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Evaluation of a Primary Open-Angle Glaucoma Prediction Model Using Long-term Intraocular Pressure Variability Data

A Secondary Analysis of 2 Randomized Clinical Trials

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IMPORTANCE The contribution of long-term intraocular pressure (IOP) variability to the development of primary open-angle glaucoma is still controversial.

OBJECTIVE To assess whether long-term IOP variability data improve a prediction model for the development of primary open-angle glaucoma (POAG) in individuals with untreated ocular hypertension.

DESIGN, SETTING, AND PARTICIPANTS This post hoc secondary analysis of 2 randomized clinical trials included data from 709 of 819 participants in the observation group of the Ocular Hypertension Treatment Study (OHTS) followed up from February 28, 1994, to June 1, 2002, and 397 of 500 participants in the placebo group of the European Glaucoma Prevention Study (EGPS) followed up from January 1, 1997, to September 30, 2003. Data analyses were completed between January 1, 2019, and March 15, 2020.

EXPOSURES The original prediction model for the development of POAG included the following baseline factors: age, IOP, central corneal thickness, vertical cup-disc ratio, and pattern SD. This analysis tested whether substitution of baseline IOP with mean follow-up IOP, SD of IOP, maximum IOP, range of IOP, or coefficient of variation IOP would improve predictive accuracy.

MAIN OUTCOMES AND MEASURES The C statistic was used to compare the predictive accuracy of multivariable landmark Cox proportional hazards regression models for the development of POAG.

RESULTS Data from the OHTS consisted of 97 POAG end points from 709 of 819 participants (416 [58.7%] women; 177 [25.0%] African American and 490 [69.1%] white; mean [SD] age, 55.7 [9.59] years; median [range] follow-up, 6.9 [0.96-8.15] years). Data from the EGPS consisted of 44 POAG end points from 397 of 500 participants in the placebo group (201 [50.1%] women; 397 [100%] white; mean [SD] age, 57.8 [9.76] years; median [range] follow-up, 4.9 [1.45-5.76] years). The C statistic for the original prediction model was 0.741. When a measure of follow-up IOP was substituted for baseline IOP in this prediction model, the C statistics were as follows: mean follow-up IOP, 0.784; maximum IOP, 0.781; SD of IOP, 0.745; range of IOP, 0.741; and coefficient of variation IOP, 0.729. The C statistics in the EGPS were similarly ordered. No measure of IOP variability, when added to the prediction model that included mean follow-up IOP, age, central corneal thickness, vertical cup-disc ratio, and pattern SD, increased the C statistic by more than 0.007 in either cohort.

CONCLUSIONS AND RELEVANCE Evidence from the OHTS and the EGPS suggests that long-term variability does not add substantial explanatory power to the prediction model as to which individuals with untreated ocular hypertension will develop POAG.

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Author Audio Interview

Supplemental content

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Higher intraocular pressure (IOP) is an important risk factor for the development and progression of glaucoma and currently the only modifiable factor.[1-5] However, mean follow-up IOP does not capture the dynamic changes in pressure from visit to visit, such as peaks, troughs, and ranges that may be independently associated with the development and course of the disease.

Controversy still exists about the effects of long-term variability of IOP. Some studies[6-13] have found that variability is an independent risk factor for glaucoma development or progression beyond the mean follow-up IOP, whereas other studies[2,14-16] have not. This controversy may reflect objective differences in the studies, including diagnosis (ocular hypertension, normal-tension glaucoma, or high-tension glaucoma), the range of IOP in the patients, the duration of follow-up and frequency of pressure measurements, the method of tonometry, and whether the patients received medical or surgical therapy. Patients with worsening primary open-angle glaucoma (POAG) or IOP above a therapeutic goal may undergo multiple changes in treatment, which may confound the association between disease course and IOP variability. In addition, poor adherence and persistence with medication or poor tolerance of medication may be associated with IOP variability and disease progression. Data were previously analyzed on long-term IOP variability in the entire Ocular Hypertension Treatment Study (OHTS) and European Glaucoma Prevention Study (EGPS) cohorts.[17] In view of the continuing controversy about the effects of long-term IOP variability and because practitioners are uncertain about how to integrate these measures into clinical care, we evaluated this topic again. To reduce the influence of potential confounding factors and to assess the association of long-term IOP variability with the incidence of POAG in patients with ocular hypertension, we restricted the analysis sample to include only participants enrolled in the observation group of the OHTS and the placebo group of the EGPS. To test reproducibility of results from OHTS, data from EGPS were analyzed separately and reported separately.

