Baseline Topographic Optic Disc Measurements Are Associated With the Development of Primary Open-Angle Glaucoma

The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study

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Objective: To determine whether baseline confocal scanning laser ophthalmoscopy (CSLO) optic disc topographic measurements are associated with the development of primary open-angle glaucoma (POAG) in individuals with ocular hypertension.

Methods: Eight hundred sixty-five eyes from 438 participants in the CSLO Ancillary Study to the Ocular Hypertension Treatment Study with good-quality baseline CSLO images were included in this study. Each baseline CSLO parameter was assessed in univariate and multivariate proportional hazards models to determine its association with the development of POAG.

Results: Forty-one eyes from 36 CSLO Ancillary Study participants developed POAG. Several baseline topographic optic disc measurements were significantly associated with the development of POAG in both univariate and multivariate analyses, including larger cup-disc area ratio, mean cup depth, mean height contour, cup volume, reference plane height, and smaller rim area, rim area to disc area, and rim volume. In addition, classification as "outside normal limits" by the Heidelberg Retina Tomograph classification and the Moorfields Regression Analysis classifications (overall, global, temporal inferior, nasal inferior, and superior temporal regions) was significantly associated with the development of POAG. Within the follow-up period of this analysis, the positive predictive value of CSLO indexes ranged from 14% (Heidelberg Retina Tomograph classification and Moorfields Regression Analysis overall classification) to 40% for Moorfields Regression Analysis temporal superior classification.

Conclusions: Several baseline topographic optic disc measurements alone or when combined with baseline clinical and demographic factors were significantly associated with the development of POAG among Ocular Hypertension Treatment Study participants. Longer follow-up is required to evaluate the true predictive accuracy of CSLO measures.

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NUMEROUS STUDIES HAVE assessed the ability of confocal scanning laser ophthalmoscopy (CSLO) optic disc measurements to discriminate between healthy eyes and eyes with established glaucoma in cross-sectional studies. Estimates of sensitivity and specificity range from 58% to 88% and 73% to 96%, respectively.[1-8] Few studies have evaluated CSLO optic disc topography in ocular hypertensive eyes without glaucomatous-appearing optic discs or visual field damage.[9] The Ocular Hypertension Treatment Study (OHTS), with its large cohort of participants with ocular hypertension without clinically evident optic disc or visual field damage at study entry, provides a unique opportunity to detect changes in the optic disc prior to the determination of primary open-angle glaucoma (POAG) by OHTS criteria. One of the primary aims of the CSLO Ancillary Study to the OHTS was to describe the association of baseline CSLO optic disc topographic measurements and indexes with the development of POAG among participants enrolled in this ancillary study.[10,11] To our knowledge, this is the first report to evaluate whether CSLO topographic optic disc measurements are associated with the development of glaucomatous optic disc or visual field damage in patients with ocular hypertension.

The OHTS, a multicenter randomized clinical trial, demonstrated that topical

ocular hypotensive medication was effective in delaying or preventing the onset of POAG.[12-14] In addition, the OHTS identified baseline demographic, clinical, and ocular characteristics, including age, vertical and horizontal cup-disc ratio, pattern standard deviation, central corneal thickness, and intraocular pressure (IOP), as predictors for the development of POAG in the OHTS.[14]

The aim of the present report was to describe the association of baseline CSLO optic disc topographic measurements with the development of POAG among participants in the CSLO Ancillary Study to the OHTS.

METHODS

The study design and baseline characteristics of the baseline CSLO Ancillary Study to the OHTS have been described previously.[10,11] In brief, participants in the OHTS CSLO Ancillary Study were recruited from 7 of the 22 OHTS clinics (Hamilton Glaucoma Center, University of California, San Diego, La Jolla; Devers Eye Institute, Portland, Ore; Henry Ford Medical Center, Troy, Mich; Jules Stein Eye Institute, University of California, Los Angeles; University of California, Davis, Sacramento; Scheie Eye Institute, University of Pennsylvania, Philadelphia; and New York Eye and Ear Infirmary, New York). All participants met the inclusion and exclusion criteria outlined for the OHTS.[12] In brief, subjects with ocular hypertension ranging from 24 to 32 mm Hg in at least one eye and 21 to 32 mm Hg in the fellow eye were eligible. At entry to the OHTS, each participant was required to have 2 normal, reliable (fewer than 33% false positives, false negatives, and fixation losses) automated achromatic 30-2 visual field results (Zeiss-Humphrey Systems, Dublin, Calif). Normal field results required global indexes within the 95% age-specific population norms and glaucoma hemifield test results within the 97% age-specific population norm based on STATPAC 2 analysis as verified by the Visual Field Reading Center, Davis, Calif.[15] At entry to the OHTS, participants also were required to have normal-appearing optic discs based on clinical examination and review of full-frame 35-mm pairs or split-frame simultaneous stereoscopic optic disc photographs. All photographs were assessed by 2 independent, masked, certified graders at the Optic Disc Reading Center, Miami, Fla.[16] Participants were excluded from the study if the review of their photographs documented a localized notch or thinning of the neuroretinal rim, a diffuse or localized area of pallor, an optic disc hemorrhage, or an asymmetry between the 2 eyes in the cup-disc ratios greater than 0.2. The Optic Disc Reading Center graders estimated horizontal and vertical cup-disc ratios by contour.

A description of baseline clinical, demographic, and ocular information collected in the OHTS has been reported previously.[12,14] Central corneal thickness measurements were completed about 2 years after randomization of the last participant.

The primary end points for the OHTS were the development of a confirmed visual field abnormality or a confirmed clinically significant optic disc deterioration attributed to POAG.[14] Abnormalities were independently identified by masked, certified readers at the Visual Field and Optic Disc Reading Centers. The masked End Point Committee then determined whether these confirmed abnormalities were attributable to POAG.

