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Ocular Outcomes of Glucagon-Like Peptide-1 Receptor Agonists Versus Sodium-Glucose Cotransporter-2 Inhibitors in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Real-World Evidence

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Abstract

While sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) offer proven cardiometabolic benefits, clinical evidence regarding their comparative ocular safety remains complex and contradictory. This study aimed to evaluate the ocular outcomes of SGLT2is versus GLP-1RAs in patients with type 2 diabetes. We conducted a systematic literature search across PubMed, Scopus, and CENTRAL through September 2026 and identified active-comparator real-world cohort studies comparing SGLT2is and GLP-1RAs in diabetic adults. The primary outcome evaluated was proliferative diabetic retinopathy (PDR) progression. Secondary outcomes included diabetic macular edema (DME) and nonarteritic anterior ischemic optic neuropathy (NAION). Random-effects models were utilized to calculate pooled risk ratios (RRs) with 95% confidence intervals (CIs). Risk of bias was assessed using the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool. Four real-world cohort studies provided quantitative data for meta-analytic synthesis. Pooled analysis demonstrated no statistically significant difference in PDR progression risk between GLP-1RA and SGLT2i initiation (RR = 1.08, 95% CI: 0.95-1.23, $p = 0.25$; $I^2 = 93\%$). However, GLP-1RA initiation was associated with a statistically significant 48% increased risk of DME (RR = 1.48, 95% CI: 1.36-1.62, $p < 0.00001$; $I^2 = 69\%$) and a 39% increased risk of NAION (RR = 1.39, 95% CI: 1.20-1.60, $p < 0.00001$; $I^2 = 0\%$) compared to SGLT2i initiation. In conclusion, while overall PDR progression risk remains comparable between drug classes, GLP-1RA initiation is associated with significantly higher risks of DME and NAION relative to SGLT2i initiation. Individualized ocular risk profiles should be evaluated when selecting second-line antidiabetic agents.

Categories: Pharmacology, Ophthalmology, Internal Medicine

Keywords: diabetes mellitus, diabetic macular edema, diabetic retinopathy, glp-1ra, sgl2is

Introduction And Background

Diabetes mellitus represents a major global health burden, with diabetic retinopathy (DR) remaining the most common microvascular complication and a leading cause of preventable visual impairment and blindness among working-age adults [1-6]. Prolonged hyperglycemia triggers complex pathophysiological processes within the retinal neurovascular unit, including microvascular capillary endothelial damage, pericyte loss, oxidative stress, neuroinflammation, and breakdown of the blood-retinal barrier [1,3-7]. These structural and functional alterations promote progressive ischemia and capillary leakage, facilitating the transition from non-proliferative stages to proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) [1,3,5]. Beyond classical microangiopathy, retinal neurodegeneration involving retinal ganglion cell dysfunction and glial activation is increasingly recognized as an intrinsic, early component of diabetic ocular disease [3,5,7].

The clinical management of type 2 diabetes has evolved substantially with the introduction of modern second-line antidiabetic drug classes, most notably sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) [1,3,6-8]. In addition to robust glycemic control and weight reduction, both classes offer extensive systemic cardiovascular and renal benefits [1,3,6-8]. Receptors and target transporters for both drug classes are expressed directly within human ocular tissues, with GLP-1

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receptors localized in the ganglion cell layer and retinal glia, and SGLT2 channels identified within retinal microvasculature and pericytes [3-5,7]. Preclinical investigations demonstrate that GLP-1RAs exert neuroprotective, antioxidant, and anti-inflammatory effects that preserve blood-retinal barrier integrity and attenuate neurosensory cell apoptosis [3,5,7]. Similarly, SGLT2is exhibit retinoprotective properties in experimental models by suppressing glucotoxic stress, reducing oxidative damage and pro-inflammatory cytokine expression, and mitigating microvascular permeability [3-5].

Despite promising experimental findings, clinical evidence regarding the ocular safety and efficacy of these agents remains complex and contradictory [1-3,6]. Concerns were initially flagged by the landmark SUSTAIN-6 trial, which reported an increased incidence of diabetic retinopathy complications following semaglutide initiation [1,2,7-9]. Subsequent analyses suggested that this finding was predominantly driven by the “early worsening” phenomenon: a transient exacerbation of microvascular ischemia secondary to rapid and substantial glycemic reduction, rather than direct drug toxicity [1,6-8]. Conversely, subsequent meta-analyses of randomized controlled trials assessing GLP-1RAs have demonstrated neutral overall risk estimates for diabetic retinopathy progression and vision-threatening optic nerve events [2,6,9,10]. Meanwhile, large-scale real-world observational cohorts indicate that SGLT2is may offer superior ocular protection, demonstrating significantly lower hazards for diabetic retinopathy progression, DME, open-angle glaucoma, and cataracts when compared against GLP-1RAs or other antidiabetic therapies [3-5].

