

How Often Eye x All: Incidence Rates of All Health Outcomes Following Initiation of Ophthalmic Drugs

Hsin Yi Chen, BS¹, Thamir Alshammari, PhD^{2,3}, Tara Anand, PhD¹, Cindy X. Cai, MD, MS^{4,5}, Kerry Goetz, MS, PhD⁶, Michelle Hribar, PhD⁷, Nitish Mehta, MD⁸, Jacqueline C. Stocking, PhD, MBA, MSN⁹, Brian Toy, MD¹⁰, George Hripcsak, MD, MS¹

¹Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, NY

²Department of Clinical Practice, Jazan University, Jazan, Jazan, Saudi Arabia

³Pharmacy Practice Research Unit, Jazan University, Jazan, Saudi Arabia

⁴Wilmer Eye Institute, Johns Hopkins School of Medicine, Baltimore, MD

⁵Biomedical Informatics and Data Science, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

⁶National Eye Institute, National Institutes of Health, Bethesda, MD

⁷Department of Ophthalmology and Visual Sciences, University of Illinois College of Medicine, Chicago, IL

⁸Department of Ophthalmology, NYU Langone Health, New York, NY

⁹Department of Internal Medicine, University of California Davis, Davis, CA

¹⁰Roski Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

Background

Incidence rate estimation is foundational to pharmacoepidemiology, providing clinicians and researchers with interpretable, absolute measures of risk that contextualize clinical events following drug initiation. While incidence rates are not causal, the total observed frequency of conditions following treatment initiation—regardless of whether it's driven by the drug, the underlying indication, or baseline comorbidities—has direct implications for clinical monitoring and drug surveillance.

Ophthalmic drugs represent a particularly undercharacterized domain in large-scale drug safety research¹. Many ophthalmic drugs share active ingredients with systemic formulations, including NSAIDs, corticosteroids, antibiotics, and beta-blockers, and systemic absorption following topical ocular application is well documented for several drug classes^{2,3}. Notably, topical timolol has been associated with systemic cardiovascular⁴ and pulmonary effects^{5,6}, and intravitreal anti-VEGF agents have raised questions about systemic vascular exposure⁷.

Here, we systematically characterize the incidence of health outcomes following ophthalmic drug initiation. We aim to produce a standardized, reproducible reference that provides an empirical foundation for future hypothesis-driven research.

Methods

We conducted a retrospective observational cohort study using routinely collected health care data from the Columbia University Irving Medical Center (CUIMC) database mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM)⁸ in May 2026.

Ophthalmic drug exposures were identified using RxNorm dose form relationships (dose form group “ophthalmic product”) and a curated list of injectable ophthalmic agents (including intravitreal anti-VEGF therapies, corticosteroids, antimicrobials, and complement inhibitors), rolled up to the ingredient level, yielding 477 candidate ophthalmic drugs. Combination products contribute to each constituent ingredient's cohort. Cohort entry was defined as the first recorded exposure to each drug between January 1, 2015 and December 31, 2024, with patients required to have at least one year of prior observation. Drugs with no observed exposures meeting inclusion criteria were excluded, resulting in 83 active drug cohorts.

Health outcomes were defined as incident SNOMED-CT condition codes mapped from ICD-9-CM, ICD-10-CM, problem lists, and billing codes, filtered to 16,395 representative concepts using percentile-based thresholds on concept frequency and hierarchy depth. Outcomes with no eligible patients were excluded, yielding 13,319 active outcome cohorts spanning 17 organ-system categories. Incidence was calculated as both a rate (events per 100 person-years) and a proportion across four time-at-risk (TAR) windows: 30 days, 365 days, on-treatment, and intent-to-treat (ITT). A 365-day lookback period was applied to define incident outcomes. Results were suppressed for target-outcome pairs with fewer than 1,000 persons at risk or 1-4 events. Outcomes were mapped to their closest parent organ-system category in the SNOMED disorder hierarchy; drugs were grouped by WHO ATC ophthalmology (S01) class at the third and, where possible, fourth ATC level. Analyses were executed using the OHDSI HADES suite⁹ orchestrated via Strategus¹⁰.