Key Points

Question Do long-term intraocular pressure variability data improve a prediction model for which individuals with untreated ocular hypertension will develop primary open-angle glaucoma?

Findings In this post hoc secondary analysis of 2 randomized clinical trials that included 709 individuals, the mean follow-up intraocular pressure improved a prediction model for developing primary open-angle glaucoma that included the following baseline factors: age, central corneal thickness, vertical cup-disc ratio, and pattern SD. Adding intraocular pressure SD, maximum, range, or coefficient of variation to a model that included mean follow-up intraocular pressure and baseline factors did not significantly increase predictive accuracy.

Meaning These findings suggest that the inclusion of data on long-term intraocular pressure variability are unlikely to improve prediction models for the development of primary open-angle glaucoma in individuals with untreated ocular hypertension.

Methods

This post hoc secondary analysis of 2 randomized clinical trials used data from the OHTS and EGPS. The OHTS[2,18] and the EGPS[19] were randomized clinical trials that tested the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the development of POAG in individuals with ocular hypertension. The OHTS and the EGPS protocols are described in their respective baseline design articles[18,19] but are briefly described here. The protocols of the OHTS and EGPS were approved by the institutional review boards of each participating clinic and resource center. Each participant provided written informed consent. All data were deidentified.

In the OHTS phase 1, participants were randomized in equal proportions to receive topical ocular hypotensive medication or close observation. The participants were randomized to observation on February 28, 1994, and followed up to the end of phase 1 on June 1, 2002, and had at least 2 postrandomization visits and complete data for baseline factors (age, IOP, central corneal thickness [CCT], pattern SD [PSD], and vertical cup-disc ratio [VCDR]). In the EGPS, participants were randomized to receive dorzolamide or placebo drops. The EGPS participants were randomized to placebo on January 1, 1997, and followed up to September 30, 2003; these individuals had at least 2 follow-up visits after the 6-month surrogate baseline and complete data for baseline predictors. Key similarities between the studies were (1) similar inclusion and exclusion criteria; (2) IOP measurements by Goldmann tonometry using the Advanced Glaucoma Intervention Study (AGIS) protocol[20]; (3) follow-up visits at 6-month intervals for 5 years or until a censoring event; (4) masked determination and reproducibility of optic nerve deterioration and/or visual field abnormality; and (5) masked end point committee to determine whether reproducible optic nerve deterioration and/or visual field abnormality were cause by POAG.

In the OHTS and EGPS, the end point date for POAG was defined as the date of the first abnormal visual field or optic disc photograph that masked readers determined met the criteria for reproducible change and the end point committee attributed to POAG. The protocol for ascertainment of POAG end points is described in detail elsewhere.[21] Data were censored after POAG diagnosis or after initiation of ocular hypotensive treatment.

Measures of IOP

In the OHTS and EGPS, IOP was assessed every 6 months by Goldmann applanation tonometry using the AGIS protocol.[20] We calculated the following measures of follow-up IOP: (1) mean follow-up IOP, (2) SD IOP, (3) maximum IOP, (4) range of IOP, and (5) coefficient of variation (CV) IOP (SD IOP divided by mean follow-up IOP).

Statistical Analysis

We used an adaptation of conventional Cox proportional hazards regression modeling (ie, landmark analysis)[22] because conventional Cox proportional hazards regression modeling does not permit calculation of predictive accuracy (C statistic) with

time-dependent covariates.[23] Previous studies[16,24] have calculated measures of long-term IOP variability by aggregating all IOPs from baseline to a censoring event or end of follow-up. Aggregate measures do not capture time-dependent changes and differences in duration of follow-up. In a landmark analysis, conventional Cox proportional hazards regression models are recalculated at prespecified time points (landmark point) using participants still at risk of developing an end point. Time-dependent covariates (eg, measures of IOP variability) are refreshed with all IOPs from baseline to the landmark point. Van Houwelingen et al[22] found that the time-dependent effects can be well approximated with this approach. A landmark analysis enables the application of a wealth of theory developed for conventional Cox proportional hazards regression models to calculate predictive accuracy (C statistic) and graphic tools, such as Kaplan-Meier estimates.