Despite these emerging observational signals and distinct mechanistic profiles, randomized controlled trials directly comparing the ocular outcomes of SGLT2is and GLP-1RAs head-to-head are currently lacking [3,9,10]. Furthermore, major cardiovascular outcome trials were not originally designed with prospective, standardized ophthalmologic grading, relying instead on unadjudicated, post-hoc adverse event reporting that risks misclassification and underreporting. To bridge this critical evidence gap, there is an urgent need to perform a comprehensive head-to-head meta-analysis of available observational data and real-world evidence comparing SGLT2is directly against GLP-1RAs. Therefore, the primary objective of this systematic review and meta-analysis is to quantitatively synthesize real-world evidence to evaluate the comparative ocular outcomes of SGLT2is versus GLP-1RAs across primary ophthalmic endpoints, including diabetic retinopathy progression (proliferative), DME, and nonarteritic anterior ischemic optic neuropathy (NAION), in patients with type 2 diabetes.

Review

Methodology

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [11].

Information Sources and Search Strategy

A systematic search was conducted across PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception up to September 2026. Search terms combined MeSH vocabulary and text keywords for SGLT2is (e.g., empagliflozin, dapagliflozin, canagliflozin), GLP-1RAs (e.g., semaglutide, dulaglutide, liraglutide), real-world observational designs, target trial emulations, and specific ocular outcomes including diabetic retinopathy, macular edema, and NAION. Reference lists of eligible studies were manually reviewed, and no language restrictions were applied.

Eligibility Criteria and Outcomes

Eligible studies comprised randomized controlled trials; real-world active-comparator, new-user observational cohort studies; and target trial emulations in adult patients (18 years or more) diagnosed with type 2 diabetes that compared ocular outcomes of GLP-1RAs versus SGLT2is. Confounding adjustment using propensity score matching (PSM), inverse probability of treatment weighting (IPTW), or overlap weighting was required for inclusion. Single-arm, unadjusted, cross-sectional, and non-human studies were excluded.

The primary outcome evaluated was the cumulative risk of PDR. The secondary outcomes were cumulative risks of DME and NAION.

Study Selection and Data Extraction

All retrieved citations were uploaded to the Rayyan web-based platform [12] for automated deduplication and systematic screening. Two reviewers independently screened titles and abstracts in parallel, followed by full-text evaluation against the predefined eligibility criteria, with any discrepancies resolved through consensus. Data were extracted into a standardized collection template capturing study characteristics, real-world database sources, sample sizes, propensity weighting methods, baseline HbA1c, and adjusted effect estimates of events with sample sizes or risk ratios (RRs) with 95% confidence intervals (CIs) for our outcomes.

Risk of Bias and Quality Assessment

Methodological quality and risk of bias of all included real-world observational cohort studies and target trial emulations were evaluated independently by two reviewers using the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool [13]. The assessment evaluated seven bias domains: baseline confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement validity, and selective outcome reporting. Each domain was rated to derive an overall risk of bias classification.

Statistical Analysis and Data Synthesis

All quantitative analyses and meta-analytic pooling were executed using Review Manager (RevMan, version 5.3). Adjusted log RRs with their standard errors and 95% CIs were synthesized using the inverse-variance method. To account for clinical and database heterogeneity across real-world cohorts, all primary analyses were performed using DerSimonian-Laird random-effects models. We clarify that quantitative pooling is restricted to studies reporting size effects by measuring RRs or event counts for PDR progression, DME, and NAION, while studies employing competing-risk subdistribution hazard ratios (SHRs) from Fine-Gray models or reported effect measures with hazard ratios (HRs) or 10-year multi-organ registries were synthesized qualitatively, as we could not combine them with RRs to create mathematical incongruity. Between-study heterogeneity was quantified using the I^2 statistic and Cochran's Q test.

