Adjusting Intraocular Pressure for Central Corneal Thickness Does Not Improve Prediction Models for Primary Open-Angle Glaucoma

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Purpose: To determine if the accuracy of the baseline prediction model for the development of primary open-angle glaucoma (POAG) in patients with ocular hypertension can be improved by correcting intraocular pressure (IOP) for central corneal thickness (CCT).

Design: Reanalysis of the baseline prediction model for the development of POAG from the Ocular Hypertension Treatment Study (OHTS) substituting IOP adjusted for CCT using 5 different correction formulae for unadjusted IOP.

Participants: A total of 1433 of 1636 participants randomized to OHTS who had complete baseline data for factors in the prediction model: age, IOP, CCT, vertical cup-to-disc ratio (VCDR), and pattern standard deviation (PSD).

Methods: Reanalysis of the prediction model for the risk of developing POAG using the same baseline variables (age, IOP, CCT, VCDR, and PSD) except that IOP was adjusted for CCT using correction formulae. A separate Cox proportional hazards model was run using IOP adjusted for CCT by each of the 5 formulae published to date. Models were run including and excluding CCT.

Main Outcome Measures: Predictive accuracy of each Cox proportional hazards model was assessed using the *c*-statistic and calibration chi-square.

Results: C-statistics for prediction models that used IOP adjusted for CCT by various formulas ranged from 0.75 to 0.77, no better than the original prediction model (0.77) that did not adjust IOP for CCT. Calibration chi-square was acceptable for all models. Baseline IOP, whether adjusted for CCT or not, was statistically significant in all models including those with CCT in the same model. The CCT was statistically significant in all models including those with IOP adjusted for CCT in the same model.

Conclusions: The calculation of individual risk for developing POAG in ocular hypertensive individuals is simpler and equally accurate using IOP and CCT as measured, rather than applying an adjustment formula to correct IOP for CCT.

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Central corneal thickness (CCT) is among the strongest independent predictors for the development of primary open-angle glaucoma (POAG) in the Ocular Hypertension Treatment Study (OHTS)[1] and the European Glaucoma Prevention Study (EGPS).[2] The risk of developing POAG doubled for every 40 μm decrease in CCT from the overall mean of 573.3 μm in the OHTS and EGPS pooled sample.[3] Other independent predictive factors for the development of POAG in the OHTS and EGPS prediction models were baseline age, intraocular pressure (IOP), vertical cup-to-disc ratio (VCDR), and pattern standard deviation (PSD). Other studies have also reported similar associations between CCT and the incidence of POAG[4–6] or the prevalence of POAG.[7–9]

Although CCT and IOP have an independent effect on the risk of developing POAG, in fact, these 2 factors interact. When Goldmann applanation tonometry (GAT) was introduced in the 1950s, the thickness of the cornea was recognized as a potential confounder to IOP measurement.[10] As optical and ultrasonic pachymeters became widely available, researchers realized that CCT varied greatly between individuals. Since then, a number of investigators have developed formulae to "adjust" IOP as measured by GAT for CCT.[11–15] These formulae have been based on cannulation studies of eyes during cataract surgery,[11,12,15] meta-analyses of published datasets,[14] or engineering models of the applanated cornea.[13]

Why CCT is such a powerful predictor of POAG is unknown. Some clinicians think that the only reason CCT is

in the prediction model for the development of POAG is to correct IOP for mismeasurement. To address this issue, we correct IOP for CCT using published correction formulae described previously. If the influence of CCT on GAT fully explains CCT's role as a predictive factor, correcting IOP using these formulae should cause CCT to drop out of the predictive model.

Neither the OHTS nor the EGPS prediction model for the development of POAG adjusted baseline IOP for corneal thickness by correction formulae. To determine whether doing so might improve the predictive ability of the model, we recalculated the predictive model for the development of POAG substituting the value of IOP adjusted for CCT for the unadjusted IOP. We compare the predictive accuracy of the original prediction model with unadjusted values of IOP to prediction models with values of IOP adjusted for CCT using correction formulae by Ehlers et al,[11] Whitacre et al,[12] Orssengo and Pye,[13] Doughty and Zaman,[14] and Kohlhaas et al.[15]

Materials and Methods

The OHTS is an unmasked randomized trial of the safety and efficacy of topical ocular hypotensive medication in preventing or delaying the development of POAG in individuals with ocular hypertension. The design and methods of OHTS have been described and can be found at http://ohts.wustl.edu (accessed March 1, 2011) and are briefly summarized in this article.[16,17] Eligibility criteria included age 40–80 years, a qualifying IOP $\geq$24 mmHg and $\leq$32 mmHg in 1 eye and $\geq$21 mmHg and $\leq$32 mmHg in the fellow eye. Both eyes had to meet eye-specific criteria, including gonioscopically open angles, normal and reliable visual fields, and normal optic discs. Individuals signed an informed consent approved by the institutional review board of each participating clinic.