As described previously,[10,11] CSLO examinations were obtained with the Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering, GmbH, Dossenheim, Germany) during the visit for the OHTS dilated examination. At each annual OHTS CSLO Ancillary Study visit, three 10° images centered on the optic disc were obtained of both eyes and three 15° images were obtained of the right eye. If both 10° and 15° good-quality images were available, the 10° images were used in this analysis. Corneal curvature measurements were used to correct images for magnification error. Corrective lenses were used during image acquisition when astigmatism was greater than 1 diopter. Mean images were used for statistical analyses. All CSLO images were obtained by operators certified by the CSLO Reading Center at the University of California, San Diego. The CSLO Reading Center also conducted all quality assessment and image processing.[10] Contour lines outlining the disc margin were drawn by a certified operator while viewing a copy of stereoscopic photographs of the optic disc from the Optic Disc Reading Center.[10]

The CSLO Ancillary Study to the OHTS was funded after the initiation of enrollment in the OHTS. Therefore, many participants completed their first CSLO examination visit after their baseline or randomization visit.[10] In this interval, some of these participants developed optic disc deterioration or visual field abnormality that was subsequently confirmed and attributed to POAG. If the first CSLO measurement took place after the OHTS examination, with a suspicious finding later confirmed as POAG, that eye was excluded from the analysis. The date for a POAG end point was the first date of 3 consecutive, abnormal visual field test results or the first date of 2 consecutive sets of stereophotographs showing clinically significant deterioration that classified the eye as reaching a POAG end point. The sample for this report consisted of all images from the first CSLO visit with good-quality images to the closure date for this report or to the first suspicious date of POAG, whichever was first. As described previously,[10] approximately 23% of participants had their first good-quality CSLO images obtained at the OHTS baseline visit, 36% at the 6-month or 12-month visit, 29% at the 18-month or 24-month visit, and 12% at later visits.

Details describing the HRT and the topographic measurements available have been presented in detail elsewhere.[10,17] In this report, we analyzed the baseline values for the following CSLO parameters and composite indexes: disc area, cup area and volume, cup-disc area ratio, rim-disc area ratio, mean cup depth, retinal nerve fiber layer (RNFL) thickness and cross-sectional area, rim area and volume, mean height contour, reference plane height, cup shape, Moorfields Regression Analysis (MRA) (classified as outside normal limits or not outside normal limits), and HRT classification (outside normal limits vs within normal limits), as well as the continuous variable HRT classification 2. The MRA compared the log of the measured neuroretinal rim area with the predicted age-corrected rim area (adjusted for optic disc area) and determined whether the predicted values were outside the 99.9% confidence limits of normal values.[18] The MRA was evaluated globally and in the following 6 regions (with 0° as temporal): temporal superior (46°-90°), nasal superior (91°-135°), nasal (136°-225°), nasal inferior (226°-270°), temporal inferior (271°-315°), and temporal (316°-45°). In addition, if any of the regional or global values were outside normal limits then the MRA overall measurement was defined as outside normal limits. The reference plane height was used to differentiate between neuroretinal rim area and the optic cup.[19] Using standard HRT software (version 2.01), the reference plane height was calculated 50 µm posterior to the mean height contour along a small temporal section of the contour line. Cup area, cup-disc area ratio, cup volume below the reference plane, RNFL thickness and cross-sectional area, and rim area were measured using this reference plane. Other parameters, including mean height contour, cup shape, and mean cup depth, were measured from the curved surface. The standard deviation of the mean image is a measure of image quality.

The CSLO Ancillary Study protocol was approved by the institutional review boards of each clinic participating in the ancillary study. Written informed consent for participation in the ancillary study was obtained from OHTS participants.

The analysis data set included OHTS and CSLO baseline data and POAG end points with initial suspicious dates before October 2003 that were confirmed and entered into the database by February 9, 2004. All descriptive tables (means and percentages) report the average of the right and left eyes.

The association of each CSLO parameter and composite index for the development of POAG was assessed individually in univariate analyses with Cox proportional hazards models using the PHREG procedure of SAS (SAS Institute Inc, Cary, NC). Data for both eyes of the participant were included in the model and the method of Lee et al[20] was used to adjust for the correlation of the 2 eyes from the same participant. The CSLO variable units were standardized for analysis in proportional hazard models. The units of analyses were chosen so that each variable would have an approximate standard deviation of 1. Baseline CSLO parameters and composite indexes were also assessed in multivariate Cox proportional hazards models that adjusted for baseline factors predictive of POAG in the overall OHTS sample of 1636 participants (age, IOP, pattern standard deviation, history of heart disease, and central corneal thickness).[14,21] These multivariate models did not adjust for baseline horizontal or vertical cup-disc ratios as determined by the Optic Disc Reading Center from stereoscopic photographs for 2 reasons: (1) the objective was to estimate the independent contribution of the CSLO parameter as the sole indicator of disc status and (2) the inability to resolve statistically the independent contribution of cup-disc ratio from the independent contribution of CSLO parameters because of their high intercorrelations.[10] Medication was included in the univariate and multivariate models as a time-dependent covariate because of the initiation of ocular hypotensive medications for the observation group in 2002.

Because many CSLO parameters are closely related to each other or are composite scores, we selected the best CSLO predictor(s) from each of 5 families of variables: (1) cup (includes mean cup depth and cup volume), (2) neuroretinal rim (includes rim area, rim area/disc area, mean height contour, and rim volume), (3) MRA classification (includes global and regional results), (4) RNFL (includes RNFL thickness and cross-sectional area), and (5) reference plane height (in its own category) of CSLO measures using the score criterion of the PHREG procedure of SAS software. The score criterion as implemented in PHREG was used to determine if the addition of more than 1 CSLO variable increased the explanatory power of the model. Hazard ratios for each putative predictive factor are reported with 95% confidence intervals. For the purpose of illustration, we include Kaplan-Meier plots of the univariate cumulative probability of developing POAG for selected CSLO measures.

RESULTS

Eight hundred seventy-four eyes from 439 participants had good-quality baseline CSLO images and were eligible for inclusion in this analysis.[10] Nine eyes were excluded because the initial CSLO measurement was on the same day or after the first suspicious date for a POAG end point. One participant had both eyes excluded. Therefore, the analysis sample for this report consists of 865 eyes of 438 participants. Baseline demographic, clinical, and ocular factors of the 438 CSLO Ancillary Study participants included in this analysis are reported in **Table 1** and **Table 2**. Seventy-four (17%) of the CSLO participants were African American, 253 (58%) were female, and 141 (32%) reported a family history of glaucoma (Table 1).

Forty-one eyes of 36 CSLO participants developed POAG after the initial CSLO measurement. Five participants developed bilateral POAG and 31 developed unilateral POAG during the follow-up period in this report. Of the 41 eyes with POAG, 9 initially reached end point based on visual field results alone, 31 initially on stereophotographs alone, and 1 based on concurrent visual field results and stereophotographs. Of the 31 eyes that were only initially classified as having POAG on the basis of stereophotographs, 1 went on to develop visual field damage attributable to POAG. Six of the 9 eyes classified as having POAG based on visual field results later developed optic disc changes attributable to POAG. There were 824 eyes from the 432 participants who did not develop POAG.