A minimum of 5 to 10 future end points are needed per covariate for a reliable prediction model.[25] Thus, with as many as 6 factors in a multivariable model (mean follow-up IOP and a measure of IOP variability plus 4 factors from the original baseline model: age, CCT, VCDR, and PSD), landmark models could be fit when at least 30 future POAG conversions were available. In the OHTS, 9 landmark analyses were possible at 12 months with 97 end points in the future and so forth until the last analysis at 60 months with 38 end points in the future. In the EGPS, 3 landmark analyses were possible at 18 months with 44 end points, 24 months with 34 end points, and 30 months with 30 end points in the future. At each landmark point, Cox proportional hazards regression models were run for each measure of follow-up IOP as follows. First, we ran univariate models to estimate the contribution of each measure of follow-up IOP with no adjustment for baseline factors. Second, we substituted a measure of follow-up IOP for baseline IOP in the original prediction model that included baseline age, CCT, VCDR, and PSD. Third, we added a measure of IOP variability (SD IOP, maximum IOP, range of IOP, or CV IOP) to a model that included mean follow-up IOP, baseline age, CCT, VCDR, and PSD. Time zero was reset at each landmark point.

At each landmark point, predictive accuracy (C statistic) and hazard ratios (HRs) were calculated for each Cox proportional hazards regression model. The C statistics across landmark points of each model were averaged to estimate predictive accuracy over the entire follow-up period. The mean HRs across the landmark points were estimated using Cox proportional hazards regression models stratified by landmark points, and 95% CIs were obtained based on the robust sandwich variance. The homogeneity of the HRs across strata was assessed by testing the interaction term between landmark points and each IOP measure in the Cox proportional hazards regression model. To enable comparisons of HRs among different variables and models and across the OHTS and EGPS studies, IOP measures were standardized by scaling them to the SD of the variable in the OHTS data (ie, 3 mm Hg for mean IOP, 1 mm Hg for SD IOP, 4 mm Hg for maximum IOP, 3.5 mm Hg for range IOP, and 0.05 for CV IOP). All analyses were 2-sided, and statistical significance was set at $P < .05$. Statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc) and the survival library in the statistical package R (R Foundation for Statistical Computing). The rationale for a landmark rather than conventional multivariable Cox proportional hazards regression models is provided in the eAppendix in the Supplement. Conventional Cox proportional hazards regression modeling was also performed, and these results compared with those form the landmark analyses are given in in eTable 1 in the Supplement. Data analyses were completed between January 1, 2019, and March 15, 2020.

Results

Data from the OHTS consisted of 97 POAG end points from 709 of 819 participants (416 [58.7%] women; 177 [25.0%] African American and 490 [69.1%] white; mean [SD] age, 55.7 [9.59] years; median [range] follow-up, 6.9 [0.96-8.15] years). Data from the EGPS consisted of 44 POAG end points from 397 of 500 placebo participants (201 [50.1%] women; 397 [100%] white; mean [SD] age, 57.8 [9.76] years; median [range] follow-up, 4.9 [1.45-5.76] years). Descriptive statistics for demographic, baseline, and follow-up measures in the OHTS and EGPS are reported in **Table 1**. The OHTS participants had a median of 14 IOP measurements (range, 3-17) and a median follow-up of 6.9 years (range, 1.0-8.1 years). The EGPS participants had a median of 10 IOP measurements (range, 3-10) with a median follow-up of 4.9 years (range, 1.5-5.8 years).

In the OHTS, the highest correlations (Pearson correlation coefficient) were among measure of follow-up IOP variability (SD IOP, range of IOP, and CV IOP), which ranged from 0.868 to 0.917. Maximum IOP was moderately correlated with other measures of IOP variability (Pearson correlation coefficient range, 0.325-0.640) and highly correlated with mean follow-up IOP (Pearson correlation coefficient, 0.852). Mean follow-up IOP was modestly correlated with other measures of IOP variability with correlations from −0.119 to 0.256 (eTable 2 in the Supplement). The correlational structure among measures of follow-up IOP in the EGPS closely resembled those of the OHTS (eTable 3 in the Supplement).

Results from the univariate landmark Cox proportional hazards regression models are reported in **Table 2**. In the OHTS, all measures of follow-up IOP (mean follow-up IOP: HR, 2.03; 95% CI, 1.68-2.46; SD IOP: HR, 1.29; 95% CI, 1.14-1.46; maximum IOP: HR, 1.93; 95% CI, 1.64-2.26; and range of IOP: HR, 1.40; 95% CI, 1.18-1.66), except CV IOP (HR, 1.14; 95% CI, 0.96-1.36), were statistically significant in univariate models, which did not include baseline factors (Table 2). The largest differences in measures of follow-up IOP between participants who did not develop POAG and those who developed POAG were in mean follow-up IOP (HR, 2.03; 95% CI, 1.68-2.46) and maximum IOP (HR, 1.93; 95% CI, 1.64-2.26) (Table 2). Univariate models with the highest C statistics were for mean follow-up IOP (C statistic, 0.705) and maximum IOP (C statistic, 0.707) (Table 2). Similarly, in the EGPS, the greatest difference between participants who did not develop POAG and those who did was in mean follow-up IOP (HR, 1.58; 95% CI, 1.18-2.12) and maximum IOP (HR, 1.66; 95% CI, 1.21-2.21). C statistics were