Results

Across 83 drug cohorts, 13,319 outcome cohorts, and four TAR windows, we generated 25,412,652 drug-outcome-TAR incidence estimates. After excluding denominators fewer than 1,000 persons and suppressing cells with 1-4 events, 3,490,904 estimates remained, of which 1,084,719 had an incidence rate greater than zero per 100 person-years.

Given the scale of these estimates, we focused on a single TAR (ITT 365-day; 301,581 total estimates) and three drug classes: anti-infectives (ATC S01A; 46 drugs), anti-inflammatory agents/corticosteroids (ATC S01B; 18 drugs), and antiglaucoma/IOP-lowering agents (ATC S01E; 27 drugs). An overview of the results can be seen in Figure 1.

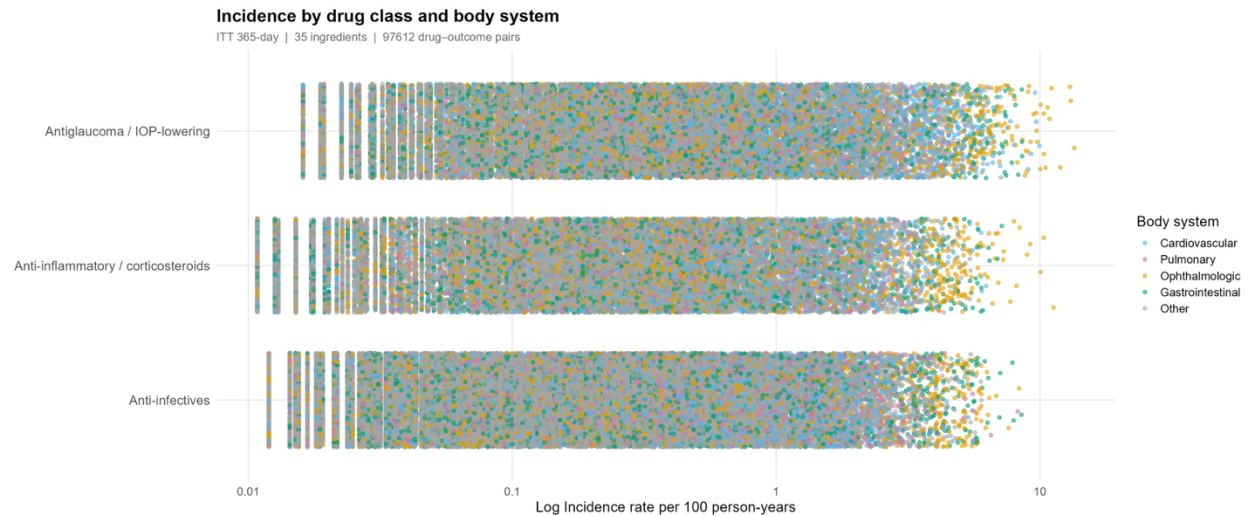


Figure 1. Dot plot of incidence rates (events per 100 person-years, x-axis is on the log scale) by primary ATC drug class (y-axis) and SNOMED-mapped outcome body system. Three drug classes are shown: anti-infectives, anti-inflammatory/corticosteroids, and antiglaucoma/IOP-lowering agents. Highlighted body systems are cardiovascular, pulmonary, ophthalmologic, and gastrointestinal; remaining mapped body systems are grouped as “Other” (gray). One dot corresponds to one drug ingredient–outcome pair.

When ophthalmic outcomes were included, the highest observed incidence rates were predominantly indications for the drug itself (Table 1). Antiglaucoma agents illustrate this most clearly: the three highest incidence rates among topical latanoprost, timolol, and brimonidine were all for glaucoma (12.99-13.48 per 100 person-years). This likely reflects the limitation in our use of a 365-day clean-window for ophthalmic outcomes: patients with pre-existing glaucoma diagnosed beyond that window would not have been excluded as prevalent cases. Similarly, bromfenac, a topical NSAID commonly used following ocular surgery, showed its highest incidence rates for astigmatism and adnexal and orbital disorders (6.19-7.29 per 100 person-years), consistent with the post-surgical population in which it is prescribed¹¹.