Median follow-up from the first CSLO examination to the first suspicious date for POAG was 48.4 months (mean±SD, 48.4±25.2 months). Median follow-up from the first CSLO examination to the last usable visual field test result or photograph was 84.1 months (mean±SD, 79.5±20.8 months) for eyes that did not develop POAG. Median OHTS follow-up from the baseline OHTS visit to the first suspicious date for POAG or last usable visual field result or photograph for eyes that did not develop POAG was 97.3 months (mean±SD, 93.3±19.7 months).

In univariate analysis, baseline clinical and ocular factors and CSLO topographic optic disc measurements were associated with the development of POAG (**Table 3**). Specifically, baseline clinical and ocular factors, including a history of heart disease, thinner central corneal thickness, and larger, stereophotograph-based horizontal and vertical cup-disc diameter ratios, were significantly predictive of POAG. Baseline age, IOP, and visual field pattern standard deviation were associated with the development of POAG in the expected direction but did not reach statistical significance in this subset of OHTS participants. Baseline race, sex, family history of glaucoma, history of high or low blood pressure, myopia, and baseline visual field mean deviation were not associated with the development of POAG in this study population (data not shown).

Several baseline topographic optic disc measurements were significantly associated with the development of POAG in both univariate and multivariate analysis. Table 3 reports the results of 26 multivariate models (1 multivariate model for each of 26 CSLO parameters) to test the independent relationship of each CSLO parameter with POAG, adjusting for baseline age, IOP, central corneal thickness, visual field pattern standard deviation, and history of heart disease. Classification of "outside normal limits" by HRT classification, MRA overall and global classifications, and MRA classifications for the temporal inferior, nasal inferior, and temporal superior regions were significantly associated with the development of POAG, with multivariate hazard ratios (95% confidence interval) of 2.54 (1.31-4.90), 2.39 (1.02-5.62), 3.37 (1.13-9.99), 5.80 (1.60-21.0), 4.19 (1.61-10.91), and 3.28 (0.98-10.98), respectively.

The topographic measurements in which larger values at baseline were significantly associated with the development of POAG included cup-disc area ratio, mean

Table 1. Baseline Demographic and Clinical Characteristics by POAG Status (Average of the Eyes)*

Characteristic	No. (%) Not at POAG End Point	No. (%) POAG End Point	No. (%) All
Race			
Other	333 (91.5)	31 (8.5)	**364 (100)**
African American	69 (93.2)	5 (6.8)	**74 (100)**
Sex			
Female	235 (92.9)	18 (7.1)	**253 (100)**
Male	167 (90.3)	18 (9.7)	**185 (100)**
Parent/sibling family history of glaucoma			
No	269 (90.6)	28 (9.4)	**297 (100)**
Yes	133 (94.3)	8 (5.7)	**141 (100)**
Systemic β-blockers			
No	388 (91.7)	35 (8.3)	**423 (100)**
Yes	14 (93.3)	1 (6.7)	**15 (100)**
Calcium channel blocker			
No	369 (92.3)	31 (7.8)	**400 (100)**
Yes	33 (86.8)	5 (13.2)	**38 (100)**
History of migraine			
No	347 (91.3)	33 (8.7)	**380 (100)**
Yes	55 (94.8)	3 (5.2)	**58 (100)**
History of diabetes mellitus			
No	363 (91.0)	36 (9.0)	**399 (100)**
Yes	39 (100)	0	**39 (100)**
History of high blood pressure			
No	272 (91.6)	25 (8.4)	**297 (100)**
Yes	130 (92.2)	11 (7.8)	**141 (100)**
History of low blood pressure			
No	381 (91.8)	34 (8.2)	**415 (100)**
Yes	21 (91.3)	2 (8.7)	**23 (100)**
History of heart disease			
No	387 (92.6)	31 (7.4)	**418 (100)**
Yes	15 (75.0)	5 (25.0)	**20 (100)**
History of stroke			
No	401 (91.8)	36 (8.2)	**437 (100)**
Yes	1 (100)	0	**1 (100)**
Myopia ≤ −1 D			
No	257 (92.4)	21 (7.6)	**278 (100)**
Yes	145 (90.6)	15 (9.4)	**160 (100)**
HRT classification			
Outside normal limits	128 (86.5)	20 (13.5)	**148 (100)**
Within normal limits	274 (94.5)	16 (5.5)	**290 (100)**
MRA			
Overall			
Outside normal limits	61 (85.9)	10 (14.1)	**71 (100)**
Within normal limits	341 (92.9)	26 (7.1)	**367 (100)**
Global			
Outside normal limits	14 (73.7)	5 (26.3)	**19 (100)**
Within normal limits	388 (92.6)	31 (7.4)	**419 (100)**
Nasal			
Outside normal limits	31 (81.6)	7 (18.4)	**38 (100)**
Within normal limits	371 (92.8)	29 (7.3)	**400 (100)**
Nasal inferior			
Outside normal limits	24 (77.4)	7 (22.6)	**31 (100)**
Within normal limits	378 (92.9)	29 (7.1)	**407 (100)**
Nasal superior			
Outside normal limits	23 (88.5)	3 (11.5)	**26 (100)**
Within normal limits	379 (92.0)	33 (8.0)	**412 (100)**
Temporal			
Outside normal limits	11 (84.6)	2 (15.4)	**13 (100)**
Within normal limits	391 (92.0)	34 (8.0)	**425 (100)**
Temporal inferior			
Outside normal limits	13 (81.3)	3 (18.8)	**16 (100)**
Within normal limits	389 (92.2)	33 (7.8)	**422 (100)**
Temporal superior			
Outside normal limits	6 (60.0)	4 (40.0)	**10 (100)**
Within normal limits	396 (92.5)	32 (7.5)	**428 (100)**

Abbreviations: D, diopter; HRT, Heidelberg Retina Tomograph; MRA, Moorfields Regression Analysis; POAG, primary open-angle glaucoma.
*One observation per participant was included. If either eye had abnormal test results then the patient was labeled abnormal.

(continued)

cup depth, mean height contour, cup volume below reference, and reference plane height. The topographic measurements in which smaller values at baseline were significantly associated with the development of POAG included rim area, rim area disc area, rim volume above reference, and HRT classification 1 as a continuous variable. Kaplan-Meier survival curves for selected CSLO parameters are presented in the **Figure**. Disc area, cup volume below surface, cup shape, and RNFL thickness were not significantly associated with the development of POAG in the univariate or multivariate models.

