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Differential Effect of Glaucoma Medications on Dry Eye Incidence

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Background

Dry eye is the most common ocular disease complicating the management of glaucoma.

Proposed causal mechanisms: Ocular surface toxicity due to ophthalmic preservatives (e.g. BAK), specific drug exposures, or multiple drug exposures

Purpose

Problem: The relative incidence of dry eye with various glaucoma medications is poorly characterized.

Hypothesis: Glaucoma medications differentially affect dry eye incidence.

Question: Using a large historical dataset, can one estimate the relative risk of incident dry eye to commonly used topical glaucoma medications?

Methods

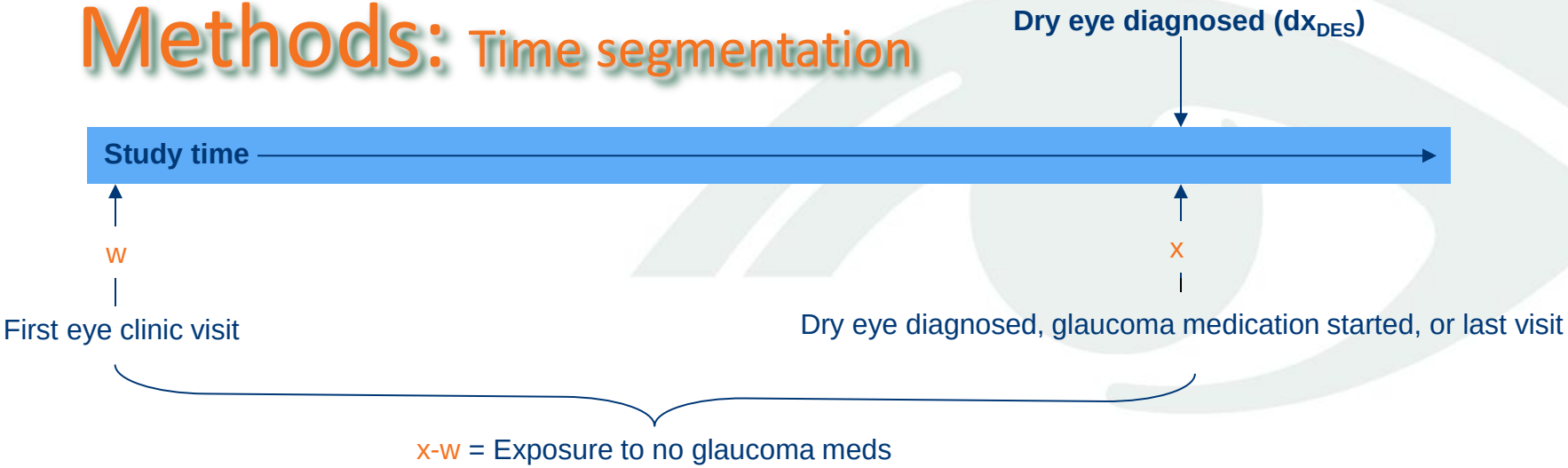
Design: Retrospective cohort study utilizing coding and pharmacy data from the Veterans Affairs (VA) National Patient Database

Population: 2.5% random sample (N=55,935) of patients seen in VA eye clinics (N=2,203,986) nationally over a 13 year period (1999-2012)

Statistics: Life table analysis was used to estimate the incidence of dry eye in patients with and without exposure to glaucoma medications.

