Non-arteritic Anterior Ischemic Optic Neuropathy and Semaglutide Use

An Advisory to Ophthalmologists and Other Health Care Professionals

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Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute monocular optic neuropathy in individuals aged 50 years and older.[1] Despite this, it is considered a rare disease with an incidence of between 2.3 to 10.2 cases per 100,000 persons.[1,2] It typically presents as sudden, painless vision loss in one eye and is associated with optic disc edema.[3] It is believed to be caused by hypoperfusion of the posterior ciliary arteries that supply the prelaminar optic nerve. Several systemic risk factors have been identified, and these include advanced age, diabetes mellitus, hyperlipidemia, central obesity, a history of smoking, and obstructive sleep apnea.[3-9] An important ocular risk factor is a structurally crowded optic disc, commonly referred to as a "disc-at-risk."[3,10] Other less common predisposing factors include optic disc drusen and optic disc edema due to other causes such as papilledema.[11,12] Certain medications have also been implicated in the development of NAION. These include amiodarone, phosphodiesterase type-5 inhibitors, interferon alpha, and more recently, semaglutide, which is a glucagon-like peptide-1 receptor agonist (GLP-1RA) used in the treatment of Type 2 diabetes mellitus (T2DM) and obesity.[13-16] Vision loss in NAION is usually permanent. To date, there is no established treatment to reverse or restore visual function.[3]

An informal survey conducted among the members of the Neuro-ophthalmology Society of the Philippines (NOSP) yielded no anecdotal reports of NAION patients on semaglutide. Current evidence on the association between semaglutide use and NAION drawn from large-scale studies is moderate and remains conflicting (see **Table 1**).[16-22] At present, a causal relationship

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between semaglutide and NAION cannot be firmly established. Given the available evidence and the low incidence of NAION, the NOSP recommends the following:

NOSP recommendations

1. **Patient Counseling:** Physicians should counsel patients on the rare but potential risk of vision loss associated with semaglutide. This discussion should emphasize that the absolute risk remains low and that the benefits of semaglutide—particularly in glycemic control and cardiovascular risk reduction—generally outweigh this risk.

2. **Ocular Screening:** The NOSP supports the routine and timely screening for diabetic retinopathy in accordance with existing clinical guidelines. While screening for a crowded optic disc phenotype prior to semaglutide initiation is theoretically reasonable and clinically prudent, it is not recommended at this time due to a lack of evidence supporting its utility and cost-effectiveness. Similarly, given the rarity of NAION, there is currently no evidence to support routine ophthalmologic monitoring for patients on semaglutide or other GLP-1RA.

3. **Referral for Visual Symptoms:** Patients with pre-existing visual impairment prior to starting semaglutide or any GLP-1RA or those experiencing sudden changes in vision during treatment should be promptly referred to an ophthalmologist or neuro-ophthalmologist. Early evaluation is essential to rule out alternative causes of vision loss and to identify possible early signs of NAION.

4. **Product Information Update:** NAION and vision loss should be included in the product information leaflet or drug pamphlet for semaglutide. Including this potential—albeit rare—adverse effect would help ensure that both healthcare providers and patients are informed, encourage early recognition of symptoms, and support timely referral. This approach is aligned with current pharmacovigilance principles that emphasize transparency regarding serious but rare adverse events, even in the absence of confirmed causality.

5. **Caution Against Inappropriate Use:** While semaglutide has a generally favorable risk-benefit profile, clinicians should exercise caution in prescribing it or other GLP-1RAs for weight loss in moderately overweight individuals with low cardiovascular risk. In such populations, the relevance of rare but serious adverse events—such as NAION—may be heightened and should factor into shared decision making.

Disclaimer: These recommendations are based solely on currently available evidence concerning the association between semaglutide use and NAION. Other potential risks such as worsening of diabetic retinopathy and the development of neovascular age-related macular degeneration were not included in the review of available literature and were not factored into the recommendations. The guidance on ocular screening and monitoring may be revised as new evidence emerges.

Basis for recommendations

The study design, findings, strengths, and limitations of seven published studies, including one meta-analysis, on semaglutide and NAION, is presented in **Table 1**.[16-22] Notably, most available studies to date made use of large databases. While database studies are valuable for detecting potential associations in large populations, they carry several inherent limitations that affect the interpretation and generalizability of their findings—particularly when investigating rare outcomes like NAION. Most are retrospective and observational in design, precluding the establishment of causality and leaving the findings vulnerable to both measured and unmeasured confounding factors. Critical clinical variables, such as anatomical risk factors (e.g., a "disc-at-risk"), disease severity, fluctuations in glycemic control, and detailed ocular history, are often absent or poorly recorded in these datasets. Diagnostic accuracy is another major concern as studies often rely on nonspecific International Classification of Diseases (ICD) codes that may misclassify NAION or fail to differentiate new cases from pre-existing ones. Although statistical techniques like propensity score matching are sometimes applied, residual confounding and indication bias—where more medically complex patients are more likely to receive medications like semaglutide—remain significant concerns. These databases also frequently lack granular data on drug dosage, timing, and adherence, limiting analysis of potential dose-response relationships. Moreover,

many of these studies draw from U.S. or European populations, which are predominantly composed of Caucasian patients. Given known racial differences in NAION incidence—including lower rates reported among Asians—findings from these cohorts may not be directly applicable to the Filipino population. Selection bias from data drawn from specialized centers and limitations in reporting rare events due to privacy regulations further constrain interpretation. These factors underscore the need for cautious interpretation and the importance of complementary studies using well-characterized clinical data and diverse patient populations.

