

Association Between Semaglutide and Risk of Central Retinal Artery Occlusion in Type 2 Diabetes and Obesity: A Retrospective Matched-Cohort Analysis

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INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a recent class of therapies for Type 2 Diabetes Mellitus (T2DM), lowering blood glucose levels and promoting weight loss via activation of GLP-1 receptors located in the gastrointestinal tract, pancreas, and brain.¹ The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN)² and the trial investigating Peptide Innovation for Early Diabetes Treatment (PIONEER)² demonstrated improved cardiovascular outcomes in patients receiving GLP-1 RAs. They suggest that GLP-1 RAs are associated with a reduction in small vessel occlusions via their anti-inflammatory, anti-oxidative stress, and pro-microvascular blood flow effects.³ Within this class, semaglutide distinguishes itself by its potent receptor affinity, prolonged half-life (approximately 165 to 184 hours), superior glycemic control, and weight-loss efficacy compared to shorter-acting GLP-1 RAs such as lixisenatide and exenatide.⁴ However, these pharmacological distinctions also raise important questions about the safety profile of semaglutide, particularly in comparison to other agents in the same class.

The reduced risk of systemic vascular complications in patients using GLP-1 RAs raises the question of the association of GLP-1 RA use with ocular-specific microvascular complications. The ocular conditions of interest include central and branch retinal artery occlusion (CRAO and BRAO), visual field defects, color-vision changes, acute vision loss, and vascular complications such as retinal neovascularization (proliferative and nonproliferative), vitreous hemorrhage, retinal microaneurysms, optic atrophy, and vascular-related glaucoma. These complications lead to substantial visual impairment, limiting activities daily living (ADLs) and instrumental activities of daily living (IADLs), resulting in a negative impact on overall independence.⁴