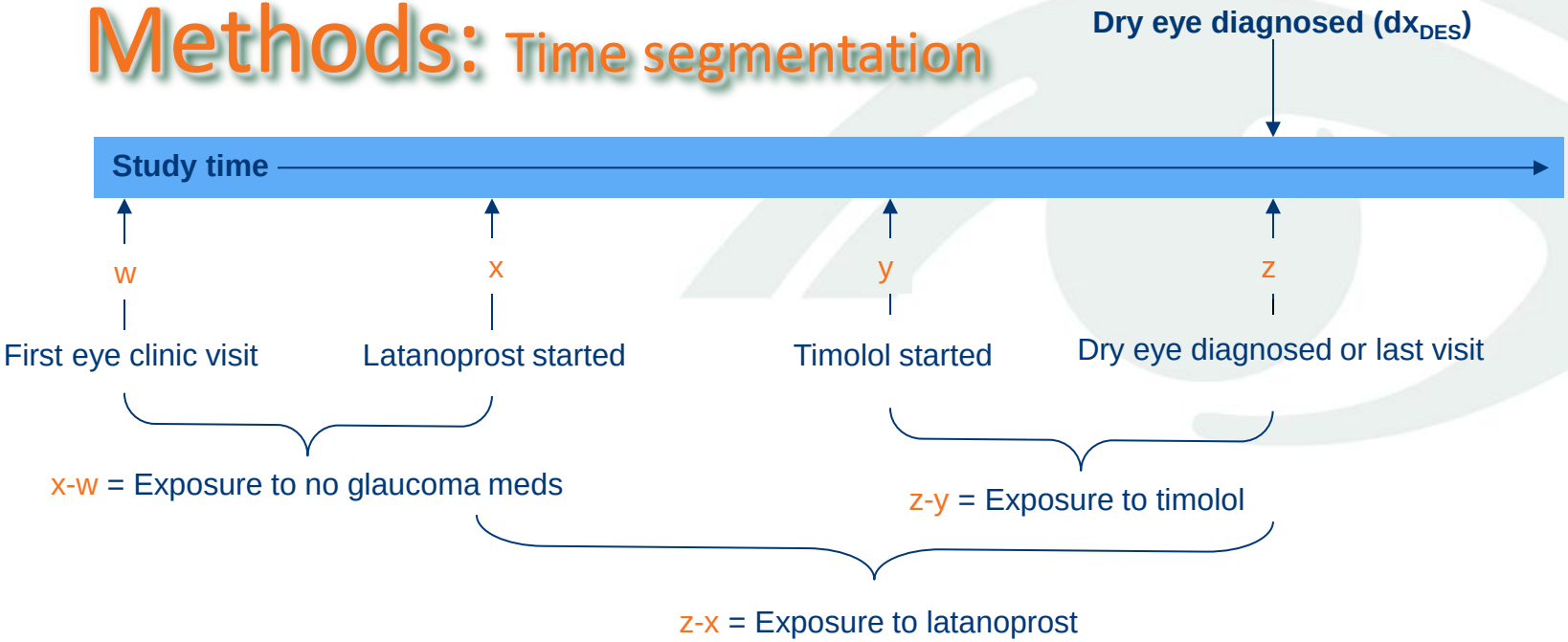
Time-dependent Cox proportional hazards regression was used to model the effect of exposure to glaucoma medications on dry eye incidence.

Methods: Time segmentation



$$\text{Absolute Risk}_{\text{no exposure}} = \text{Prob}(dx_{DES})^{x-w}$$

Methods: Time segmentation



$$\text{Risk Ratio}_{\text{timolol}} = \text{Prob}(dx_{DES})^{z-y} / \text{Prob}(dx_{DES})^{x-w}$$