Beginning in February of 1994, 1636 individuals were randomized to either observation or treatment with topical ocular hypotensive medication. All topical ocular hypotensive medications available commercially in the United States were available from the OHTS central pharmacy. Medication was selected at the clinician's discretion.

Follow-up Visits and Tests

Semiannual visits included an ocular and medical history, refraction, best-corrected visual acuity, full threshold Humphrey white-on-white 30-2 visual field test, slit-lamp examination, IOP measurement, and direct ophthalmoscopy. In addition, annual visits included dilated fundus examination and stereoscopic optic disc photography.

Intraocular pressure was measured by 2 certified study personnel, an operator and a recorder, using a calibrated GAT. The operator initially set the dial at 10 mmHg and then looked through the slit-lamp and adjusted the dial while the recorder read and recorded the results. This procedure was repeated on the same eye. If the 2 readings differed by $\leq$2 mmHg, the average of the 2 readings served as the visit IOP. If the 2 readings differed by >2 mmHg, a third reading was performed and the median of the 3 readings served as the visit IOP.

Central corneal thickness was measured at the clinical center by calibrated ultrasonic pachymeters (Pachette 500, DGH Technologies, Exton, PA). We began to collect CCT measurements in early 1999, approximately 2 years after randomization of the last par-

ticipant. The protocol for measurement of CCT is described in a previously published article.[18]

Determination of Primary Open-Angle Glaucoma

Primary open-angle glaucoma was defined as the development of a reproducible visual field abnormality or reproducible, clinically significant optic disc deterioration attributed to POAG by the masked Endpoint Committee. Criteria for reproducible visual field abnormality were 3 consecutive reliable visual fields judged abnormal (corrected PSD of P<5% or a glaucoma hemifield test outside normal limits by STATPAC 2 criteria) by masked readers at the Visual Field Reading Center, University of California Davis, Sacramento, California.[19]

Criteria for reproducible optic disc deterioration were 2 consecutive sets of optic disc photographs showing generalized or localized thinning of the optic disc neuroretinal rim compared with baseline stereoscopic optic disc photographs as determined by masked certified readers at the Optic Disc Reading Center, Bascom Palmer Eye Institute, Miami, Florida.[20]

When either Reading Center determined the occurrence of a reproducible end point, the masked Endpoint Committee reviewed the participant's clinical and medical history to determine if the end point was due to POAG.

Statistical Analysis

The analysis dataset for this report consists of data collected prospectively in OHTS from the start of randomization in February 1994 to June 2002 when participants were managed according to their randomization assignment. This includes participants with complete data for factors in the prediction model for the development of POAG: baseline age, IOP, CCT, VCDR, and PSD.[3] A total of 1433 of the 1636 randomized participants had complete baseline data (717 observation participants and 716 medication participants). Participants completed a median follow-up of 7.0 years. The analysis dataset included 102 incident cases of POAG in the observation group and 41 incident cases of POAG in the medication group. Cox proportional hazard models stratified by randomization group were run with the same predictors as the OHTS/ EGPS prediction model: baseline age, IOP, CCT, VCDR, and PSD. For eye-specific variables, the average of right and left eyes was used. Separate Cox proportional hazards models stratified by randomization group were rerun with values for baseline IOP corrected for CCT using formulae published by Ehlers et al,[11] Whitacre et al,[12] Orssengo and Pye,[13] Doughty and Zaman,[14] and Kohlhaas et al.[15] Models with baseline IOP adjusted for CCT by various formulae were run with and without CCT in the model to determine if CCT made an independent contribution to the risk of developing POAG. The Pearson correlation coefficient between unadjusted IOP and CCT in this sample is −0.03.[1] The Orssengo and Pye formula assumed a mean CCT for this sample of 1433 participants (580 μm) and a value for the radius of curvature of the central anterior surface of 7.80.[21] The formulae are given in Table 1 (available at http://aaojournal.org).