Results

Search Results and Included Study Characteristics

A comprehensive systematic database search across PubMed (n = 389), Scopus (n = 584), and CENTRAL (n = 128) identified 1,101 total records. Following the removal of 342 duplicate records, 759 unique citations underwent title and abstract screening, resulting in the exclusion of 724 irrelevant records. Full-text evaluations were performed on 35 retrieved reports. Of these, 29 reports were excluded due to a lack of direct head-to-head comparisons (n = 22), duplicate cohorts (n = 4), or missing prespecified ophthalmic endpoints (n = 3). Consequently, six real-world observational cohort studies [3,14-18] met all eligibility criteria for qualitative systematic review, of which four studies [14-16,18] provided quantitative data for meta-analytic pooling (Figure 1).

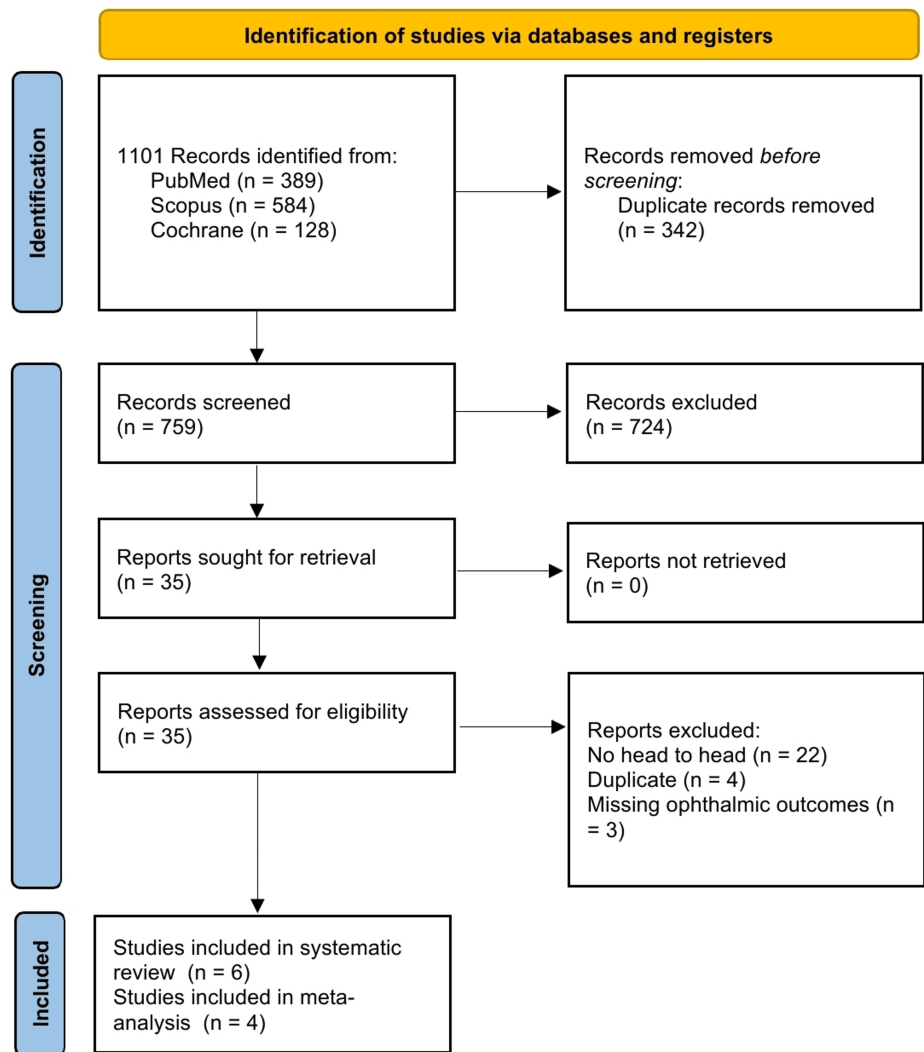


FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram of study selection.

The six included studies comprised target trial emulations and retrospective new-user active-comparator cohorts capturing diverse multi-center database networks and national Electronic Health Record (EHR) registries. Sample sizes varied substantially across cohorts, ranging from 12,962 participants (6,481 propensity-matched pairs) in Wai et al. [18] to 588,168 participants in Choi et al. [14]. All studies employed rigorous statistical adjustments for baseline confounding, including 1:1 PSM, IPTW, or overlap weighting. Mean participant age across studies ranged from 60.1 to 65.3 years, with male representation ranging from 53.2% to 95.3%. Total follow-up duration across the real-world cohorts ranged from 1.6 years up to 10 years. For details, see Table 1.