Table 1. Demographic and Clinical Characteristics at Baseline and Follow-up in the OHTS Observation Group and the EGPS Placebo Group by POAG Status

Characteristic	Patients by POAG status			
	OHTS observation group (n = 709)		EGPS placebo group (n = 397)	
	No (n = 612)	Yes (n = 97)	No (n = 353)	Yes (n = 44)
Demographic characteristics, No. (%)				
Sex				
Female	368 (88.5)	48 (11.5)	177 (88.1)	24 (11.9)
Male	244 (82.3)	49 (16.7)	176 (89.8)	20 (10.2)
Race/ethnicity				
American Indian or Alaskan Native	1 (50.0)	1 (50.0)	0	0
Asian or Pacific Islander	7 (87.5)	1 (12.5)	0	0
Black, not Hispanic	147 (83.0)	30 (17.0)	0	0
Hispanic	19 (73.1)	7 (26.9)	0	0
White	433 (88.4)	57 (11.6)	353 (88.9)	44 (11.1)
Other	5 (83.3)	1 (16.7)	0	0
Clinical characteristics, mean (SD)				
Baseline				
Age, y	55.3 (9.6)	58.1 (9.1)	57.2 (9.8)	62.3 (8.7)
IOP, mm Hg	24.8 (2.9)	26.2 (3.1)	23.4 (1.6)	23.7 (2.0)
Central corneal thickness, μm	578.2 (37.1)	550.9 (37.1)	575.1 (34.6)	554.2 (37.7)
Vertical cup-disc ratio	0.38 (0.20)	0.49 (0.18)	0.31 (0.14)	0.36 (0.14)
Pattern SD, dB	1.9 (0.2)	2.0 (0.3)	2.0 (0.6)	2.1 (0.5)
Follow-up				
IOP, mm Hg				
Mean follow-up	23.8 (3.0)	27.1 (3.1)	20.1 (2.5)	21.7 (3.4)
SD	2.5 (1.0)	3.0 (1.5)	2.2 (0.9)	2.3 (1.0)
Maximum	28.1 (3.8)	31.4 (4.6)	23.4 (3.1)	24.7 (3.9)
Range	8.4 (3.3)	8.7 (4.4)	6.4 (2.7)	5.9 (2.8)
Coefficient of variation	0.11 (0.04)	0.11 (0.05)	0.11 (0.05)	0.11 (0.05)

Abbreviations: EGPS, European Glaucoma Prevention Study; IOP, intraocular pressure; OHTS, Ocular Hypertension Treatment Study; POAG, primary open-angle glaucoma.

Table 2. Univariate HRs (95% CIs) and C Statistics From Landmark Cox Proportional Hazards Regression Models for the OHTS Observation Group and the EGPS Placebo Group

Variable	OHTS observation group		EGPS placebo group	
	HR (95% CI)	C statistic	HR (95% CI)	C statistic
Baseline IOP per 3 mm Hg	1.58 (1.29-1.92)	0.634	1.32 (0.98-1.78)	0.563
Mean follow-up IOP per 3 mm Hg	2.03 (1.68-2.46)	0.705	1.58 (1.18-2.12)	0.622
SD IOP per 1 mm Hg	1.29 (1.14-1.46)	0.608	1.17 (0.91-1.51)	0.552
Maximum IOP per 4 mm Hg	1.93 (1.64-2.26)	0.707	1.66 (1.21-2.28)	0.622
Range IOP per 3.5 mm Hg	1.40 (1.18-1.66)	0.604	1.30 (0.86-1.97)	0.556
CV IOP per 0.05 mm Hg	1.14 (0.96-1.36)	0.559	1.04 (0.79-1.37)	0.523

Abbreviations: CV, coefficient of variation; EGPS, European Glaucoma Prevention Study; HR, hazard ratio; IOP, intraocular pressure; OHTS, Ocular Hypertension Treatment Study.

0.622 for both measures in univariate models. SD IOP (HR, 1.17; 95% CI, 0.91-1.51), range of IOP (HR, 1.30; 95% CI, 0.86-1.97), and CV IOP (HR, 1.04; 95% CI, 0.79-1.37) were not statistically significant and had C statistics of 0.552 (SD IOP), 0.556 (range of IOP), and 0.523 (CV IOP).