To compare the predictive accuracy of the prediction models, we calculated the c-statistic and calibration chi-square. The c-statistic ranges from 0.5 (chance) to 1.0 (perfect agreement) and indicates degree of agreement between the ordering of the estimated and observed probability of a dichotomous end point.[22] When CCT is included in the model, all formulae except the one by Orssengo and Pye[13] will have nearly identical c-statistics by definition because the formulae are linear adjustments to IOP that do not affect the relative ranking of unadjusted IOP to the risk of developing POAG. The calibration chi-square indicates whether the model over- or underestimates the actual number of POAG
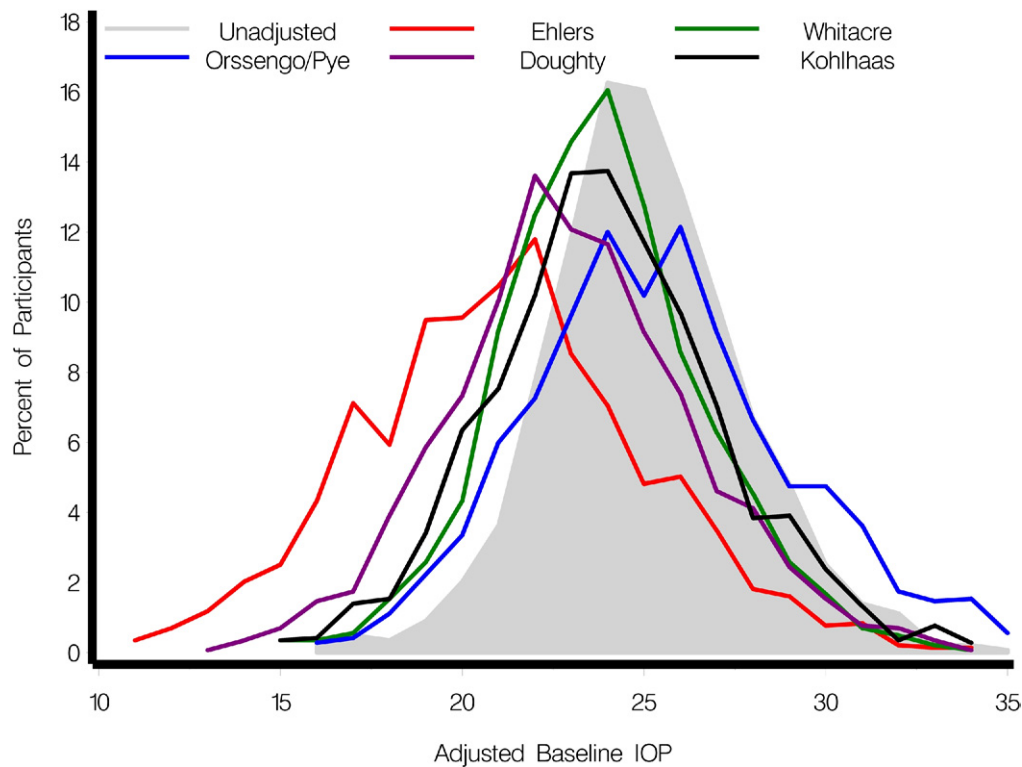
Figure 1. Distribution of baseline intraocular pressure (IOP) adjusted using the formulae from Ehlers et al,[11] Whitacre et al,[12] Orssengo and Pye,[13] Doughty and Zaman,[14] and Kohlhaas et al.[15]

events for each model by decile of risk. A calibration chi-square of ≤20.00 indicates acceptable agreement between the predicted and observed event rates.[22] The *c*-statistic and calibration chi-square were calculated using the Design library from the Comprehensive R Archive Network (R Development Core Team, v2.3-0; available at: http://cran.r-project.org/web/packages/Design/index.html; accessed March 1, 2011).

Results

Figure 1 shows the distribution of the baseline IOP adjusted using the formulae from Ehlers et al,[11] Whitacre et al,[12] Orssengo and Pye,[13] Doughty and Zaman,[14] and Kohlhaas et al.[15] The correlations between adjusted IOPs calculated from these formulae were high (range, 0.87–0.99). Table 2 (available at http://aaojournal.org) reports baseline age, VCDR, PSD, CCT, and IOP (unadjusted and adjusted for CCT) for participants who did and did not develop POAG. Table 3 reports the multivariate hazard ratio (HR) for the risk of developing POAG for baseline IOP, as adjusted for CCT by the aforementioned formulae. In all models, the HR for adjusted IOP was statistically significant with and without CCT in the model. There was little difference in the size of the HR in the models among the various IOP correction formulae. The HR with the lowest value for CCT adjusted IOP was 1.10 (95% confidence interval [CI], 1.04–1.15) for the Orssengo and Pye[13] formula in a model that included CCT. The HR with the highest value for CCT adjusted IOP was 1.17 (95% CI, 1.12–1.23) for the Doughty and Zaman[14] formula and the Kohlhaas et al[15] formula in a model that did not include CCT (Table 3).