Of the 438 participants enrolled in the CSLO Ancillary Study who had satisfied OHTS eligibility criteria, 34% (n=148) had baseline CSLO values in one or both eyes that were outside normal limits by the HRT classification discriminant function, 16% (n=71) by MRA overall, 9% (n=38) by MRA nasal, 6% (n=31) by MRA nasal inferior, and 4% (n=19) for MRA global, down to 2% (n=10) for MRA temporal superior. Among those with values outside normal limits at baseline, the percentage of participants developing POAG (positive predictive value) was 13.5% (20/148) by HRT classification, 14.1% (10/71) by MRA overall, 18.4% (7/38) by MRA nasal, 22.6% (7/31) by MRA nasal inferior, 26.3% (5/19) by MRA global, and 40% (4/10) by MRA temporal superior (Table 1).

Among the 36 participants who developed POAG, 55% had values outside normal limits by HRT classification and 28% had values outside normal limits by MRA overall. All other indexes had sensitivity less than 20%, that is, at least 80% of those participants who developed POAG had values within the normal limits at baseline.

Among the 402 participants who did not develop POAG within the follow-up period in this report, 68% had HRT classification values within normal limits at baseline and 98% to 92% had MRA indexes within normal limits at baseline.

The following baseline CSLO measures were the most strongly associated with the development of POAG from

Table 2. Baseline Demographic and Ocular Characteristics by POAG Status (Average of the Eyes)

Characteristic	Not at POAG End Point		POAG End Point		All	
	Sample Size	Mean ± SD	Sample Size	Mean ± SD	Sample Size	Mean ± SD
Age, y	402	54.8 ± 9.1	36	57.5 ± 9.4	438	55.0 ± 9.2
IOP, mm Hg	402	25.0 ± 2.3	36	25.1 ± 2.8	438	25.0 ± 2.4
Central corneal thickness, µm	363	577.0 ± 37.0	33	554.3 ± 37.4	396	575.1 ± 37.5
Visual field pattern standard deviation, dB	402	1.90 ± 0.21	36	1.95 ± 0.20	438	1.91 ± 0.21
Visual field pattern corrected standard deviation, dB	402	1.12 ± 0.35	36	1.18 ± 0.33	438	1.13 ± 0.35
Visual field mean deviation, dB	402	0.41 ± 1.09	36	0.09 ± 1.16	438	0.38 ± 1.10
Horizontal cup-disc ratio	402	0.36 ± 0.19	36	0.42 ± 0.18	438	0.36 ± 0.19
Vertical cup-disc ratio	402	0.38 ± 0.19	36	0.47 ± 0.18	438	0.39 ± 0.19
CSLO measures						
Disc area, mm^2	402	1.930 ± 0.382	36	1.849 ± 0.371	438	1.923 ± 0.381
Cup area, mm^2	402	0.550 ± 0.356	36	0.600 ± 0.341	438	0.554 ± 0.355
Cup area to disc area	402	0.617 ± 0.144	36	0.644 ± 0.114	438	0.619 ± 0.142
Mean cup depth, mm	402	0.228 ± 0.094	36	0.269 ± 0.117	438	0.231 ± 0.097
RNFL thickness, mm	402	0.248 ± 0.057	36	0.245 ± 0.065	438	0.248 ± 0.057
Standard deviation of mean image, mm	402	18.172 ± 6.866	36	19.774 ± 7.544	438	18.304 ± 6.929
Cup shape	402	–0.198 ± 0.065	36	–0.186 ± 0.068	438	–0.197 ± 0.066
Cup volume below surface, mm^3	402	0.310 ± 0.213	36	0.351 ± 0.221	438	0.314 ± 0.213
Rim volume above reference, mm^3	402	0.359 ± 0.122	36	0.326 ± 0.114	438	0.356 ± 0.122
Cup volume below reference, mm^3	402	0.145 ± 0.140	36	0.185 ± 0.175	438	0.148 ± 0.143
Rim area, mm^2	402	1.379 ± 0.257	36	1.249 ± 0.267	438	1.369 ± 0.260
Rim area to disc area	402	0.731 ± 0.140	36	0.691 ± 0.141	438	0.728 ± 0.140
Reference plane height, mm	402	0.318 ± 0.091	36	0.366 ± 0.084	438	0.322 ± 0.091
HRT classification 1	402	1.209 ± 1.494	36	0.559 ± 1.458	438	1.155 ± 1.500
Corneal curvature, mm	402	7.741 ± 0.260	36	7.788 ± 0.276	438	7.745 ± 0.261
Mean height contour, mm	402	0.070 ± 0.076	36	0.121 ± 0.061	438	0.074 ± 0.076
RNFL cross-sectional area, mm^2	402	1.216 ± 0.292	36	1.167 ± 0.314	438	1.212 ± 0.294

Abbreviations: CSLO, confocal scanning laser ophthalmoscopy; HRT, Heidelberg Retina Tomograph; IOP, intraocular pressure; POAG, primary open-angle glaucoma; RNFL, retinal nerve fiber layer.

their respective CSLO families (as per the score statistic): cup area, cup depth, rim area, mean contour height, reference plane height, RNFL cross section, and MRA global. These measurements were used to determine whether the addition of more than 1 CSLO variable increased the explanatory power of the multivariate OHTS baseline prediction model. When added to the OHTS baseline prediction model that did not include stereophotograph-based vertical cup-to-disc ratio, mean height contour was the best single CSLO variable. When rim area was added with mean height contour to the OHTS baseline prediction model, both retained their statistically significant effect. When added with mean height contour to the OHTS baseline prediction model, none of the other parameters attained statistical significance.

COMMENT

This study determined that many baseline CSLO topographic optic disc measurements were significantly associated with the development of POAG in the CSLO Ancillary Study to the OHTS. These data suggest that CSLO topographic optic disc measurements, when combined with other known predictive factors such as age, IOP, and central corneal thickness, could assist the eye care professional in assessing the likelihood of developing POAG. To our knowledge, this is the first report to document that CSLO topographic optic disc measurements are significantly associated with the development of glaucomatous optic disc or visual field damage in patients with ocular hypertension.

A larger baseline mean height contour was one of the most consistent predictors of POAG in the multivariate models. A 0.1-mm-larger mean height contour was associated with a 2.7-fold increase in POAG risk in the multivariate model, and a similar magnitude of association was seen in the univariate model. The mean height contour is measured from anterior to posterior so that as there is loss of retinal nerve fibers, the mean height contour increases. A simple gauge of the univariate effect is obtained when the eyes are divided into 2 groups, one group equal to or higher than the median and the other lower than the median mean height contour. The Kaplan-Meier estimate of the development of POAG at 96 months shows that approximately 7% of eyes higher than the mean height contour and rim area median developed POAG compared with 2% of eyes lower than the median (Figure).