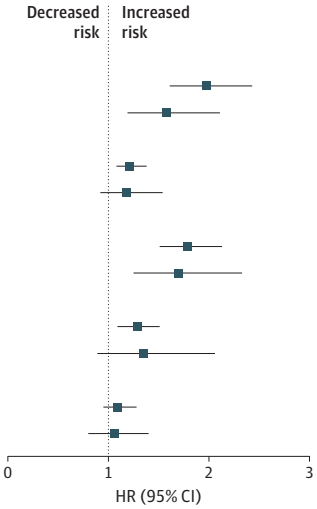
We examined whether the predictive accuracy of the original prediction model that included baseline age, IOP, CCT, VCDR, and PSD could be improved by substituting baseline IOP with a measure of follow-up IOP. The predictive accuracy of the original model as measured by the C statistic was 0.741, in which a C statistic of 0.50 indicates random accuracy and 1.00 indicates perfect accuracy. When baseline IOP was substituted by mean follow-up IOP, the C statistic for the model increased to 0.784 and 0.781 when baseline IOP was substituted by maximum IOP. The C statistic for the model with SD IOP (C statistic, 0.745) showed an improvement, but substituting baseline IOP with either range of IOP (C statistic, 0.741) or CV IOP (C statistic, 0.729) did not improve the C statistic. In the EGPS, the C statistic for the original prediction model with baseline IOP, age, CCT, VCDR, and PSD was 0.723, which did not increase when baseline IOP was substituted by mean follow-up IOP (C statistic, 0.710), SD IOP (C statistic, 0.694), maximum IOP (C statistic, 0.706), range of IOP (C statistic, 0.694), or CV IOP (C statistic, 0.694) (**Figure**, A).

To assess whether any measure of IOP variability could improve the predictive accuracy of a model that included mean

Figure. Forest Plots for Follow-up Intraocular Pressure (IOP) Measures From Landmark Cox Proportional Hazards Regression Models of the Ocular Hypertension Treatment Study (OHTS) Observation Group and the European Glaucoma Prevention Study (EGPS) Placebo Group

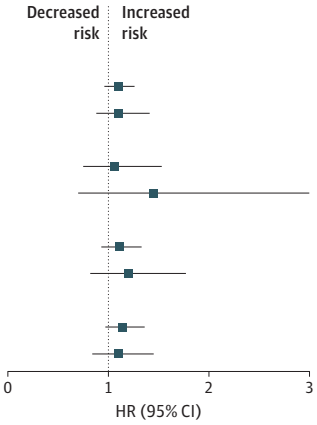
A Follow-up IOP measures

Variable	HR (95% CI)	C-statistic
Mean follow-up IOP		
OHTS	1.98 (1.61-2.43)	0.784
EGPS	1.59 (1.19-2.11)	0.710
SD IOP		
OHTS	1.22 (1.08-1.38)	0.745
EGPS	1.19 (0.92-1.54)	0.694
Maximum IOP		
OHTS	1.79 (1.51-2.13)	0.781
EGPS	1.70 (1.25-2.33)	0.706
Range IOP		
OHTS	1.29 (1.09-1.51)	0.741
EGPS	1.35 (0.89-2.06)	0.694
CV IOP		
OHTS	1.10 (0.95-1.28)	0.729
EGPS	1.06 (0.80-1.40)	0.694



B Long-term IOP variability

Variable	HR (95% CI)	C-statistic
SD IOP		
OHTS	1.10 (0.96-1.26)	0.791
EGPS	1.11 (0.88-1.41)	0.708
Maximum IOP		
OHTS	1.07 (0.75-1.53)	0.785
EGPS	1.45 (0.70-3.02)	0.709
Range IOP		
OHTS	1.11 (0.93-1.33)	0.789
EGPS	1.20 (0.82-1.77)	0.708
CV IOP		
OHTS	1.15 (0.97-1.36)	0.791
EGPS	1.11 (0.84-1.45)	0.710



A, Forest plot of models that substitute a measure of follow-up IOP for baseline IOP in the model that includes baseline age, central cornea thickness (CCT), vertical cup-disc ratio (VCDR), and pattern SD (PSD). B, Forest plot of models that add a measure of long-term IOP variability to a model that includes mean follow-up IOP, baseline age, CCT, VCDR, and PSD. For the hazard ratios (HRs), approximately 1-SD change in the OHTS observation group data occurred as follows: mean IOP, 3 mm Hg; SD IOP, 1 mm Hg; maximum IOP, 4 mm Hg; range of IOP, 3.5 mm Hg; and coefficient of variation (CV) IOP, 0.05 mm Hg. The 95% CIs that include 1.0 are not statistically significant at $P < .05$.