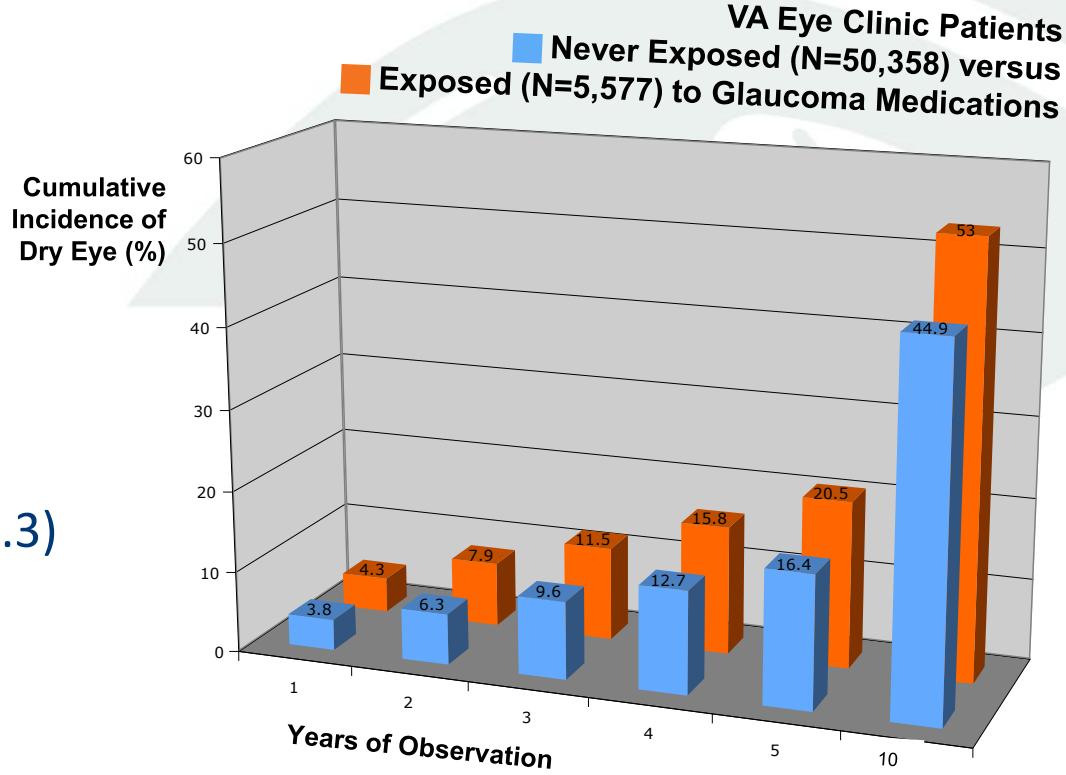
Results:

Life Table Analysis

Exposure to glaucoma medications increased the risk of incident dry eye

Relative Risk: 1.26 (CI 1.2-1.3)

Significance: p<0.001



Results: Cox Proportional Hazards Regression

Risk Factor	Risk Ratio (CI)	P-value
Female gender	1.63 (1.52 – 1.74)	<0.001
Decade of age	1.09 (1.07 – 1.12)	<0.001
Beta-blocker	1.01 (0.90 – 1.13)	0.94
Brimonidine	1.31 (1.19 – 1.43)	<0.001
CAI (topical)	1.21 (1.10 – 1.32)	<0.001
CAI (systemic)	1.56 (1.13 – 2.17)	0.008
Dorzolamide/timolol	1.23 (1.10 – 1.36)	<0.001
Latanoprost	0.96 (0.86 – 1.08)	0.96
Travoprost	1.24 (1.16 – 1.33)	<0.001
Travoprost-Z	1.47 (1.34 – 1.60)	<0.001

Exposure to 6 out of 8 individual glaucoma medications conferred significantly increased risk of developing dry eye.

Discussion

Question: Are the differential effects of individual medication exposures mediated by the medications themselves, or by other mediating or confounding variables?

A. Why were beta-blockers and latanoprost not significantly associated with incident dry eye?

B. Why were systemic CAIs and travoprost-Z more strongly associated with incident dry eye than other medications?

Discussion

Possible mediating variables:

1. BAK exposure varies by agent and dosing schedule
2. Effect of medication order in escalation of medical therapy

   E.g. Patients on travoprost-Z were more likely to be on multiple agents than those on beta-blockers or latanoprost (100% vs. 82%, vs. 92%, $p<0.001$ by χ^2). It is possible that the effect of travoprost-Z exposure is mediated in part by the number of other agents the patient is on.

Future directions: Cox regression analysis controlling for cumulative daily BAK exposure and number of glaucoma medications.

Conclusions

Exposure to one or more glaucoma medication as well as 6 out of 8 individual medications demonstrated a significant effect on the incidence of dry eye, with risk ratios ranging from 1.21-1.56 ($p<0.008$).

Because glaucoma medications were not randomly assigned, we cannot exclude the possibility that mediating and confounding variables may, in part, account for the results.

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