Baseline classification as outside normal limits by HRT classification and MRA global and regional measurements was significantly associated with the development of POAG, with hazard ratios ranging from 2.5 to 5.8. Specifically, in the multivariate models, a global, nasal inferior, and temporal inferior MRA classification as outside normal limits increased the POAG risk by 3.4-, 4.2-, and 5.8-fold, respectively. An HRT classification of outside normal limits increased the risk 2.5-fold. Although a baseline outside normal limits classification was significantly associated with the development of POAG,

Table 3. Univariate and Multivariate Hazard Ratios and 95% Confidence Intervals (CIs) for the Development of POAG (Average of the Eyes)

	Hazard Ratio (95% CI)	
	Univariate	Multivariate*
CSLO measures		
Disc area (per 0.4 mm^2 greater)	0.84 (0.58-1.20)	0.86 (0.57-1.30)
Cup area (per 0.3 mm^2 greater)	1.22 (0.96-1.55)	1.21 (0.96-1.53)
Cup area-to-disc area (per 0.1 greater)	1.23 (1.00-1.50)	1.25 (1.02-1.53)
Mean cup depth (per 0.1 mm greater)	1.58 (1.14-2.20)	1.60 (1.15-2.22)
RNFL thickness (per 0.1 mm greater)	0.60 (0.34-1.06)	0.66 (0.35-1.23)
Standard deviation of mean image (per 6 μm greater)	1.15 (0.92-1.43)	1.04 (0.80-1.37)
Cup shape (per 0.1 greater)	1.24 (0.78-1.97)	1.02 (0.62-1.67)
Cup volume below surface (per 0.1 mm^3 greater)	1.11 (0.96-1.28)	1.10 (0.97-1.25)
Rim area (per 0.2 greater)	0.58 (0.43-0.79)	0.57 (0.42-0.78)
Rim area/disc area (per 0.1 greater)	0.75 (0.60-0.94)	0.76 (0.62-0.93)
Reference height (per 0.1 mm greater)	1.42 (1.04-1.93)	1.49 (1.03-2.17)
Corneal curvature (per 0.2 mm greater)	1.16 (0.90-1.49)	1.03 (0.79-1.36)
RNFL cross-section (per 0.3 mm^2 greater)	0.68 (0.49-0.95)	0.72 (0.48-1.06)
Mean height contour (per 0.1 mm greater)	2.59 (1.69-3.98)	2.69 (1.62-4.49)
Rim volume above reference (per 0.1 mm^3 greater)	0.63 (0.45-0.87)	0.65 (0.47-0.91)
Cup volume below reference (per 0.1 mm^3 greater)	1.24 (1.02-1.52)	1.20 (1.01-1.43)
HRT classification 1 (per 1 unit greater)	0.72 (0.59-0.89)	0.75 (0.62-0.92)
CSLO indexes		
HRT classification, outside normal limits vs within normal limits	2.47 (1.31-4.65)	2.54 (1.31-4.90)
MRA (outside normal limits vs within normal limits)		
Overall	2.72 (1.19-6.21)	2.39 (1.02-5.62)
Global	5.64 (1.94-16.44)	3.37 (1.13-9.99)
Nasal	1.99 (0.74-5.37)	1.59 (0.48-5.24)
Nasal inferior	4.44 (1.77-11.12)	4.19 (1.61-10.91)
Nasal superior	1.97 (0.43-8.96)	0.72 (0.11-4.63)
Temporal	3.28 (0.82-13.18)	2.48 (0.66-9.22)
Temporal inferior	5.02 (1.53-16.51)	5.80 (1.60-21.00)
Temporal superior	8.88 (2.58-30.56)	3.28 (0.98-10.98)
OHTS predictive factors		
Age (per decade)	1.27 (0.92-1.76)	NA
History of heart disease	4.25 (1.63-11.08)	NA
IOP (per mm Hg)	1.11 (0.99-1.23)	NA
CCT (per 40 μm thinner)	2.14 (1.44-3.18)	NA
PSD (per 0.2 dB greater)	1.15 (0.93-1.43)	NA
Horizontal cup-disc ratio (per 0.1 larger)	1.27 (1.09-1.49)	NA
Vertical cup-disc ratio (per 0.1 larger)	1.40 (1.16-1.68)	NA

Abbreviations: CCT, central corneal thickness; CSLO, confocal scanning laser ophthalmoscopy; HRT, Heidelberg Retina Tomograph; IOP, intraocular pressure; MRA, Moorfields Regression Analysis; NA, not applicable; OHTS, Ocular Hypertension Treatment Study; POAG, primary open-angle glaucoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

*Multivariate model contains baseline age, IOP, PSD, CCT, and history of heart disease, with medication status as a time-dependent covariate. One hundred twelve eyes were excluded from the multivariate analyses because of missing CCT values.

most of the participants with values outside normal limits did not develop POAG within the time frame of this report. For example, 20 (14%) of the 148 participants with an outside normal limits HRT classification and 10 (14%) of the 71 participants with an MRA overall classification outside normal limits developed a POAG end point (Table 1) during the follow-up period. However, longer follow-up will be required to evaluate the true predictive accuracy of the CSLO measures. The incident cases of POAG in the OHTS represent POAG at its inception, early in the disease process. It is also important to determine whether the participants with POAG end points and CSLO and MRA classifications within normal limits at baseline had measurements outside normal limits during their later follow-up CSLO examinations.

The follow-up time included in this analysis was approximately 20 months longer than that of the OHTS article describing baseline predictors of POAG.[14] In addition, the current study included both eyes in the analysis, whereas the patient was the unit of analysis in previous reports from the OHTS.[14,21] With the exception of the proportion of African American participants, the distribution of demographic and clinical characteristics of the 438 CSLO Ancillary Study participants was similar to that of the 1636 OHTS participants.[10] The CSLO Ancillary Study to the OHTS included approximately 17% African American participants and the OHTS included approximately 25% African American participants. Therefore, the results of the CSLO study are likely to be generalizable to OHTS participants and other patients with ocular hypertension who are similar to OHTS participants. However, the statistical power of the CSLO study to detect associations was lower than the OHTS, and this is reflected in Table 3 by the widths of the confidence intervals for the relative hazards.