follow-up IOP and baseline factors (age, CCT, VCDR, and PSD), we added measures of IOP variability to the model 1 at time (SD IOP, maximum IOP, range of IOP, or CV IOP). In the OHTS, no measure of IOP variability when added to this model was statistically significant (Figure, B): SD IOP (HR, 1.10; 95% CI, 0.96-1.26), maximum IOP (HR, 1.07; 95% CI, 0.75-1.53), range of IOP (HR, 1.11; 95% CI 0.93-1.33), and CV IOP (HR, 1.15; 95% CI, 0.97-1.36). Furthermore, adding a measure of IOP variability to the baseline model that included mean follow-up IOP did not meaningfully increase the C statistic (0.784). C statistics were 0.791 for SD IOP, 0.785 for maximum IOP, 0.789 for range of IOP, and 0.791 for CV IOP. The largest increase in the C statistic from adding IOP variability to the model was only 0.007 (Figure, B). Results in the EGPS were comparable to those of the OHTS. In the EGPS, no measure of IOP variability was statistically significant when added to the model that included mean follow-up IOP and baseline factors (SD IOP: HR, 1.11; 95% CI, 0.88-1.41; maximum IOP: HR, 1.45; 95% CI, 0.70-3.02; range of IOP: HR, 1.20; 95% CI, 0.82-1.77; and CV IOP: HR, 1.11; 95% CI, 0.84-1.45). Nor did the C statistic of 0.710 for the model with mean follow-up IOP and baseline factors increase with the addition of SD IOP (C statistic, 0.708), maximum IOP (C statistic, 0.709), range of IOP (C statistic, 0.708), or CV IOP (C statistic, 0.710) (Figure, B). None of the interactions between mean follow-up IOP and measures of IOP variability were statistically significant in the OHTS or EGPS.

Discussion

Because IOP is currently the only modifiable risk factor for glaucoma, understanding how dynamic variation in IOP is associated with onset and progression of the disease may play a crucial role in management. The OHTS[26] previously reported that a baseline model that included age, IOP, CCT, VCDR, and PSD was useful in identifying which participants with ocular hy-

pertension were at higher risk for developing POAG. This baseline model was confirmed in the EGPS[27] and by Medeiros et al.[28] In this study, we examined whether predictive accuracy could be improved by adding mean follow-up IOP and measures of long-term IOP variability to the baseline prediction model. This question was tested using data from patients with ocular hypertension not receiving active treatment to avoid possible confounding owing to treatment changes, medication intolerance, and/or medication adherence and persistence that could be associated with increased IOP variability and the risk of POAG. Previous reports[29,30] from the OHTS and EGPS on the association between IOP variability and risk of developing POAG pooled treated and untreated participants, possibly obscuring the true association between IOP variability and risk of developing glaucoma. Because of the continuing controversy about IOP variability and disease progression, we reanalyzed data using only participants in the OHTS observation group and the EGPS placebo group.

In the OHTS, all measures of follow-up IOP (mean follow-up IOP, SD IOP, maximum IOP, and range of IOP) except CV IOP were moderately predictive of POAG in univariate landmark Cox proportional hazards regression models, with C statistics ranging from 0.604 to 0.707. The highest C statistics were observed for mean follow-up IOP (C statistic, 0.705) and maximum IOP (C statistic, 0.707) owing largely to their high intercorrelation of 0.852. The C statistic for the original prediction model (0.741), which included baseline age, IOP, CCT, VCDR, and PSD, increased to 0.784 when baseline IOP was substituted with mean follow-up IOP and 0.781 when substituted with maximum IOP. None of the other measures of follow-up IOP performed as well. We then assessed whether predictive accuracy could be improved by adding a measure of long-term IOP variability to a model that included mean follow-up IOP and baseline factors. In these models, none of the measures of long-term IOP variability were statistically significant, and their addition to the model did not meaningfully improve the C statistic. The largest improvement in the C statistic was 0.007. These results were replicated in the EGPS cohort.

We analyzed data using a landmark analysis adaptation of the Cox proportional hazards regression model, which has been used widely in many other fields of medicine to incorporate time-varying covariates.[31] In landmark analysis, conventional Cox proportional hazards regression models are run at each landmark point as time 0, thus adjusting for time-dependent covariates and variable duration of follow-up and enabling the calculation of predictive accuracy (C statistic). In contrast, conventional Cox proportional hazards regression models use all data accrued up to a censoring event, thereby failing to take into account that affected individuals have a shorter follow-up than unaffected individuals because of censoring. Because factors such as maximum IOP and IOP range are sensitive to the number of IOP measurements, conventional Cox proportional hazards regression models can lead to a paradoxical result (ie, higher maximum IOP and greater IOP range can appear to be protective of POAG). This statistical paradox is shown using the OHTS data in eTable 1 in the Supplement.