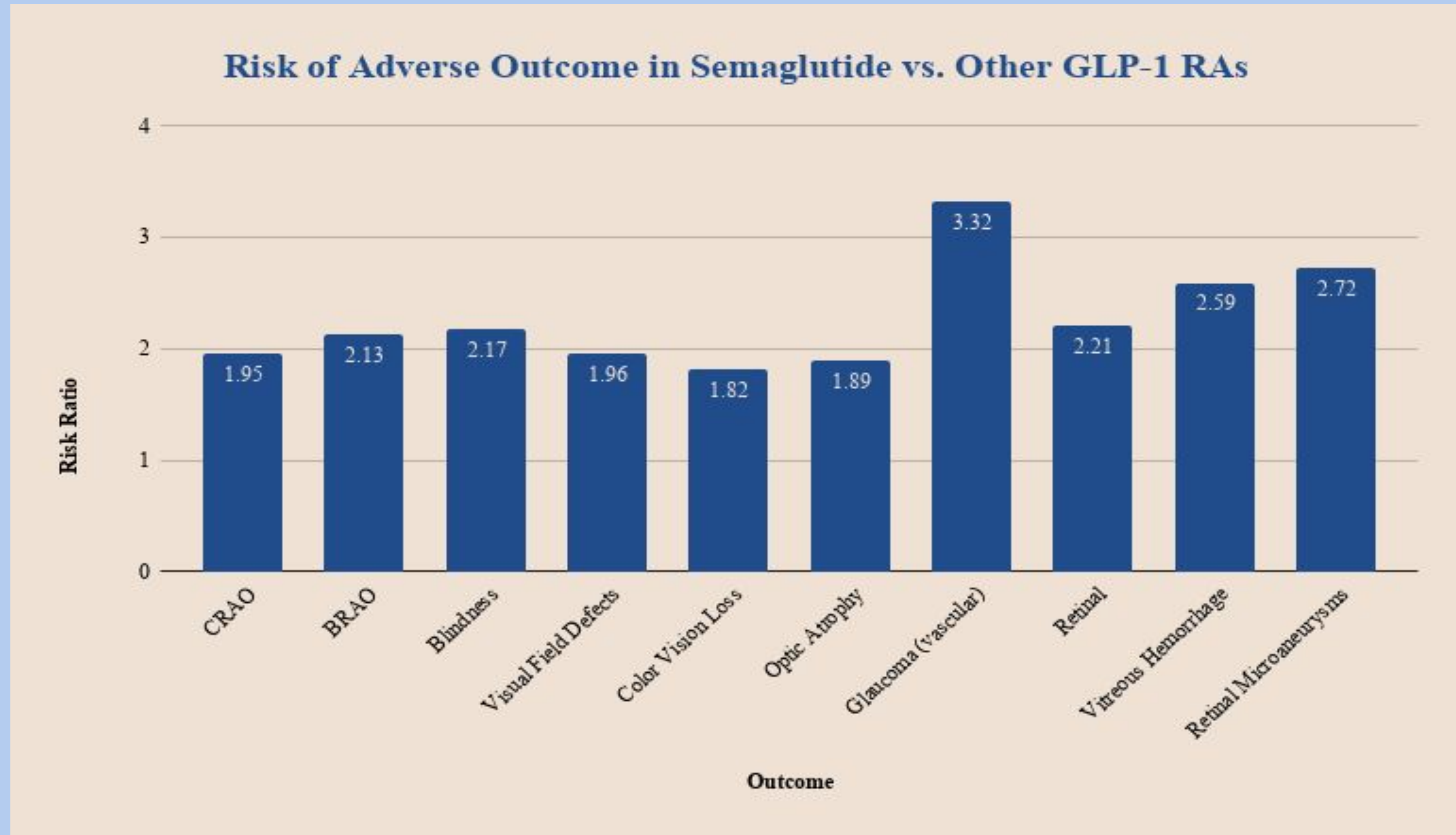
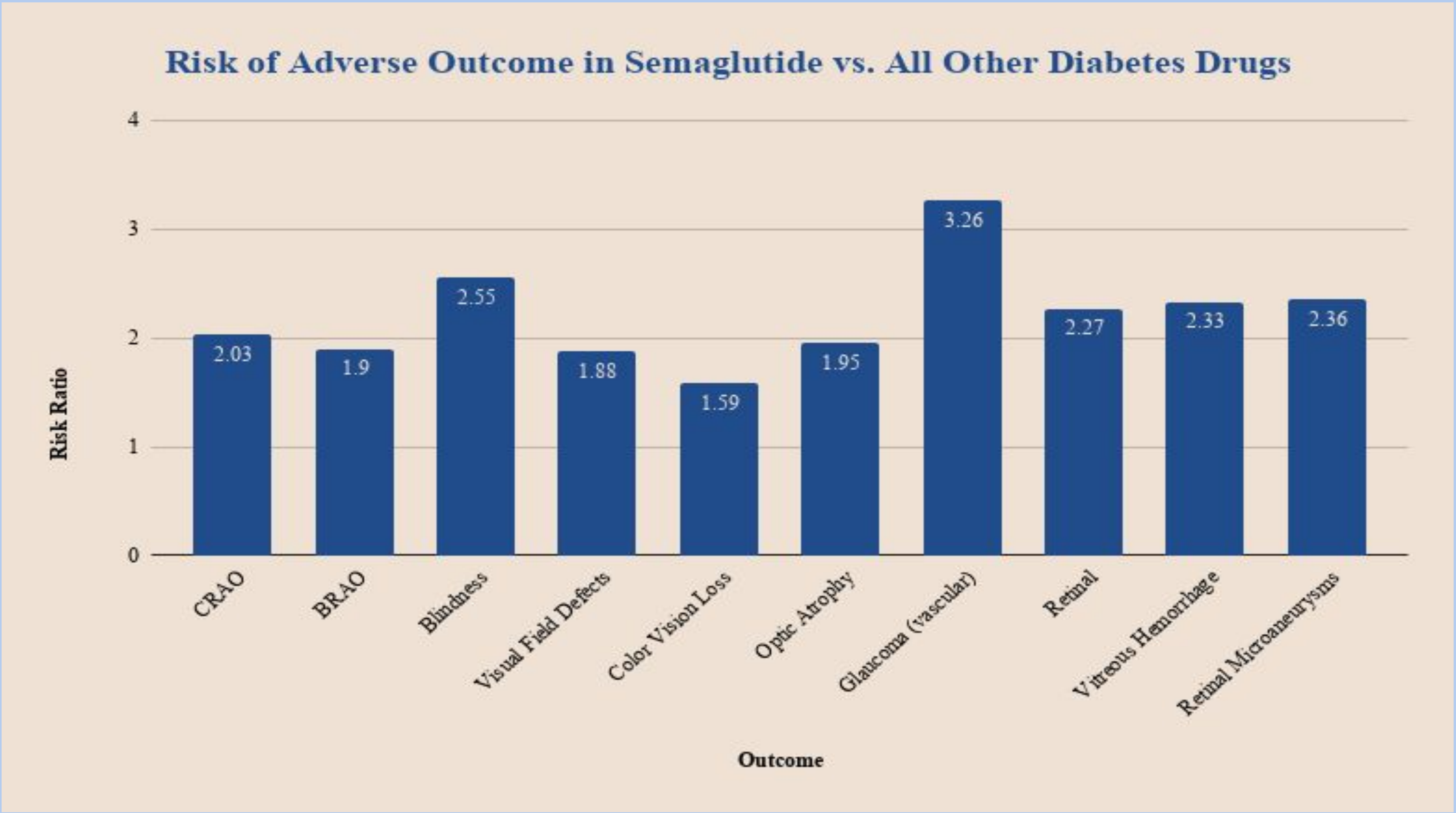
A global pharmacovigilance analysis using the FDA Adverse Event Reporting System (FAERS) investigating GLP-1 RAs (semaglutide, liraglutide, and exenatide) found significantly stronger signals for ophthalmic adverse drug reactions (OADRs) with semaglutide, including retinopathy and visual impairment.¹⁰ Semaglutide has been associated with advanced retinopathy complications such as retinal or vitreous detachment and retinal or vitreous hemorrhage more often than its GLP-1 RA counterparts. These comparative findings imply that semaglutide's distinct properties, including higher potency, longer half-life, and greater blood-retina exposure, may contribute to its elevated ocular risk profile. This concern appears to be less pronounced with other GLP-1 agents or with older classes of diabetes medications such as sulfonylureas or DPP-4 inhibitors.⁵