It can be argued that larger optic cups and smaller neuroretinal rim measurements are an early sign of glaucoma and not a risk factor for developing POAG. However, the participants included in this analysis had, at the time of their CSLO examination, normal-appearing visual field results and did not have optic discs classified as glaucomatous based on independent, standardized assessment by certified graders of stereophotographs. As discussed previously,[14] this replicates the first clinical ex-

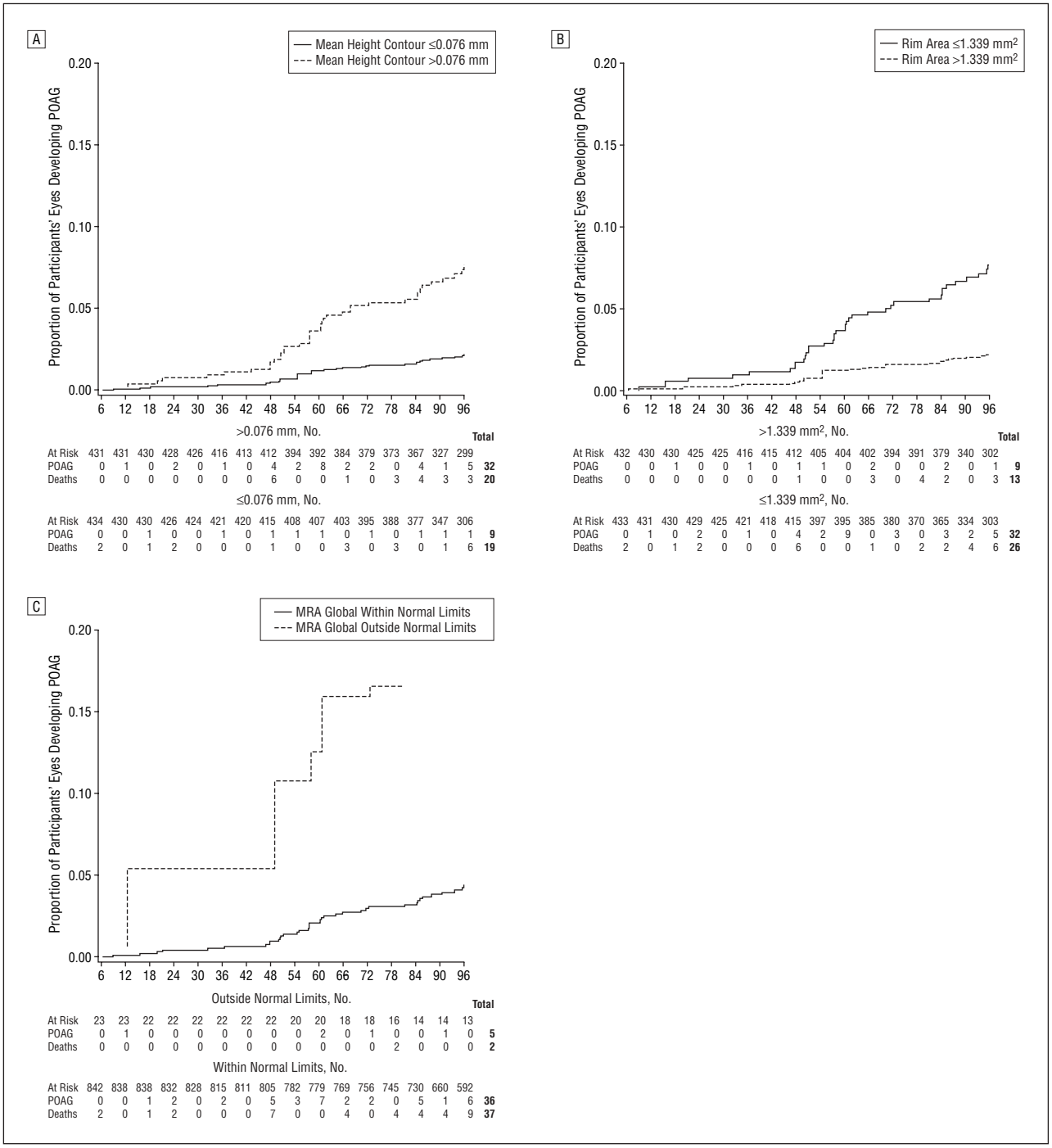

Figure. Kaplan-Meier plots of the univariate cumulative probability of developing primary open-angle glaucoma (POAG) by (A) mean height contour equal to or above the median value (dashed line) compared with lower than the median value (bold line), (B) rim area equal to or lower than the median value (dashed line) compared with higher than the median value (bold line), and (C) Moorfields Regression Analysis (MRA) (global) with values outside normal limits (dashed lines) compared with those within normal limits (bold line). Both eyes of the participant were included, and the model adjusts for the correlation between eyes.

amination of a patient. It is often difficult to determine whether a large cup or a narrow rim represent glaucoma or the range of normal variation in a healthy eye. By analyzing CSLO topographic optic disc measurements, we determined that certain optic disc features were associated with the development of POAG, even when the optic disc was not classified as glaucomatous on stereophotographic assessment. Similarly, stereophotograph-based horizontal and vertical cup-to-disc diameter ratios were predictive of POAG in the current study and in the original OHTS analysis.[14] In the univariate analysis, the CSLO cup-to-disc area ratio (per 0.1) had a similar hazards ratio to the stereophotograph-based assessment of horizontal and vertical cup-to-disc diameter ratios with hazard ratios (95% confidence interval) of 1.23 (1.00-1.50), 1.25 (1.14-1.38), and 1.32 (1.19-1.46), respectively.

As reported in the OHTS analysis and other studies, African American participants have a higher risk of de-

veloping POAG.[14,22-24] However, in the OHTS analysis, African American participants had thinner central corneal thickness and larger vertical cup-to-disc diameter ratios so that when these measurements were included in the multivariate analysis, race was no longer a predictor of POAG. We previously reported in the same study population that the larger baseline optic cups, neuroretinal rims, and cup-to-disc area ratios in African American compared with other participants are largely explained by their larger optic disc area.[11] We therefore postulated that a large disc size may be an important predictor of POAG in OHTS participants. The results of the current analysis did not confirm this hypothesis.

