Semaglutide Not Linked to Increased AMD Risk in New Analysis

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> The potential for systemic medications to impact ocular health is a persistent concern for clinicians, particularly with widely prescribed agents. Given the increasing use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) like semaglutide for type 2 diabetes and weight management, a critical question has been whether these drugs influence the risk of age-related macular degeneration (AMD), a leading cause of irreversible vision loss. A recent analysis indicates no such link.

KEY TAKEAWAYS

- The Pivot: Concerns regarding a potential association between GLP-1 RAs and AMD risk have been addressed by new data.
- The Data: The hazard ratio for AMD incidence in semaglutide users versus non-users was 0.98 (95% CI: 0.85-1.13, p=0.78).
- The Action: Clinicians can continue prescribing semaglutide without additional concern for AMD risk based on current evidence.

The widespread adoption of GLP-1 RAs, including semaglutide, has prompted scrutiny into their long-term safety profile across various organ systems. Ocular adverse events, while rare, can have significant patient impact. Specifically, the potential for these agents to influence retinal vascular health or exacerbate pre-existing conditions like AMD has been a subject of clinical interest. This is particularly relevant given the metabolic effects of GLP-1 RAs and the known associations between metabolic dysfunction and AMD progression.1

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss among older adults globally. Its pathogenesis is multifactorial, involving genetic predispositions, environmental factors, and systemic conditions such as cardiovascular disease, hypertension, and diabetes. Given that GLP-1 RAs are primarily prescribed for type 2 diabetes and weight management, conditions often co-occurring with AMD risk factors, understanding any potential ocular impact is crucial for comprehensive patient care and long-term prescribing decisions. The metabolic improvements observed with GLP-1 RAs, including better glycemic control, weight reduction, and improvements in lipid profiles and blood pressure, theoretically could have beneficial or neutral effects on ocular health. However, direct effects on retinal vasculature or cellular processes remain a subject of ongoing investigation.

The Analysis

A retrospective cohort study was conducted using a large, de-identified administrative claims database, encompassing patients with type 2 diabetes. The primary objective was to evaluate the incidence of new-onset AMD in patients initiating

semaglutide compared to a matched cohort of patients initiating other non-GLP-1 RA antidiabetic medications. Patients were required to have no prior diagnosis of AMD and at least 12 months of continuous enrolment prior to the index date.2

The study design employed a new-user cohort approach to minimize confounding by indication. Patients were identified based on their first prescription fill for either semaglutide or a comparator non-GLP-1 RA antidiabetic medication (e.g., metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, or insulin). The comparator group was chosen to represent a broad range of standard-of-care antidiabetic treatments, ensuring a relevant control for patients with type 2 diabetes. Propensity score matching was performed using a greedy matching algorithm with a caliper width of 0.2 standard deviations of the logit of the propensity score. This rigorous matching process aimed to balance over 50 baseline characteristics between the semaglutide and control cohorts, including demographic factors, diabetes-related parameters, and a comprehensive list of comorbidities and concomitant medications known to influence AMD risk or diabetes management.2

The study population included 124,567 patients initiating semaglutide and an equal number of propensity score-matched controls. Matching criteria included age, sex, duration of diabetes, baseline HbA1c, body mass index (BMI), and presence of common comorbidities such as hypertension, dyslipidaemia, and diabetic retinopathy. The mean age of participants was 62.5 years, and 52% were female. The follow-up period extended for a median of 2.8 years.2

The primary outcome was the first documented diagnosis of AMD (ICD-10 codes H35.30-H35.32) during the follow-up period. Secondary outcomes included analyses stratified by AMD subtype (dry vs. wet) and duration of semaglutide exposure.2

Key Findings

During the follow-up period, 1,870 new cases of AMD were identified in the semaglutide cohort, compared to 1,915 cases in the control cohort. The unadjusted incidence rate of AMD was 5.1 per 1,000 person-years in the semaglutide group and 5.2 per 1,000 person-years in the control group.2

After adjusting for residual confounding factors, the hazard ratio (HR) for AMD incidence in semaglutide users compared to non-users was 0.98 (95% CI: 0.85-1.13, P=.78). This indicates no statistically significant difference in AMD risk between the two groups. Subgroup analyses for dry AMD (HR: 0.97, 95% CI: 0.83-1.12, P=.71) and wet AMD (HR: 1.02, 95% CI: 0.79-1.32, P=.88) also showed no significant associations. Furthermore, analyses stratified by duration of semaglutide exposure did not reveal any emerging risk with longer use.2

The study's reliance on administrative claims data means that unmeasured confounders, such as specific genetic predispositions to AMD or detailed lifestyle factors, could not be fully accounted for. Diagnostic accuracy of AMD coding in claims data, while generally reliable for population-level studies, may not capture all nuances of disease onset or severity. For instance, early stages of dry AMD might not be consistently coded until progression. Additionally, the follow-up duration, while substantial, may not be sufficient to detect very long-term effects, particularly for a slowly progressive condition like AMD. The median follow-up of 2.8 years provides robust short-to-medium term insights, but AMD development can span decades. However, the large sample size and robust propensity score matching mitigate some of these limitations, providing a strong indication that semaglutide does not confer an increased risk of AMD. Future prospective studies with detailed ophthalmic examinations could further confirm these findings.2

CLINICAL IMPLICATIONS

The absence of an association between semaglutide and AMD risk provides welcome reassurance for clinicians managing patients with type 2 diabetes and obesity. Given the substantial cardiovascular and metabolic benefits of GLP-1 RAs, any potential ocular safety signal would have necessitated careful risk-benefit discussions. This data allows prescribers to focus on the established benefits of semaglutide without adding AMD to the list of potential adverse event considerations, streamlining patient counselling and treatment initiation.

For patients, this means that a medication offering significant improvements in glycaemic control and weight can be used without the added anxiety of potentially accelerating vision loss from AMD. This clarity is particularly important as the demographic of GLP-1 RA users often overlaps with the age groups at higher risk for AMD. The pharmaceutical industry, specifically Novo Nordisk, benefits from this data, as it helps to solidify the safety profile of semaglutide, potentially easing regulatory scrutiny and reinforcing its market position against competitors in an increasingly crowded therapeutic class.

While this study offers valuable insights, it underscores the ongoing need for comprehensive post-marketing surveillance and real-world evidence generation for all widely used medications. The initial concerns, though now largely alleviated for AMD, highlight the importance of vigilance in identifying potential long-term effects of novel therapies. Clinicians should continue to monitor for all known and emerging adverse events, but for now, AMD risk does not appear to be a factor in semaglutide prescribing decisions.

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