Our analyses suggest that IOP variability does not substantially add to the prediction model as to which patients with ocular hypertension will develop POAG. Mean follow-up IOP was a stronger predictive factor than any measure of long-term IOP variability in the prediction model. In addition, mean follow-up IOP is easy to calculate, more consistent over time, and less dependent on duration of follow-up. The results of this report agree with those reported by the Diagnostic Innovations in Glaucoma Study,[16] which also found no association between long-term IOP variability and the development of POAG in 126 individuals with untreated ocular hypertension. In contrast, the population-based Los Angeles Latino Eye Study[32] reported an association of higher IOP variability (maximum IOP, range IOP, and SD IOP) with the risk of POAG in untreated individuals for whom IOP variability was calculated from 3 IOP measurements at baseline and 3 IOP measurements 5 years later. This association between greater IOP variability and development of POAG was statistically significant only in the patients in the lowest tertile of IOP. A recent review[33] concluded that the association of IOP variability with development of POAG was strongest among treated patients with low mean levels of IOP.

Limitations

This report has several limitations, and the results must be interpreted cautiously. The OHTS and EGPS were limited to participants with ocular hypertension with baseline IOPS in the range of 21 to 32 mm Hg. Furthermore, the OHTS and EGPS participants were receiving no active ocular hypotensive therapy. Thus, these results should be not be extrapolated to patients with lower levels of IOP, treated patients, or patients with glaucoma. Both the OHTS and EGPS used the AGIS protocol for measuring IOP, which is more extensive and standardized than is typical in many clinical settings.[20] The IOP measurements were taken during typical office hours and did not include diurnal or nocturnal measurements.

Conclusions

In this study, mean follow-up IOP improved a prediction model for developing POAG that included the following baseline factors: age, CCT, VCDR, and PSD. Adding SD IOP, maximum, range, or coefficient of variation to a model that included mean follow-up IOP and baseline factors did not significantly increase predictive accuracy. These findings suggest that the inclusion of data on long-term IOP variability are unlikely to improve prediction models for the development of POAG in individuals with untreated ocular hypertension.

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REFERENCES

1. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E; Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol*. 2003;121(1):48-56. doi:10.1001/archopht.121.1.48

2. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120(6):701-713. doi:10.1001/archopht.120.6.701

3. Lichter PR, Musch DC, Gillespie BW, et al; CIGTS Study Group. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. 2001;108(11):1943-1953. doi:10.1016/S0161-6420(01)00873-9

4. Van Veldhuisen PC, Ederer F, Gaasterland DE, et al; The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS), 7: the relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol*. 2000;130(4):429-440. doi:10.1016/S0002-9394(00)00538-9

5. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol*. 1998;126(4):498-505. doi:10.1016/S0002-9394(98)00272-4

6. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al; Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology*. 2004;111(9):1627-1635. doi:10.1016/j.ophtha.2004.02.017

7. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. *Ophthalmology*. 2008;115(7):1123-1129.e3. doi:10.1016/j.ophtha.2007.10.031

8. Musch DC, Gillespie BW, Lichter PR, Niziol LM, Janz NK; CIGTS Study Investigators. Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. *Ophthalmology*. 2009;116(2):200-207. doi:10.1016/j.ophtha.2008.08.051

9. Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R; CIGTS Study Group. Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology*. 2011;118(9):1766-1773. doi:10.1016/j.ophtha.2011.01.047

10. Fujino Y, Asaoka R, Murata H, et al; Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG) Construction Group. Evaluation of glaucoma progression in large-scale clinical data: the Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG). *Invest Ophthalmol Vis Sci*. 2016;57(4):2012-2020. doi:10.1167/iovs.15-19046

11. Stewart WC, Kolker AE, Sharpe ED, et al. Factors associated with long-term progression or stability in primary open-angle glaucoma. *Am J Ophthalmol*. 2000;130(3):274-279. doi:10.1016/S0002-9394(00)00487-6

12. Hong S, Seong GJ, Hong YJ. Long-term intraocular pressure fluctuation and progressive visual field deterioration in patients with glaucoma and low intraocular pressures after a triple procedure. *Arch Ophthalmol*. 2007;125(8):1010-1013. doi:10.1001/archopht.125.8.1010

13. Lee PP, Walt JW, Rosenblatt LC, Siegartel LR, Stern LS; Glaucoma Care Study Group. Association between intraocular pressure variation and glaucoma progression: data from a United States chart review. *Am J Ophthalmol*. 2007;144(6):901-907. doi:10.1016/j.ajo.2007.07.040