The CCT was a statistically significant independent predictor for the development of POAG in all prediction models that included

baseline age, VCDR, PSD, CCT, and IOP (unadjusted and adjusted for CCT. In models that included both adjusted IOP and CCT, the HR for CCT ranged from 1.38 (95% CI, 1.07–1.77) to 1.69 (95% CI, 1.40–2.05) depending on the correction formula (Table 3). The Pearson correlation coefficient between CCT and CCT adjusted IOP ranged from −0.53 (Kohlhaas et al[15]) to −0.71 (Ehlers et al[11]).

C-statistics for predictive accuracy of models using baseline IOP corrected for CCT by formula ranged from 0.754 to 0.775 overall, no better than the original prediction model for the development of glaucoma (0.774) that used unadjusted IOP (Table 3). There was virtually no difference in the *c*-statistic among models using various correction formulae for CCT. The maximum difference between the highest and lowest *c*-statistic among all models in Table 3 was 0.027.

Calibration chi-squares of all prediction models in Table 3 were <20.00, indicating an acceptable fit. The calibration chi-square for the original prediction model with unadjusted IOP was 7.86 and ranged from 2.43 to 7.86 for models using CCT-adjusted IOP. Models that included both CCT-adjusted IOP and CCT performed slightly worse (higher calibration chi-square of 5.32 to 7.86) partly because of the high correlation between CCT-adjusted IOP and CCT.

Discussion

The predictive accuracy of the OHTS/EGPS prediction model for the development of POAG was not improved by correcting IOP for CCT using formulae published by Ehlers et al,[11] Whitacre et al,[12] Orssengo and Pye,[13] Doughty and Zaman,[14] and Kohlhaas et al.[15] *C*-statistics for these prediction models using corrected IOP ranged from 0.75 to 0.77,

Table 3. Comparison of Prediction Models for the Development of Primary Open-Angle Glaucoma When the Model Uses Unadjusted Intraocular Pressure Versus Intraocular Pressure Adjusted by Formula for Central Corneal Thickness

	Baseline IOP (mmHg) HR (95% CI)	CCT (40 μm decrease) HR (95% CI)	C-Statistic	Calibration Chi-Square
OHTS prediction model*				
Baseline age, unadjusted IOP, CCT, PSD, and VCDR				
Model with CCT (as above)	1.11 (1.05–1.17)	1.84 (1.53–2.21)	0.774	7.86
Model without CCT	1.12 (1.06–1.19)	n/a	0.747	3.57
Ehlers et al[11] adjusted IOP				
Model with CCT	1.11 (1.05–1.17)	1.38 (1.07–1.77)	0.774	7.86
Model without CCT	1.16 (1.12–1.21)	n/a	0.770	4.60
Whitacre et al[12] adjusted IOP				
Model with CCT	1.11 (1.05–1.17)	1.69 (1.40–2.05)	0.774	7.86
Model without CCT	1.16 (1.10–1.22)	n/a	0.754	2.59
Orssengo and Pye[13] adjusted IOP				
Model with CCT	1.10 (1.04–1.15)	1.42 (1.12–1.80)	0.775	5.32
Model without CCT	1.15 (1.11–1.19)	n/a	0.770	3.83
Doughty and Zaman[14] adjusted IOP				
Model with CCT	1.11 (1.05–1.17)	1.50 (1.20–1.87)	0.774	7.86
Model without CCT	1.17 (1.12–1.23)	n/a	0.766	2.14
Kohlhaas et al[15] adjusted IOP				
Model with CCT	1.11 (1.05–1.17)	1.55 (1.25–1.91)	0.774	7.86
Model without CCT	1.17 (1.12–1.23)	n/a	0.763	2.43