Study	Study design and matching method	Sample size (N) (GLP-1RA)/(SGLT2i)	Mean age (years) (GLP-1RA/SGLT2i)	Male sex (%) (GLP-1RA/SGLT2i)	Baseline HbA1c (%) (GLP-1RA/SGLT2i)	Baseline BMI (kg/m²) (GLP-1RA/SGLT2i)	Follow-up duration	Primary outcomes evaluated
Choi et al. (2026) [14]	Target trial emulation; propensity score weighting	Total: 588,168 (139,546)/(448,622)	(65.3/65.0)	(90.2/95.3)	(8.61 ± 2.43)/(8.23 ± 1.66)	(35.77 ± 7.01)/(32.84 ± 6.30)	3 years	NAION, PDR
Eleftheriadou et al. (2024) [15]	Retrospective cohort; 1:1 PSM	(139,117)/(139,117) matched pairs	(62.1/62.1)	(53.2/52.5)	—	—	Up to 5 years	PDR, DME
Heberer et al. (2026) [16]	Target trial emulation; active-comparator new-user; overlap weighting	Total: 102,361 (11,478)/(90,883)	(60.1/60.1)	(85.5/85.5)	(7 ± 1.4)/(7.3 ± 1.5)	(38.8 ± 7.4)/(33.6 ± 6.4)	Median 2.1 years (up to 7 years)	NAION
Wai et al. (2024) [18]	Retrospective cohort; 1:1 PSM	(6,481)/(6,481) matched pairs	(64.8/64.9)	(53.4/53.1)	(8.49 ± 1.93)/(8.31 ± 1.88)	(33.8 ± 6.75)/(31.7 ± 6.93)	3 years	PDR, DME
Lin et al. (2023) [17]	Target trial emulation; active-comparator new-user; IPTW	Total: 23,378 (1,887)/(21,491)	(60.3/61.0)	(59.7/59.4)	(9.08 ± 1.75)/(8.58 ± 1.63)	(29.1 ± 5.4)/(28.0 ± 4.8)	Mean 1.6/1.8 years	DR, PDR
Lin et al. (2026) [3]	Retrospective cohort; 1:1 PSM	(68,283)/(68,283) matched pairs	(61.2/61.3)	(54.1/53.0)	—	(36.20 ± 7.92)/(32.52 ± 7.39)	Up to 10 years	Open-angle glaucoma, ocular hypertension, cataract, DR, DME

TABLE 1: Summary of baseline characteristics of included studies.

EHR: Electronic Health Record; HCO: healthcare organization; IPTW: inverse probability of treatment weighting; NAION: nonarteritic anterior ischemic optic neuropathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; DME: diabetic macular edema; PPV: pars plana vitrectomy; PRP: panretinal photocoagulation; PSM: propensity score matching; SGLT2i: sodium-glucose cotransporter-2 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist

Risk of Bias Assessment

Methodological quality and risk of bias across the six included real-world observational cohorts were evaluated using the ROBINS-I tool. Two nationwide target trial emulations utilizing integrated EHR systems [14,16] were judged as having a low overall risk of bias across all seven domains, benefiting from active-comparator new-user designs, clinically validated outcome coding, and comprehensive propensity score overlap weighting. The remaining four multi-center observational cohort studies [3,15,17,18] were classified as having a moderate overall risk of bias, primarily driven by the potential for residual unmeasured confounding inherent to global federated health networks and reliance on administrative diagnostic codes without centralized ophthalmic image adjudication. For details, see Figure 2.

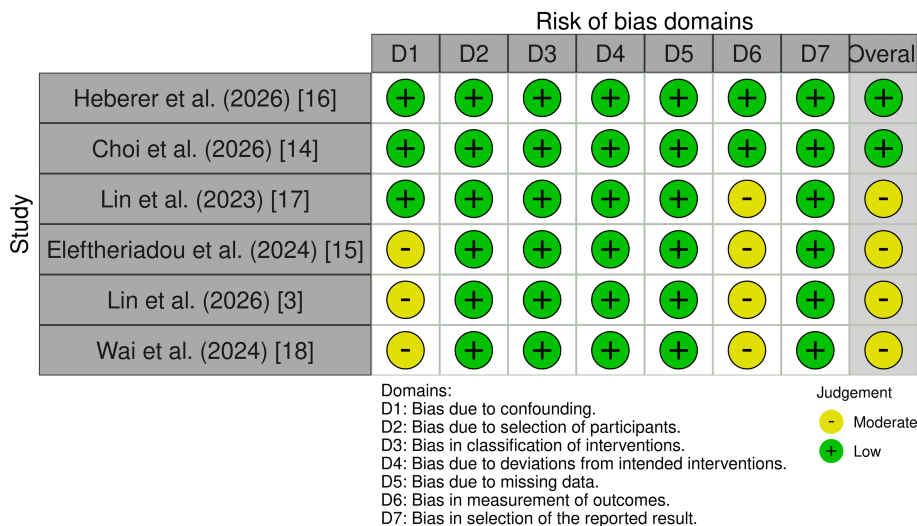


FIGURE 2: Results of risk of bias assessment using the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool.