Drug	Outcome	Body System	Incidence Rate (per 100 person years)
Anti-infectives			
Trimethoprim	Disorder of upper digestive tract	GI	8.50
Moxifloxacin	Disorder of ocular adnexa	Ophthalmologic	8.34
Trimethoprim	Inflammatory disorder of upper respiratory tract	Pulmonary	8.23
Anti-inflammatory / corticosteroids			
Bromfenac	Astigmatism	Ophthalmologic	7.29
Bromfenac	Disorder of ocular adnexa	Ophthalmologic	6.95
Bromfenac	Disorder of orbit proper	Ophthalmologic	6.19
Antiglaucoma / IOP-lowering			
Latanoprost	Glaucoma	Ophthalmologic	13.48
Timolol	Glaucoma	Ophthalmologic	13.08
Brimonidine	Glaucoma	Ophthalmologic	12.99

Table 1. Top three Incidence rates of clinical conditions following initiation of selected ophthalmic drug classes, among patients in the CUIIMC database with at least one year of prior observation and no prior diagnosis of the outcome of interest. Incidence rates are expressed per 100 person-years at risk.

When ophthalmic outcomes were excluded (Table 2), the highest incidence rates were concentrated in the pulmonary, cardiovascular, and gastrointestinal systems. Among anti-infectives, trimethoprim showed its highest incidence rates for gastrointestinal and upper respiratory conditions (7.94–8.50 per 100 person-years), likely reflecting the underlying infectious burden in treated patients. Among anti-inflammatory agents, diclofenac showed elevated rates for upper gastrointestinal disorders and gastroesophageal reflux disease (6.44–7.16 per 100 person-years). Among antiglaucoma agents, vascular disorders were the most frequent non-ophthalmic outcome, with consistent rates across latanoprost (9.95), bimatoprost (9.68), and timolol (9.57 per 100 person-years). The consistency of this signal across mechanistically distinct agents suggests shared patient-level cardiovascular comorbidity in the glaucoma population as the most likely explanation, though timolol's known systemic cardiovascular effects when administered topically cannot be excluded^{4,12}.

Drug	Outcome	Body System	Incidence Rate (per 100 person years)
Anti-infectives			
Trimethoprim	Disorder of upper digestive tract	Gastrointestinal	8.50
Trimethoprim	Inflammatory disorder of upper respiratory tract	Pulmonary	8.23
Trimethoprim	Inflammatory disorder of digestive system	Gastrointestinal	7.94
Anti-inflammatory / corticosteroids			
Diclofenac	Disorder of upper digestive tract	Gastrointestinal	7.16
Diclofenac	Disorder of gastrointestinal tract	Gastrointestinal	6.90
Diclofenac	Gastroesophageal reflux disease without esophagitis	Gastrointestinal	6.44
Antiglaucoma / IOP-lowering			
Latanoprost	Vascular disorder	Cardiovascular	9.95
Bimatoprost	Vascular disorder	Cardiovascular	9.68
Timolol	Vascular disorder	Cardiovascular	9.57

Table 2. Top three Incidence rates of *non-ophthalmic* clinical conditions following initiation of selected topical ophthalmic drug classes, among patients in the CUIIMC database with at least one year of prior observation and no prior diagnosis of the outcome of interest. Incidence rates are expressed per 100 person-years at risk.

Conclusion

This study demonstrates the feasibility of systematically characterizing incidence rates across hundreds of ophthalmic drug-outcome combinations using real-world data mapped to the OMOP CDM. Our findings illustrate both the utility and the limitation of unadjusted incidence rates: they define an empirical upper bound on drug-attributable risk but require careful contextualization against background rates and patient characteristics before causal inference can be considered. We emphasize that these findings are exploratory and descriptive in nature and should not be used to inform or revise clinical guidelines.