14. Bengtsson B, Leske MC, Hyman L, Heijl A; Early Manifest Glaucoma Trial Group. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114(2):205-209. doi:10.1016/j.ophtha.2006.07.060

15. De Moraes CG, Juthani VJ, Liebmann JM, et al. Risk factors for visual field progression in treated glaucoma. *Arch Ophthalmol*. 2011;129(5):562-568. doi:10.1001/archophthalmol.2011.72

16. Medeiros FA, Weinreb RN, Zangwill LM, et al. Long-term intraocular pressure fluctuations and risk of conversion from ocular hypertension to glaucoma. *Ophthalmology*. 2008;115(6):934-940. doi:10.1016/j.ophtha.2007.08.012

17. Gordon MO, Torri V, Miglior S, et al; Ocular Hypertension Treatment Study Group; European Glaucoma Prevention Study Group. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology*. 2007;114(1):10-19. doi:10.1016/j.ophtha.2006.08.031

18. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol*. 1999;117(5):573-583. doi:10.1001/archopht.117.5.573

19. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I; European Glaucoma Prevention Study Group. The European glaucoma prevention study design and baseline description of the participants. *Ophthalmology*. 2002;109(9):1612-1621. doi:10.1016/S0161-6420(02)01167-3

20. Ederer F, Gaasterland DE, Sullivan EK; AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS), 1: study design and methods and baseline characteristics of study

patients. *Control Clin Trials*. 1994;15(4):299-325. doi:10.1016/0197-2456(94)90046-9

21. Gordon MO, Higginbotham EJ, Heuer DK, et al; Ocular Hypertension Treatment Study. Assessment of the impact of an endpoint committee in the Ocular Hypertension Treatment Study. *Am J Ophthalmol*. 2019;199:193-199. doi:10.1016/j.ajo.2018.11.006

22. van Houwelingen HC. Dynamic prediction by landmarking in event history analysis. *Scand J Stat*. 2007;34(1):70-85. doi:10.1111/j.1467-9469.2006.00529.x

23. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health*. 1999;20:145-157. doi:10.1146/annurev.publhealth.20.1.145

24. Matlach J, Bender S, König J, Binder H, Pfeiffer N, Hoffmann EM. Investigation of intraocular pressure fluctuation as a risk factor of glaucoma progression. *Clin Ophthalmol*. 2018;13:9-16. doi:10.2147/OPTH.S186526

25. Hair JF Jr, Black WC, Babin BJ, Anderson RE. *Multivariate Data Analysis*. 7th ed. Pearson Education Ltd; 2010.

26. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120(6):714-720. doi:10.1001/archopht.120.6.714

27. Miglior S, Pfeiffer N, Torri V, Zeyen T, Cunha-Vaz J, Adamsons I; European Glaucoma Prevention Study (EGPS) Group. Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. *Ophthalmology*. 2007;114(1):3-9. doi:10.1016/j.ophtha.2006.05.075

28. Medeiros FA, Weinreb RN, Sample PA, et al. Validation of a predictive model to estimate the risk of conversion from ocular hypertension to glaucoma. *Arch Ophthalmol*. 2005;123(10):1351-1360. doi:10.1001/archopht.123.10.1351

29. Miglior S, Torri V, Zeyen T, Pfeiffer N, Vaz JC, Adamsons I; EGPS Group. Intercurrent factors associated with the development of open-angle glaucoma in the European glaucoma prevention study. *Am J Ophthalmol*. 2007;144(2):266-275. doi:10.1016/j.ajo.2007.04.040

30. Gao F, Miller JP, Xiong C, Beiser JA, Gordon M; The Ocular Hypertension Treatment Study (OHTS) Group. A joint-modeling approach to assess the impact of biomarker variability on the risk of developing clinical outcome. *Stat Methods Appt*. 2011;20(1):83-100. doi:10.1007/s10260-010-0150-z

31. van Houwelingen HC, Putter H. *Dynamic Prediction in Clinical Survival Analysis*. CRC Press Inc; 2011. doi:10.1201/b11311

32. Jiang X, Torres M, Varma R; Los Angeles Latino Eye Study Group. Variation in intraocular pressure and the risk of developing open-angle glaucoma: the Los Angeles Latino Eye Study. *Am J Ophthalmol*. 2018;188:51-59. doi:10.1016/j.ajo.2018.01.013

33. Kim JH, Caprioli J. Intraocular pressure fluctuation: is it important? *J Ophthalmic Vis Res*. 2018;13(2):170-174. doi:10.4103/jovr.jovr_35_18