</li> <li>• Patient must be male or female</li> <li>• Patient has been diagnosed with <b>type 2 diabetes</b></li> <li>• Patient must have a recent BMI</li> <li>• Patient must have a recent <b>HbA1c</b></li> <li>• Patient must not have a recent prior <b>optic condition</b></li> </ul> <p>Exposure Group:</p> <ul style="list-style-type: none"> <li>• Patient's first ever treatment episode with a <b>GLP-1 medication</b></li> </ul> <p>Control Group</p> <ul style="list-style-type: none"> <li>• Patients with no history of treatment with a <b>GLP-1 medication</b></li> <li>• A randomly chosen beginning of treatment on any other <b>diabetic treatments</b></li> </ul>
GLP-1 medication	<p>A medication with one of the following RxNorm codes:</p> <ul style="list-style-type: none"> <li>• Semaglutide: 1991302</li> <li>• Dulaglutide: 1551291</li> <li>• Exenatide: 60548</li> <li>• Liraglutide: 475968</li> <li>• Tirzepatide: 2601723</li> </ul> <p>Patients that took more than 1 GLP-1 medication during their 1st episode of treatment were excluded.</p>
Diabetic treatments	<p>Some treatments were excluded from analysis due to low counts.</p> <p>Insulins: Drugs with a pharmaceutical class of INSULINS and a route of IV, injection, or SubQ or a pharmaceutical class of ANTIHYPERGLY,INSULIN,LONG ACT-GLP-1 RECEPT.AGONIST</p> <p>DPP-4i: Drugs with a pharmaceutical class of ANTIHYPERGLYCEMIC, GPP-4 INHIBITORS; ANTIHYPERGLYCEMIC, GPP-4 INHIBITOR-BIGUANIDE COMBS.; ANTIHYPERGLY-SGLT-2 INHIB, DPP-4 INHIB, BIGUANIDE CB; ANTIHYPERGLYCEMIC, SGLT-2 AND DPP-4 INHIBITOR COMB</p> <p>Biguanide: ANTIHYPERGLYCEMIC, BIGUANIDE TYPE; ANTIHYPERGLYCEMIC, BIGUANIDE-DIETARY SUPPL. COMB.; ANTIHYPERGLYCEMIC, THIAZOLIDINEDIONE AND BIGUANIDE; ANTIHYPERGLYCEMIC, DPP-4 INHIBITOR-BIGUANIDE COMBS.; ANTIHYPERGLY-SGLT-2,GPP-4 INHIB,BIGUANIDE CB;</p>

	<p>ANTIHYPERTENSIVE, INSULIN-RELEASE STIM.-BIGUANIDE;</p> <p>SGLT2i: ANTIHYPERGLYCEMIC-SOD/GLUC COTRANSPORT2(SGLT2) INH; ANTIHYPERGLYCEMIC-SGLT2 INHIBITOR-BIGUANIDE COMBS.; ANTIHYPERGLY-SGLT-2 INHIB,DPP-4 INHIB, BIGUANIDE CB; ANTIHYPERGLYCEMIC- SGLT-2 INHIB,DPP-4 INHIBITOR COMB</p> <p>Sulfonylurea: ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIM.- BIGUANIDE; ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIMULANT TYPE; ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIM.-BIGUANIDE And does not contain: nateglinide or repaglinide</p> <p>Meglitinides: ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIM.- BIGUANIDE; ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIMULANT TYPE; ANTIHYPERGLYCEMIC, INSULIN-RELEASE STIM.-BIGUANIDE And does contain: nateglinide or repaglinide</p> <p>Thiazolidinediones: Pharmaceutical class contains the term THIAZOLIDINEDIONE</p> <p>The first ever treatment event with the drug is recorded provided there is evidence of at least two orders in an outpatient setting.</p>
<b>Optic condition</b>	A diagnosis with ICD-10-CM code M31.6*, H46*, or H47*
<b>Type 2 diabetes</b>	A diagnosis with ICD-10-CM code E11*
<b>Eye exam</b>	A procedure with CPT code 92004, 92014, 92002, or 92012
<b>NAION</b>	<p>A diagnosis associated with the SNOMED code 230509007 and a name containing “NAION”, “Non-arteritic AION”, or “Non-arteritic anterior ischemic optic neuropathy”</p> <p>Either two NAION diagnoses were required or a <b>NAION misdiagnosis</b> with a subsequent NAION diagnosis.</p>
<b>NAION misdiagnosis</b>	<p>A diagnosis with one of the following diagnoses:</p> <ul style="list-style-type: none"> <li>• Disc Edema: ICD-10-CM code H47.1* or H47.33*</li> <li>• Vision Loss: ICD-10-CM code H53.13*</li> <li>• Vision Defect: ICD-10-CM code H53.4*</li> </ul>
<b>Confounders</b>	<p>Age:</p> <ul style="list-style-type: none"> <li>• 18-34</li> <li>• 35-49</li> <li>• 50-64</li> <li>• 65-74</li> <li>• 75+</li> </ul>