The mean height contour and reference plane height increase as the RNFL thins. The HRT calculates RNFL thickness indirectly as the difference in retinal height between mean height contour and the reference plane height. A thinner RNFL was associated with the development of POAG, but this association did not reach statistical significance. Our results suggest that mean height contour, which is calculated based on the curved surface, is more strongly associated with the development of POAG than the CSLO RNFL thickness measurement. The association of a larger baseline reference plane height with the development of POAG may be due at least in part to the disease process. The reference plane height is defined (in HRT software version 2.01) as 50 µm posterior to the mean height contour of a temporal segment (between 350°-356°) along the contour line outlining the disc margin. This 6° segment corresponds to the location of the papillomacular bundle. If the temporal RNFL is getting thinner, then the reference plane height increases. It has been assumed that this temporal retinal surface remains stable, at least in early glaucoma.[25] Recent studies have suggested alternative reference planes to improve the ability of CSLO measurements to detect change over time.[3,26-28] Further studies are necessary to determine the most appropriate reference plane for evaluating optic disc topography.

Recently, investigators have shown that measures of the RNFL and optic disc obtained using optical imaging instruments are predictive of the development of repeatable standard automated perimetric defects in glaucoma suspects with no visual field damage at baseline.[7,29,30] Other studies have reported that change in HRT optic disc topographic measures preceded visual field changes in eyes with normal visual field results at baseline[31,32] and that changes in optic disc topography occur more frequently than visual field changes in patients with early glaucomatous visual field loss.[33] However, these studies included some participants with glaucomatous-appearing optic discs (based on independent assessment of stereophotographs)[7,29,30] or visual field loss[33] at baseline or did not include optic disc appearance as an inclusion criteria.[31,32] To our knowledge, this is the first study to prospectively document the association of baseline CSLO topographic optic disc parameters with the development of POAG among subjects with ocular hypertension with only normal visual field test results and optic discs that were not classified as glaucomatous at study entry.

These results are particularly important in light of recent evidence that ophthalmologists do not routinely document the appearance of the optic nerve as part of a regular clinical examination. In a recent survey of 395 US managed care patients, only 53% of patients received an optic disc photograph or drawing at their initial ophthalmologic visit.[34] The OHTS demonstrated that optic disc changes are often an early observable sign of glaucoma and that treatment for ocular hypertension can delay or prevent the onset of POAG. Given that we do not know how CSLO or other imaging techniques are being used in clinical practice, it is important to consider whether the cost of possible misinterpretation of results from imaging instruments to diagnose glaucoma (and the possible overtreatment owing to false positives) outweighs the benefits of providing optic disc and RNFL information to the general ophthalmologist and optometrist who would otherwise not assess the optic disc and RNFL of their patients with glaucoma.[35] As with any clinical tool, it is essential that eye care professionals understand the strengths and limitations of the technique so that decisions are based on good-quality information.

As is the case with many clinical trials, the study procedures may not be representative of routine clinical practice. In this study, all CSLO images were centrally processed according to a standard protocol. Only good-quality images were included in the analysis. Trained technicians outlined the disk margin while viewing stereoscopic photographs of the optic disc because it has been shown to reduce interobserver variation in CSLO measurements in some observers.[36] Compared with CSLO images acquired and processed in a standardized manner, it would be expected that CSLO measurements obtained during the course of routine clinical care would be more variable because many clinics are less likely to adhere to strict quality control criteria or use photographs for outlining the disc margin. Although we used stereophotographs for outlining the disc margin because it can reduce interobserver variation of CSLO measurements for some observers, the reduction in variation was small and the use of stereophotographs had little effect on intraobserver variation.[36] Nevertheless, an increase in the variability of the CSLO measurements would likely reduce their association with the development of POAG. Therefore, it remains to be determined how well these study results can be generalized to CSLO measurements obtained during routine clinical practice.

We cannot recommend any single CSLO parameter as the best for diagnosing or monitoring glaucoma. Although mean height contour, rim area, and MRA results were among the most consistent predictors in the multivariate models, the large confidence intervals of these parameters and the proximity of the lower confidence limit to 1 suggest that more data are needed before definitive recommendations can be made. In addition, given the limited sensitivity and specificity of the CSLO parameters and the variability in appearance of healthy optic discs and in the clinical appearance of optic discs with early glaucomatous damage, it clearly is not sufficient or prudent to rely on a single parameter when making clinical decisions.

The current analysis did not directly determine whether the prediction model that includes baseline CSLO mea-

surements is improved over the OHTS prediction model that includes baseline stereophotograph cup-disc ratio measurements. We previously reported that CSLO parameters are strongly correlated with stereophotograph-based cup-disc ratio measurements.[10] Given the difficulty in statistically resolving the independent contribution of highly intercorrelated measurements, additional POAG end points are needed to appropriately compare prediction models including CSLO and stereophotograph-based cup-disc ratio measurements. This comparison will therefore be the topic of a future manuscript. This study cannot evaluate whether CSLO measurements are better predictors of POAG than measurements obtained with other imaging instruments such as scanning laser polarimetry or optical coherence tomography because CSLO was the only instrument used. While the current study documents the association of baseline CSLO topographic optic disc parameters with the development of POAG among individuals with ocular hypertension, it is important that these results are confirmed in an independent population.

In summary, the CSLO Ancillary Study to the OHTS data suggest that many baseline CSLO topographic optic disc measurements, when used alone or combined with central corneal thickness, IOP, and history of vascular disease, are significantly associated with the development of POAG among individuals with ocular hypertension. Longer follow-up is required to evaluate the true predictive accuracy of CSLO measures.