Limitations include reliance on diagnostic codes for the outcomes, which may not fully capture true clinical disease' outcome granularity constraints imposed by the SNOMED hierarchy (e.g., broad categories such as "vascular disorder" dominating high-IR rankings). In addition, each drug cohort was also analyzed independently; patients initiating multiple ophthalmic drugs may contribute to more than one cohort, and drug-drug interaction effects were not evaluated. Finally, this study was restricted to a single academic medical center, which many limit generalizability.

We invite the OHDSI community to participate in a planned network replication of this study. We hope the forthcoming public-facing searchable interface will serve as a reproducible reference resource for contextualizing ophthalmologic clinical events in research and practice.

References

1. Contreras-Salinas H, Baiza-Durán LM, Bautista-Castro MA, Alonso-Rodríguez DR, Rodríguez-Herrera LY. Underreporting and Triggering Factors for Reporting ADRs of Two Ophthalmic Drugs: A Comparison between Spontaneous Reports and Active Pharmacovigilance Databases. *Healthcare*. 2022 Nov;10(11):2182. doi:10.3390/healthcare10112182
2. Urtti A, Salminen L. Minimizing systemic absorption of topically administered ophthalmic drugs. *Survey of Ophthalmology*. 1993 May 1;37(6):435–56. doi:10.1016/0039-6257(93)90141-S
3. Farkouh A, Frigo P, Czejka M. Systemic side effects of eye drops: a pharmacokinetic perspective. *Clin Ophthalmol*. 2016 Dec 7;10:2433–41. doi:10.2147/OPTH.S118409 PubMed PMID: 27994437; PubMed Central PMCID: PMC5153265.
4. Pratt NL, Ramsay EN, Kalisch Ellett LM, Nguyen TA, Roughead EE. Association between Ophthalmic Timolol and Hospitalisation for Bradycardia. *J Ophthalmol*. 2015;2015:567387. doi:10.1155/2015/567387 PubMed PMID: 25874117; PubMed Central PMCID: PMC4385589.
5. Sadiq SA, Fielding K, Vernon SA. The effect of timolol drops on respiratory function. *Eye*. 1998 May;12(3):386–9. doi:10.1038/eye.1998.91
6. Charan NB, Lakshminarayan S. Pulmonary Effects of Topical Timolol. *Arch Intern Med*. 1980 Jun 1;140(6):843–4. doi:10.1001/archinte.1980.00330180117034
7. Banerjee M, Moharana S, Padhy SK. Systemic Effects of Intravitreal Anti-VEGF Therapy: A Review of Safety across Organ Systems. *Ophthalmol Ther*. 2025 Aug;14(8):1661–84. doi:10.1007/s40123-025-01157-4 PubMed PMID: 40478389; PubMed Central PMCID: PMC12271010.
8. OMOP Common Data Model [Internet]. 2024. Available from: <https://ohdsi.github.io/CommonDataModel/>
9. Schuemie M, Reps J, Black A, Defalco F, Evans L, Fridgeirsson E, et al. Health-Analytics Data to Evidence Suite (HADES): Open-Source Software for Observational Research. *Stud Health Technol Inform*. 2024 Jan 25;310:966–70. doi:10.3233/SHTI231108 PubMed PMID: 38269952; PubMed Central PMCID: PMC10868467.

10. Sena A, Schuemie M, Gilbert J. Strategus: Coordinate and Execute OHDSI HADES Modules. [Internet]. 2025. Available from: <https://ohdsi.github.io/Strategus>
11. Rajpal RK, Ross B, Rajpal SD, Hoang K. Bromfenac ophthalmic solution for the treatment of postoperative ocular pain and inflammation: safety, efficacy, and patient adherence. *Patient Preference Adherence*. 2014;8:925–31. doi:10.2147/PPA.S46667 PubMed PMID: 25028541; PubMed Central PMCID: PMC4077855.
12. Volotinen M, Hakkola J, Pelkonen O, Vapaatalo H, Mäenpää J. Metabolism of Ophthalmic Timolol: New Aspects of an Old Drug. *Basic & Clinical Pharmacology & Toxicology*. 2011;108(5):297–303. doi:10.1111/j.1742-7843.2011.00694.x