Conclusion

Taken together, while several observational studies suggest a potential association, the lack of consistency, methodological limitations, and low absolute event rates mean that a definitive causal link between semaglutide and NAION cannot be established at this time. Additional prospective studies or pharmacoepidemiologic investigations with improved diagnostic validation and better adjustment for ocular and systemic confounders are warranted.

Table 1. Published Studies on Semaglutide and NAION

Study (Year)	Design, Setting, Population	Main Findings	Strengths	Limitations
Hathaway *et al.* (2024)	Retrospective matched cohort; single-center ophthalmology clinic registry; patients with T2DM or obesity	Increased NAION risk among semaglutide users: HR 4.28 (95% CI 1.62-11.29 T2DM cohort); HR 7.64 (95% CI 2.21-26.36 obese cohort)	Neuro-ophthalmologist–confirmed NAION diagnoses	Single-center; highly selected population; NAION incidence far greater than general population; retrospective observational design; limited confounder data
Chou *et al.* (2025)	Retrospective matched cohort; global medical records database (21 countries); patients with T2DM or obesity	No significant association between semaglutide use and NAION risk: HR 1.51 (95% CI 0.71-3.25 T2DM group after 3 yrs); HR 0.72 (95% CI 0.24-2.16 obesity group after 3 yrs)	Large, diverse sample; rigorous matching	Observational design; broad ICD-code-based; no dosage data; U.S.-biased sites; lacked optic disc/anatomical risk factors
Klonoff *et al.* (2024)	Retrospective matched cohort; U.S. electronic medical records and claims database; patients on weight loss medications	No significant increase in the risk of NAION from semaglutide or any GLP-1RA: HR 1.45 (95% CI: 0.51-4.17)	Very large dataset; comprehensive confounding control; replication in separate cohort	Observational design; claims data lacked clinical granularity such as medication dose and duration details
Cai *et al.* (2025)	Retrospective active-comparator cohort and case series analyses; 14 electronic health records and claims databases; T2DM patients	Modestly increased NAION risk with semaglutide use: IRR 1.32 (95% CI 1.14-1.54)	Large multinational sample; use of negative controls	Retrospective observational design; used nonspecific ICD codes; unable to confirm incident vs pre-existing NAION; no ocular risk factors; no semaglutide formulation distinction; residual confounding may have significantly affected result
Simonsen *et al.* (2025)	Target trial approach (hypothetical RCT); Danish and Norwegian health registries; T2DM patients on semaglutide or SGLT-2i	Increased NAION risk with semaglutide vs. SGLT-2i: HR 2.81 (95% CI 1.67-4.75)	High-quality national registry data; active comparator; strong statistical adjustment	Observational design; few NAION events; used nonspecific ICD codes
Abbass *et al.* (2025)	Retrospective matched cohort; U.S. electronic medical records and claims database; T2DM or high BMI patients	No significant increase in NAION risk with semaglutide use: RR 0.7 (95% CI 0.523-0.937 T2DM cohort after 5 yrs); RR 0.81 (95% CI 0.464-1.431 high BMI cohort after 2 yrs)	Large sample; rigorous confounder adjustment; specialist-confirmed outcomes	Observational design; possible diagnostic misclassification; lacked adherence/dose data; underrepresentation of Asians
Silverii *et al.* (2025)	Meta-analysis of 69 RCTs comparing GLP1-RAs with placebo or active comparators	No significant difference in ION risk between GLP1-RAs and comparators: OR 1.53 (95% CI 0.53–4.44); only 13 ION cases identified	High-quality RCT data	Underpowered (rare events); did not differentiate NAION vs. other ION; possible underreporting

Abbreviations: BMI – body mass index, CI – confidence interval, GLP-1 RA – glucagon-like peptide-1 receptor agonist, HR – hazard ratio, ICD – International Classification of Diseases, ION – ischemic optic neuropathy, IRR – incidence rate ratio, NAION – nonarteritic anterior ischemic optic neuropathy, OR – odds ratio, RCT – randomized controlled trial, RR – risk ratio, SGLT-2i – sodium-glucose cotransporter-2 inhibitor; T2DM – Type 2 diabetes mellitus, U.S. – United States

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