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REFERENCES

1. Bathija R, Zangwill L, Berry CC, Sample PA, Weinreb RN. Detection of early glaucomatous structural damage with confocal scanning laser tomography. *J Glaucoma*. 1998;7:121-127.
2. Zangwill LM, Bowd C, Berry CC, et al. Discriminating between normal and glaucomatous eyes using the Heidelberg retina tomograph, GDx nerve fiber analyzer, and optical coherence tomograph. *Arch Ophthalmol*. 2001;119:985-993.
3. Miglior S, Guareschi M, Albe E, Gomarasca S, Vavassori M, Orzalesi N. Detection of glaucomatous visual field changes using the Moorfields Regression Analysis of the Heidelberg Retina Tomograph. *Am J Ophthalmol*. 2003;136:26-33.
4. Miglior S, Casula M, Guareschi M, Marchetti I, Iester M, Orzalesi N. Clinical ability of Heidelberg Retinal Tomograph examination to detect glaucomatous visual field changes. *Ophthalmology*. 2001;108:1621-1627.
5. Greaney MJ, Hoffman DC, Garway-Heath DF, Nakla M, Coleman AL, Caprioli J. Comparison of optic nerve imaging methods to distinguish normal eyes from those with glaucoma. *Invest Ophthalmol Vis Sci*. 2002;43:140-145.
6. Ford BA, Artes PH, McCormick TA, Nicolela MT, LeBlanc RP, Chauhan BC. Comparison of data analysis tools for detection of glaucoma with the Heidelberg Retina Tomograph. *Ophthalmology*. 2003;110:1145-1150.
7. Bowd C, Zangwill LM, Medeiros FA, et al. Confocal scanning laser ophthalmoscopy classifiers and stereophotograph evaluation for prediction of visual field abnormalities in glaucoma-suspect eyes. *Invest Ophthalmol Vis Sci*. 2004;45:2255-2262.
8. Medeiros FA, Zangwill LM, Bowd C, Weinreb RN. Comparison of the GDx VCC scanning laser polarimeter, HRT II confocal scanning laser ophthalmoscope, and stratus OCT optical coherence tomograph for the detection of glaucoma. *Arch Ophthalmol*. 2004;122:827-837.
9. Zangwill L, Van Horn S, de Souza Lima M, Sample PA, Weinreb RN. Optic nerve head topography in ocular hypertensive eyes using confocal scanning laser ophthalmoscopy. *Am J Ophthalmol*. 1996;122:520-525.
10. Zangwill LM, Weinreb RN, Berry CC, et al. The confocal scanning laser ophthalmoscopy ancillary study to the ocular hypertension treatment study: study design and baseline factors. *Am J Ophthalmol*. 2004;137:219-227.
11. Zangwill LM, Weinreb RN, Berry CC, et al. Racial differences in optic disc topography: baseline results from the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. *Arch Ophthalmol*. 2004;122:22-28.
12. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol*. 1999;117:573-583.
13. 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;120:701-713, discussion 829-830.
14. 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;120:714-720, discussion 829-830.
15. Johnson CA, Keltner JL, Cello KE, et al. Baseline visual field characteristics in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2002;109:432-437.
16. Feuer WJ, Parrish RK II, Schiffman JC, et al. The Ocular Hypertension Treat-

ment Study: reproducibility of cup/disk ratio measurements over time at an optic disc reading center. *Am J Ophthalmol*. 2002;133:19-28.
17. Mikelberg FS, Parfitt CM, Swindale NV, Graham SL, Drance SM, Gosine R. Ability of the Heidelberg Retina Tomograph to detect early glaucomatous visual field loss. *J Glaucoma*. 1995;4:242-247.
18. Wollstein G, Garway-Heath DF, Hitchings RA. Identification of early glaucoma cases with the scanning laser ophthalmoscope. *Ophthalmology*. 1998;105:1557-1563.
19. Burk RO, Vihanninjoki K, Bartke T, et al. Development of the standard reference plane for the Heidelberg Retina Tomograph. *Graefes Arch Clin Exp Ophthalmol*. 2000;238:375-384.
20. Lee EW, Wei LJ, Amato D. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein JP, Goel PK, eds. *Survival Analysis, State of the Art*. Dordrecht: the Netherlands: Kluwer Academic; 1992:237-247.
21. Higginbotham EJ, Gordon MO, Beiser JA, et al. The Ocular Hypertension Treatment Study: topical medication delays or prevents primary open-angle glaucoma in African American individuals. *Arch Ophthalmol*. 2004;122:813-820.
22. Racette L, Wilson MR, Zangwill LM, Weinreb RN, Sample PA. Primary open-angle glaucoma in blacks: a review. *Surv Ophthalmol*. 2003;48:295-313.
23. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma: the Baltimore Eye Survey. *JAMA*. 1991;266:369-374.
24. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. *Arch Ophthalmol*. 1991;109:1090-1095.
25. Tuulonen A, Vihanninjoki K, Airaksinen PJ, Alanko H, Nieminen H. The effect of reference levels on neuroretinal rim area and rim volume measurements in the Heidelberg Retina Tomograph (HRT) [ARVO abstract]. *Invest Ophthalmol Vis Sci*. 1994;35(suppl):1729.
26. Tan JC, Hitchings RA. Reference plane definition and reproducibility in optic nerve head images. *Invest Ophthalmol Vis Sci*. 2003;44:1132-1137.
27. Tan JC, White E, Poinoosawmy D, Hitchings RA. Validity of rim area measurements by different reference planes. *J Glaucoma*. 2004;13:245-250.
28. Tan JC, Hitchings RA. Optimizing and validating an approach for identifying glaucomatous change in optic nerve topography. *Invest Ophthalmol Vis Sci*. 2004;45:1396-1403.
29. Mohammadi K, Bowd C, Weinreb RN, Medeiros FA, Sample PA, Zangwill LM. Retinal nerve fiber layer thickness measurements with scanning laser polarimetry predict glaucomatous visual field loss. *Am J Ophthalmol*. 2004;138:592-601.
30. Johnson CA, Sample PA, Zangwill LM, et al. Structure and function evaluation (SAFE), II: comparison of optic disk and visual field characteristics. *Am J Ophthalmol*. 2003;135:148-154.
31. Kamal DS, Garway-Heath DF, Hitchings RA, Fitzke FW. Use of sequential Heidelberg Retina Tomograph images to identify changes at the optic disc in ocular hypertensive patients at risk of developing glaucoma. *Br J Ophthalmol*. 2000;84:993-998.
32. Kamal DS, Viswanathan AC, Garway-Heath DF, Hitchings RA, Poinoosawmy D, Bunce C. Detection of optic disc change with the Heidelberg Retina Tomograph before confirmed visual field change in ocular hypertensives converting to early glaucoma. *Br J Ophthalmol*. 1999;83:290-294.
33. Chauhan BC, McCormick TA, Nicolela MT, LeBlanc RP. Optic disc and visual field changes in a prospective longitudinal study of patients with glaucoma: comparison of scanning laser tomography with conventional perimetry and optic disc photography. *Arch Ophthalmol*. 2001;119:1492-1499.
34. Fremont AM, Lee PP, Mangione CM, et al. Patterns of care for open-angle glaucoma in managed care. *Arch Ophthalmol*. 2003;121:777-783.
35. Zangwill L. Comparison of structural and functional methods. In: Weinreb RN, Greve EL, eds. *Glaucoma Diagnosis: Structure and Function*. The Hague, the Netherlands: Kugler; 2004:149-153.
36. Iester M, Broadway DC, Mikelberg FS, Drance SM. A comparison of healthy, ocular hypertensive, and glaucomatous optic disc topographic parameters. *J Glaucoma*. 1997;6:363-370.