Proliferative Diabetic Retinopathy

Quantitative synthesis of three cohort studies evaluated the comparative risk of PDR progression between GLP-1RA and SGLT2i initiators. The random-effects pooled RR demonstrated no statistically significant difference in PDR progression risk between GLP-1RA and SGLT2i initiation (pooled RR = 1.08, 95% CI: 0.95-1.23; Z = 1.15, p = 0.25). However, substantial between-study heterogeneity was detected across the pooled estimates (Chi² = 30.69, df = 2, p < 0.00001; Tau² = 0.01; I² = 93%). Individual study effect estimates demonstrated varying risk patterns: Choi et al. [14] (RR = 1.01, 95% CI: 0.99-1.03; weight = 36.5%) and Eleftheriadou et al. [15] (RR = 0.96, 95% CI: 0.90-1.02; weight = 33.9%) reported neutral associations, whereas Wai et al. [18] (RR = 1.35, 95% CI: 1.21-1.50; weight = 29.6%) observed an elevated risk for GLP-1RA initiators (Figure 3).

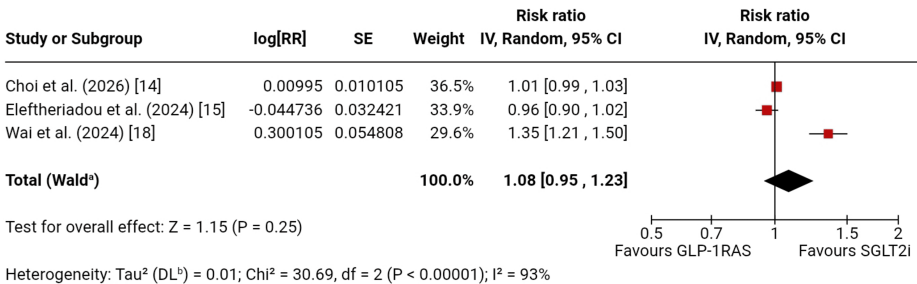


FIGURE 3: Forest plot of PDR progression risk comparing GLP-1RA versus SGLT2i initiation.

^a: CI calculated by the Wald-type method; ^b: Tau² calculated by the DerSimonian and Laird method.

PDR: proliferative diabetic retinopathy; SGLT2i: sodium-glucose cotransporter-2 Inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist

Diabetic Macular Edema

Pooled meta-analytic synthesis of two real-world studies demonstrated a statistically significant 48% increased risk of DME among patients initiated on GLP-1RAs relative to those initiated on SGLT2is (pooled RR = 1.48, 95% CI: 1.36-1.62; Z = 8.75, p < 0.00001). Moderate between-study heterogeneity was present (Chi² = 3.25, df = 1, p = 0.07; Tau² = 0.00; I² = 69%). Individual study effect estimates were: Eleftheriadou et al. [15] (RR = 1.42, 95% CI: 1.33-1.51; weight = 51.0%) and Wai et al. [18] (RR = 1.55, 95% CI: 1.44-1.66;

weight = 49.0%) consistently demonstrated elevated DME risks following GLP-1RA initiation compared to SGLT2i initiation (Figure 4).

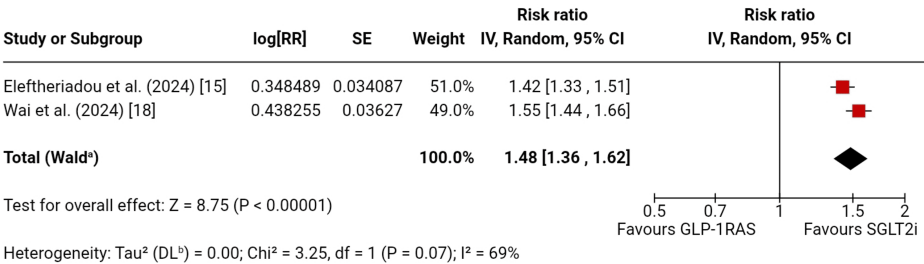


FIGURE 4: Forest plot of DME risk comparing GLP-1RA versus SGLT2i initiation.
a: CI calculated by the Wald-type method; b: Tau² calculated by the DerSimonian and Laird method.
DME: diabetic macular edema; SGLT2i: sodium-glucose cotransporter-2 Inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist

Nonarteritic Anterior Ischemic Optic Neuropathy

Pooled analysis from two target trial emulations utilizing national Veterans Health Administration databases revealed a statistically significant 39% increased risk of NAION associated with GLP-1RA initiation compared to SGLT2i initiation (pooled RR = 1.39, 95% CI: 1.20-1.60; Z = 4.48, p < 0.00001). No between-study heterogeneity was observed (Chi² = 0.93, df = 1, p = 0.34; Tau² = 0.00; I² = 0%). Individual study effect estimates were: Choi et al. [14] (RR = 1.35, 95% CI: 1.16-1.57; weight = 86.7%) and Heberer et al. [16] (RR = 1.66, 95% CI: 1.12-2.46; weight = 13.3%) identified a significantly higher risk of NAION among GLP-1RA initiators compared with SGLT2i initiators (Figure 5).

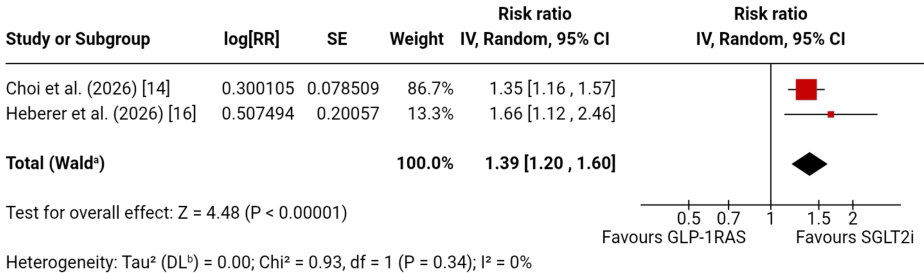


FIGURE 5: Forest plot of NAION risk comparing GLP-1RA versus SGLT2i initiation.
a: CI calculated by the Wald-type method; b: Tau² calculated by the DerSimonian and Laird method.
NAION: nonarteritic anterior ischemic optic neuropathy; SGLT2i: sodium-glucose cotransporter-2 Inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist

Discussion

This systematic review and meta-analysis synthesized real-world observational evidence to compare the head-to-head ocular safety and efficacy of GLP-1RAs versus SGLT2is in patients with type 2 diabetes. Quantitative meta-analysis demonstrated no statistically significant difference in the risk of PDR progression between GLP-1RA and SGLT2i initiation. However, GLP-1RA initiation was associated with a statistically significant 48% increased risk of DME and a 39% increased risk of NAION compared to SGLT2i initiation.
The neutral overall risk for PDR progression observed in our meta-analysis aligns with meta-analyses of randomized controlled trials, which consistently demonstrate no overall association between GLP-1RA therapy and diabetic retinopathy progression [2,6,9,10]. Major trial syntheses report pooled risk estimates close to unity, such as Alwafi et al. [2] (RR = 1.00, 95% CI: 0.71-1.43), Małyszczak et al. [9] (odds ratio (OR) = 1.08, 95% CI: 0.94-1.23), and Yang et al. [6] (RR = 1.07, 95% CI: 0.90-1.28). Signal elevations in trials such as

SUSTAIN-6 (HR = 1.76) are widely attributed to the "early worsening" phenomenon: a transient exacerbation of retinal ischemia triggered by rapid, substantial reductions in glycated hemoglobin (HbA1c) in patients with pre-existing retinopathy, rather than direct drug-induced vascular toxicity [7]. Systematic qualitative comparison with observational target trial emulations reveals important stage-specific nuances that meta-analytic pooling of overall diabetic retinopathy may obscure. In the Chang Gung Research Database target trial emulation by Lin et al. [17], initiation of SGLT2is versus GLP-1RAs yielded a comparable rate of overall diabetic retinopathy (SHR = 0.90, 95% CI: 0.79-1.03), but SGLT2is demonstrated a marked 47% risk reduction for PDR (SHR = 0.53, 95% CI: 0.42-0.68). Similarly, the global TriNetX cohort study by Lin et al. [3] confirmed that across a 10-year follow-up, SGLT2i initiation was associated with a significantly lower hazard of diabetic retinopathy progression compared with GLP-1RA initiation (HR = 0.84, 95% CI: 0.81-0.87). Together, these systematic review findings suggest that while initial diabetic retinopathy development may be similar between classes, SGLT2is offer superior protection against progression to advanced, vision-threatening proliferative stages [3,17].