CCT = central corneal thickness; CI = confidence interval; HR = hazard ratio; IOP = intraocular pressure; n/a = not applicable; OHTS = ocular hypertension treatment study; POAG = primary open-angle glaucoma; PSD = pattern standard deviation; VCDR = vertical cup-to-disc ratio.
All models are run with and without CCT in the model.
*Hazard ratios and 95% CIs may differ slightly from previous reports because of slight differences in dataset freeze date. This report includes data from February 28, 1994 to June 1, 2002.

no better than the original OHTS prediction model (0.77) that did not adjust IOP for CCT. Calibration chi-squares did not differ meaningfully among these models (2.14–7.86, <20 is acceptable) and was no better than the original prediction model (7.86). This finding should not be a surprise. Tonometry is influenced by the material properties of the cornea, of which CCT is but one component. Current correction formulae for IOP use only CCT[11,12,14,15] (or CCT + corneal curvature)[13] to "adjust" IOP estimates. One engineering model of applanation suggests that Young's modulus, a measure of material "stiffness" known to vary widely between individuals, has a stronger impact on GAT error than does CCT.[23] Available formulae do not seem to adequately correct the measurement of IOP for the biomechanical properties of the cornea on GAT.

There are several reasons that might explain why CCT is a strong predictor for the development of POAG. Central corneal thickness can be measured with high reliability in one sitting.[18] Because CCT is relatively stable over the lifetime of an adult, a single measurement of CCT is adequate in most patients. By comparison, IOP reflects transient factors that may or may not be relevant to the risk of developing POAG. The test–retest agreement between multiple IOPs at a given OHTS visit is high, but the test–retest agreement between 6-month visits is low to moderate.[24] The OHTS may not have captured information that is important to ascertaining the relationship of IOP to the risk of developing POAG. In OHTS, IOP was measured 2 to 3 times per visit during normal office hours. No diurnal measurements were

taken. Our study highlights the fact that all tonometry techniques provide only an *estimate* of "true" IOP, a physiologic parameter that can vary greatly within the individual. Goldmann tonometry is widely considered a reference standard in the conduct of clinical and regulatory trials, but even when IOP is adjusted for CCT using specialized formulae, the adjusted IOP suffers from the inherent variability of IOP and inaccuracy of IOP measurement.

In the OHTS, IOP measured by GAT was used to determine participant eligibility, to guide treatment decisions, and to construct the predictive model for the development of POAG. Had the OHTS been carried out with a perfectly accurate, cornea-independent tonometer (something that does not exist), it is entirely possible that IOP might have been a more powerful predictor for the development of POAG and that CCT might have been a less powerful predictor. However, it is worth noting that in the Early Manifest Glaucoma Trial (EMGT), IOP was not used to determine eligibility or treatment decisions, and thus the influence of CCT on GAT measurements had no opportunity to affect the incidence rate of glaucoma progression. In the EMGT, CCT was found to be an independent predictive factor for progression of POAG.[25] In the population-based, longitudinal Barbados Eye Studies, CCT measured at 9 years from baseline was an independent risk factor for incident glaucoma.[6] In the population-based Los Angeles Latino Eye Study (LALES), the prevalence of glaucoma was higher among individuals with thin CCTs than among individuals with

normal or thick CCTs across all levels of IOP.[9] The LALES investigators explored whether adjusting each IOP individually for CCT using the Doughty and Zaman algorithm[14] changed this relationship and found almost no change in the association between thin CCT and higher prevalence of glaucoma. LALES investigators concluded ". . . there is an independent risk related to CCT itself."[9] In combination with the present study, the findings of the EMGT, Barbados Eye Studies, and LALES suggest that the influence of CCT on glaucoma risk is caused by more than just tonometry artifact.

Available formulae to correct IOP measurements for CCT do not improve the accuracy of the original prediction model for the development of POAG. Nor did we find that any formula outperformed the other formulae as judged by the *c*-statistic and calibration chi-square. We caution that the accuracy of the original OHTS prediction model is estimated from data averaged over a large sample of ocular hypertensive individuals and that its accuracy in predicting outcome for a single ocular hypertensive individual cannot be reliably estimated.

In conclusion, the 5-year risk of developing POAG for an individual with ocular hypertension can be simply calculated from age, IOP, CCT, VCDR, and PSD using the risk calculator available at http://ohts.wustl.edu/risk (accessed March 1, 2011), which can be downloaded free of charge.[3] The results of our analyses suggest that the influence of corneal thickness as a prognostic factor for the development of POAG is not entirely through its effect on IOP measurement, but that CCT is a biomarker for structural or physical factors involved in the pathogenesis of POAG.

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Footnotes and Financial Disclosures

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