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Real-World Evidence Assessment of the Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

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Hathaway recently reported an association between semaglutide and risk of nonarteritic anterior ischemic optic neuropathy (NAION).[1] They reviewed 17 289 patients from an ophthalmology clinic's database. No mechanism was demonstrated, and the results are surprising given a large body of evidence supporting an anti-inflammatory effect of glucagon-like peptide (GLP).[2]

We noted the single-site nature of the study and the possibility of residual confounding in this observational study where the clinical course of patients seen at an ophthalmology clinical might not pertain to the general population.[3] We performed seven different retrospective real-world cohort analyses of adult users of glucagon-like peptide-1 receptor agonist (GLP-1RA) drugs for patients with diabetes and obesity for risk of NAION. All studies were done utilizing high-dimensional propensity score matching to control for confounders covering demographics, clinical comorbidities, treatment year, prior procedures, medications, and health care utilization that the patients had prior to beginning therapy.[4] The studies were performed on a 66 million patient nationally representative electronic health record and claims dataset,[5] rather than an ophthalmology clinic database. The primary analysis was adults who initiated GLP-1RA weight loss medications versus those who started on non-GLP-1 agonist weight loss medications without a prior history of NAOIN. A Cox proportional-hazards model to evaluate time to developing NAION demonstrated increased risk in the GLP-1RA arm prior to adjusting for comorbidities (hazard ratio [HR] = 2.95; 95% confidence interval [CI]: 1.82-4.79; $P < .0001$). However, after controlling for confounders, this difference was eliminated (HR = 1.45; 95% CI: 0.51-4.17; $P = .49$). Five sensitivity analyses were performed on the national data including limiting the GLP-1RA arm to only semaglutide (as evaluated in the Hathaway manuscript), limiting the cohorts to people with type 2 diabetes, limiting the cohorts to people with obesity, only evaluating patients who had a definitive ophthalmologic examination in the post treatment follow-up period, and comparing incidences in users of semaglutide and users of other GLP-1RA drugs (Table 1). The primary study protocol was also replicated using the 3.9 million patients within the Stanford Healthcare research repository where a similar association was observed prior to matching but eliminated after matching (Table 1). There was no significant increase in the risk of NAION from semaglutide or any GLP-1RA in any of the seven analyses after matching. The frequency of NAION in the analyses ranged from 0.07% to 0.24%.

Our analysis, although limited in its own way, suggests that the Hathaway study needs to be replicated at other sites or via a different design before changes in the use of semaglutide or GLP-1RAs are warranted, given their clearly documented benefits for diabetes and obesity.[6]

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Table 1. A Retrospective Real-World Cohort Analysis With Six Sensitivity Analyses.

Analysis number	Analysis population	Hazard ratio	95% Confidence interval	*P* value
Primary analysis	National Dataset—All GLP-1RAs vs other weight loss agents	1.45	(0.51, 4.17)	.49
Sensitivity 1	National Dataset—limited to patients with Type II DM	0.19	(0.02, 1.6)	.127
Sensitivity 2	National Dataset—limited to patients with obesity (BMI $\geq$ 30)	1.42	(0.55, 3.71)	.47
Sensitivity 3	National Dataset—limited to patients with semaglutide in GLP-1RA arm	1.31	(0.67, 2.57)	.44
Sensitivity 4	National Dataset—limited to patients with confirmed ophthalmological testing	1.23	(0.49, 3.12)	.66
Sensitivity 5	National Dataset—semaglutide vs other GLP-1RA	6.84	(0.82, 56.79)	.075
Sensitivity 6	Stanford Dataset—All GLP-1RAs vs other weight loss agents	0.94	(0.5, 1.76)	.85

Hazard ratios for seven retrospective real-world cohort analyses of adult users of GLP-1RA drugs for patients with diabetes and/or obesity for risk of NAION. Number 1 is the primary analysis. Remaining six analyses are sensitivity analyses of the primary analysis.
Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; NAION, nonarteritic anterior ischemic optic neuropathy.

Abbreviations

GLP, glucagon-like peptide; GLP-1RA; glucagon-like peptide-1 receptor agonists; NAION, nonarteritic anterior ischemic optic neuropathy.

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