The finding of a significantly higher DME risk among GLP-1RA initiators relative to SGLT2i initiators in our pooled analysis (RR = 1.48) reflects a growing body of real-world evidence supporting the distinct microvascular profiles of these agents. In the large active-comparator cohort by Lin et al. [3], SGLT2i initiation was associated with a 23% lower risk of macular edema compared to GLP-1RA initiation (HR = 0.77, 95% CI: 0.65-0.90). Furthermore, Lin et al. [17] demonstrated that SGLT2i users required significantly fewer intravitreal injections (SHR = 0.65, 95% CI: 0.47-0.91) and laser photocoagulation procedures (SHR = 0.59, 95% CI: 0.47-0.74) than GLP-1RA users. Mechanistically, the protective advantage of SGLT2is in DME likely stems from systemic hemodynamic and fluid-modulating effects [3,5,17]. SGLT2is induce osmotic diuresis and natriuresis, reduce low-grade systemic inflammation, and lower intraocular volume, which may alleviate fluid accumulation in the neurosensory retina [3,5,17]. Preclinical studies also suggest SGLT2is attenuate oxidative stress, reduce vascular permeability, and preserve blood-retinal barrier integrity [4,5,9]. In contrast, GLP-1RAs may transiently alter retinal blood flow, and the rapid initial glycemic drop often seen with GLP-1RAs can exacerbate capillary permeability and macular swelling in vulnerable eyes [1,7,8].

Our finding of a 39% increased risk of NAION among GLP-1RA initiators compared to SGLT2i initiators (RR = 1.39) reflects a consistent pharmacovigilance and observational safety signal. Real-world databases, including target trial emulations in Veterans Health Administration registries [14,16], have noted elevated HRs for NAION following GLP-1RA initiation. Proposed pathophysiological mechanisms include GLP-1RA-induced changes in nocturnal blood pressure, altered optic nerve head perfusion, or local microvascular dysregulation in susceptible optic disks [1,10]. In contrast, meta-analyses of interventional randomized controlled trials, such as Li et al. [10], report no statistically significant increase in optic nerve or vision-threatening events with GLP-1RAs (overall OR = 1.20, 95% CI: 0.73-1.97; ION OR = 1.50, 95% CI: 0.49-4.63). This divergence between trial and real-world data is largely methodological: clinical trials excluded high-risk patients, suffered from extremely low absolute event numbers, and relied on unadjudicated adverse event reporting rather than prespecified ophthalmologic screening. Active-comparator real-world cohorts capture larger, unselected populations with longer exposure durations, making them more sensitive to rare optic nerve events.

Integrating our quantitative meta-analysis with qualitative evidence from Lin et al. [17] and Lin et al. [3] highlights a clear therapeutic trade-off between ocular and systemic outcomes. Lin et al. [3] demonstrated that SGLT2is consistently outperform GLP-1RAs and DPP-4 inhibitors across multiple ocular conditions, offering reductions in open-angle glaucoma (HR = 0.88), ocular hypertension (HR = 0.78), and cataracts (HR = 0.84), alongside reductions in diabetic retinopathy and DME. Conversely, Lin et al. [3] showed that GLP-1RAs provide stronger systemic protection, significantly reducing risks of diabetic nephropathy/chronic kidney disease, liver cirrhosis, dementia, cerebral infarction, and ischemic heart disease relative to SGLT2is or DPP-4is. This distinction suggests that second-line antidiabetic selection should be tailored to individual patient risk profiles. SGLT2is may be prioritized in individuals with established or high risk for ocular microvascular complications, such as baseline macular edema or advanced retinopathy. Conversely, GLP-1RAs remain preferred when broad cardiometabolic, cerebrovascular, or weight loss benefits are the primary therapeutic objectives [3,17].

Several limitations of our study should be noted. First, all included quantitative studies were observational cohort designs, which remain susceptible to residual unmeasured confounding despite PSM and overlap weighting. Second, outcomes relied on administrative diagnostic codes without centralized fundus photograph or optical coherence tomography (OCT) image adjudication. Third, the number of eligible head-to-head cohorts for quantitative pooling was relatively small.