METHODS

This retrospective matched-cohort utilizes the Global Collaborative Network's TriNetX platform to compare deidentified electronic medical records of patients diagnosed with Type 2 Diabetes Mellitus (T2DM) and/or obesity as classified by International Classification of Diseases (ICD 10) codes. Statistical analysis was done via the TriNetX platform's Compare Outcomes Analysis, Kaplan-Meier Survival Analysis and Cox Hazards Regression Time-to-Event analysis.

RESULTS

Semaglutide treatment is associated with a reduced risk of developing CRAO and associated sequelae in comparison to 'all other diabetes drugs'. Semaglutide treatment is associated with a reduced risk of developing CRAO and associated side effects in comparison to the 'all other GLPs' cohort. After the follow-up period, CRAO occurred in 365 patients taking 'all other GLPs', in comparison to 182 patients taking semaglutide (RR, 2.006; 95% CI, 1.679-2.396). Retinal branch artery occlusion (BRAO) occurred in 422 patients taking 'all other GLPs', in comparison to 209 patients taking semaglutide (RR, 2.019; 95% CI, 1.711-2.383).



DISCUSSION

This matched-cohort analysis found that, among patients with type 2 diabetes mellitus and/or obesity, semaglutide use was associated with a lower risk of central and branch retinal artery occlusion compared with both other antidiabetic medications and other GLP-1 receptor agonists. Specifically, patients receiving alternative diabetes therapies or other GLP-1 agents demonstrated approximately a twofold higher risk of CRAO and a 1.7–2.0-fold higher risk of BRAO relative to matched semaglutide users.

These findings suggest a differential risk profile within the GLP-1 receptor agonist class and raise the possibility that semaglutide may confer a relative protective association against retinal arterial occlusive events. While prior literature has raised concern regarding GLP-1 receptor agonists and retinal vascular complications, our results indicate that this risk may not be uniform across agents.

The observed association may reflect underlying differences in pharmacologic properties, patient selection, or residual confounding. As such, these results should be interpreted cautiously and do not establish causality. Nonetheless, given the potential vision-threatening consequences of retinal artery occlusion, identifying antidiabetic therapies with more favorable ocular safety profiles remains clinically important.

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Theses authors have no disclosures.

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