	<p>Sex: male or female</p> <p>BMI:</p> <ul style="list-style-type: none"> <li>• &lt;18.5</li> <li>• 18.5-25</li> <li>• 25-30</li> <li>• 30-35</li> <li>• 35-40</li> <li>• &gt;40</li> </ul> <p>Race and ethnicity</p> <p>Type 2 diabetes</p> <p>Comorbid conditions</p> <p>Contraindicated medications</p> <p>Smoking status</p> <p>HbA1c (most recent value):</p> <ul style="list-style-type: none"> <li>• &lt;6.5</li> <li>• 6.5-8.5</li> <li>• 8.5-12</li> <li>• 12+</li> </ul>
<b>HbA1c</b>	Lab result associated with one of the following LOINC codes: 17855-8, 17856-6, 41995-2, 4548-4, 4549-2, or 55454-3
<b>Race and ethnicity</b>	The self-reported race and ethnicity of the patient. The patients were placed into categories, and could be in multiple, for White, Black, and Hispanic.
<b>Comorbid conditions</b>	<p>Essential hypertension: ICD-10-CM code I10</p> <p>Hyperlipidemia: ICD-10-CM code E78.2*-E78.5*</p> <p>CAD: ICD-10-CM code I25*</p> <p>OSA: ICD-10-CM code G47.33</p>
<b>Contraindicated medications</b>	<p>PDE5:</p> <ul style="list-style-type: none"> <li>• Sildenafil: RxNorm 136411</li> <li>• Vardenafil: RxNorm 306674</li> <li>• Tadalafil: RxNorm 358263</li> <li>• Avanafil: RxNorm 1291301</li> </ul> <p>Interferon:</p> <ul style="list-style-type: none"> <li>• Any Medication with a simple generic name containing “interferon”</li> </ul>

Table 1. Likelihood of NAION by Diabetes Medication

Covariate	Odds Ratio	Lower CI	Upper CI
Black Race	1.01	0.28	3.66
White Race	2.37	0.76	7.41
Hispanic Ethnicity	1.10	0.45	2.67
Social Vulnerability Index	0.85	0.36	2.01
CAD History	0.80	0.46	1.41
CKD History	1.70	0.99	2.91
Hyperlipidemia History	1.21	0.53	2.73
Hypertension History	1.01	0.46	2.21
Sleep Apnea History	0.78	0.44	1.37
PDE5 History	0.62	0.19	2.00
Thiazolidinedione	0.49	0.12	2.00
DPP4i	0.92	0.45	1.87
Biguanide	0.67	0.41	1.11
Sulfonylurea	1.07	0.62	1.84
SGLT2i	1.24	0.66	2.33
Insulins	<b>1.86</b>	<b>1.11</b>	<b>3.14</b>
Dulaglutide	<b>0.75</b>	<b>0.31</b>	<b>1.82</b>
Liraglutide	<b>2.79</b>	<b>1.29</b>	<b>6.02</b>
Semaglutide	<b>1.58</b>	<b>0.84</b>	<b>2.99</b>
11 or More Prior Encounters	1.15	0.53	2.54
4 to 10 Prior Encounters	0.91	0.40	2.09
Female	0.47	0.28	0.80
Age 50 to 65	1.75	0.74	4.11
Age 65 to 74	1.98	0.80	4.93
Age 75+	1.58	0.55	4.50
Current Smoker	1.25	0.59	2.66
Former Smoker	0.82	0.48	1.42
Unknown Smoking Status	1.30	0.54	3.12
Stage 1 Obesity	1.54	0.62	3.82
Stage 2 Obesity	1.07	0.39	2.95
Stage 3 Obesity	1.74	0.64	4.76
Overweight	0.57	0.20	1.61
HbA1c 10.2+	2.46	0.90	6.75
HbA1c 6.5 to 8.3	1.77	0.74	4.23
HbA1c 8.4 to 10.1	1.69	0.64	4.45