To advance current evidence, prospective randomized controlled trials incorporating standardized ophthalmologic imaging, such as OCT and OCT angiography, are essential to overcome the diagnostic misclassification inherent to administrative health registries. Furthermore, translational research must clarify the precise mechanisms governing these divergent profiles, including SGLT2i-mediated hemodynamic fluid modulation versus GLP-1RA-induced optic nerve head perfusion shifts.

Conclusions

In conclusion, while overall proliferative retinopathy risk remains comparable between classes, SGLT2is offer a clear safety advantage over GLP-1RAs regarding macular edema and ischemic optic neuropathy. Tailoring second-line antidiabetic selection to individual ocular and systemic risk profiles is vital to optimizing long-term visual and metabolic outcomes.

Appendices

Study and citation	Database and design	Sample size (N) and HbA1c/BMI	Follow-up	Primary and secondary outcomes measured	Effect estimates (95% CI)	ROBINS-I bias	Meta-analysis status
Choi et al. (2026) [14]	US VHA target trial emulation (overlap weighting)	N = 588,168 (139,546 GLP-1/448,622 SGLT2) HbA1c: 8.61% vs. 8.23% BMI: 35.8 vs. 32.8	3.0 years	Primary: NAION. Secondary: PDR, DR, macular degeneration, retinal vascular occlusion	NAION: RR = 1.35 (1.11–1.51) PDR: RR = 1.01 (0.99–1.03)	Low	Quantitative (NAION and PDR)
Eleftheriadou et al. (2024) [15]	TriNetX global retrospective cohort (1:1 PSM)	N = 278,234 (139,117 matched pairs) Insulin co-therapy	Up to 5.0 years	Primary: PDR and DME	PDR: events count/total DME: events count/total	Moderate	Quantitative (PDR and DME)
Heberer et al. (2026) [16]	US VHA Target trial emulation (overlap weighting)	N = 102,361 (11,478 Semaglutide/90,883 SGLT2) HbA1c: 7.0% vs 7.3% BMI: 38.8 vs. 33.6	Median 2.1 years (up to 7 years)	Primary: Incident NAION	NAION: events count/total	Low	Quantitative (NAION)
Wai et al. (2024) [18]	TriNetX US/global retrospective cohort (1:1 PSM)	N = 12,962 NPDR cohort (6,481 matched pairs) HbA1c: 8.49% vs. 8.31%	3.0 years	Primary: PDR progression and DME. Secondary: Vitreoretinal intervention (anti-VEGF, PRP, PPV)	PDR: RR = 1.28 (1.10–1.50) DME: RR = 1.29 (1.21–1.38)	Moderate	Quantitative (PDR and DME)
Lin et al. (2023) [17]	Chang Gung CGRD (Taiwan) Target trial emulation (IPTW)	N = 23,378 (1,887 GLP-1/21,491 SGLT2) HbA1c: 9.08% vs. 8.58%	Mean 1.8 years	Primary: Any DR, PDR, composite vitreoretinal surgery	PDR: SHR = 0.53 (0.42–0.68) Surgical: SHR = 0.58 (0.48–0.70) (SGLT2 vs GLP-1)	Moderate	Qualitative (Fine-Gray SHRs and surgical endpoints)
Lin et al. (2026) [3]	TriNetX Global retrospective cohort (1:1 PSM)	N = 136,566 (68,283 matched pairs)	10.0 years	Primary: Open-angle glaucoma, preeclampsia/ocular hypertension. Secondary: cataract, DR, DME, CKD, MI, stroke, dementia	Glaucoma: HR = 0.88 (0.81–0.95) Preeclampsia: HR = 0.78 (0.73–0.84) DR: HR = 0.84 (0.81–0.87) DME: HR = 0.77 (0.65–0.90)	Moderate	Qualitative (HR, 10-year multi-organ trade-off)

TABLE 2: A summary of study characteristics, design frameworks, exact primary and secondary outcomes measured in each original study, adjusted effect estimates, ROBINS-I risk of bias domain ratings, and meta-analytic allocation status across all six included real-world cohorts.

BMI: body mass index; ROBINS-I: Risk of Bias in Non-randomized Studies - of Interventions; VHA: Veterans Health Administration; SGLT2i: sodium-glucose cotransporter-2 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; PDR: proliferative diabetic retinopathy; DME: diabetic macular edema; NAION: nonarteritic anterior ischemic optic neuropathy; PSM: propensity score matching; VEGF: vascular endothelial growth factor; PPV: pars plana vitrectomy; PRP: panretinal photocoagulation; IPTW: inverse probability of treatment weighting; SHR: subdistribution hazard ratio; CKD: chronic kidney disease; MI: myocardial infarction

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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