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Rate of Visual Field Progression in Eyes With Optic Disc Hemorrhages in the Ocular Hypertension Treatment Study

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Objective: To compare rates of visual field (VF) change in ocular hypertensive eyes with and without optic disc hemorrhage (DH).

Methods: Ocular Hypertension Treatment Study subjects (minimum 10 reliable VF tests, followed up ≥ 5 years) were included. Trend analyses of VF sequences over time of DH and non-DH eyes were assessed by regression of mean deviation (MDR) and pointwise linear regression (PLR). The main outcome measures were rates of VF change in DH and non-DH eyes.

Results: Two thousand six hundred seven eyes (1378 participants) were included. The mean (SD) number of VF tests per eye was 23.7 (4.9) spanning a mean (SD) of 12.2 (2.0) years. At least 1 DH was detected in 187 eyes (7.2%), of which 52 eyes had recurrent DH. Mean deviation rate of change was significantly worse in DH compared with non-DH eyes (mean [SD], -0.17 [0.27] vs -0.07 [0.19] dB/y; $P < .01$). Significant PLR progression occurred more frequently in eyes with DH (odds ratio, 3.6; $P < .01$), which increased when 2 or more DHs were

present (odds ratio, 4.2; $P = .01$). Eyes initially randomized to treatment were less likely to have a DH during follow-up.

Conclusions: Eyes with DH had more rapid VF deterioration when assessed by global (MDR) or local (PLR) trend analysis than eyes without DH. Eyes with recurrent DH had similar rates of global VF change (MDR) when compared with eyes with a single DH but reached criteria for rapid PLR change more often. Intraocular pressure reduction in ocular hypertension reduces the risk of developing a DH. Ocular hypertensive eyes with DH should be monitored closely and may need more aggressive therapy.

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THE OCULAR HYPERTENSION Treatment Study (OHTS) was a randomized clinical trial that demonstrated the beneficial effect of intraocular pressure (IOP) reduction in ocular hypertension.^{1,2} Mathematical models derived

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from this data set, later validated in another clinical trial,³ allow the use of baseline variables (age, IOP, central corneal thickness, baseline visual field [VF], and optic disc status) to calculate the 5-year risk of conversion to primary open-angle glaucoma (POAG). Occurrence of optic disc hemorrhage (DH) detected on photographs by masked graders at the optic disc reading center grading stereo-optic disc photographs was shown to be a significant risk

factor that increased the risk of conversion to POAG 6-fold in a univariable analysis and approximately 3-fold in a multivariable model.⁴

Trend analysis for evaluation of glaucomatous optic nerve structural and functional damage is the subject of increasing focus among clinicians and researchers.⁵⁻⁹ The determination of disease velocity provides an objective, quantitative variable that may help predict future functional loss and worsening of vision-related quality of life.^{10,11}

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The primary purpose of the present study was to determine the velocity of VF change in OHTS participants with DH compared with those without DH. The study also uses trend-based analyses to in-

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investigate the association between DH detection and recurrence with initial randomization and progression end points.

METHODS

Baseline data and design of the OHTS have been described elsewhere.¹ All participants signed informed consent prior to entry after having the risks and benefits of participation explained to them. The institutional review boards at all clinical sites approved their respective informed consent statements and procedures. The design of the OHTS followed the tenets of the Declaration of Helsinki.

The OHTS analysis data set available for this article contained all VF data and end point determinations entered into the OHTS database as of the study closeout in March 2009. For subjects who remained in the study through the transition from OHTS I to OHTS II, there was a transition from full threshold to the Swedish interactive thresholding algorithm testing. The full cohort included 1636 subjects with ocular hypertension. Details of the randomization process and study protocol have been previously described.¹ All participants enrolled in the OHTS needed to produce at least 2 reliable full-threshold Humphrey 30-2 VF test results (Humphrey VF Analyzer, Carl Zeiss Meditec Inc), of a possible of 3 tests, that were within normal limits during the qualifying period. For the purposes of trend analysis, we chose to use the last reliable qualifying VF (whether the second or third) as our operational definition of the baseline VF test result.

Since we were investigating rates of VF change in eyes with ocular hypertension and glaucoma, we excluded from the analyses any eye reaching an end point considered nonglaucomatous (eg, retinal vein occlusion, age-related macular degeneration, or stroke) by the OHTS end point committee (261 eyes of 202 individuals). For subjects who remained in the study through the transition from OHTS I to OHTS II, there was a transition from full threshold to the Swedish interactive thresholding algorithm, and hence, test results using both algorithms were analyzed. We then included only those eyes with at least 10 reliable VF test results (false positives, false negatives, and fixation loss all <33% if the full-threshold testing algorithm was used¹; false positives <15% and false negatives and fixation loss <33% if the standard Swedish interactive thresholding algorithm was used)⁸ and 5 or more years of follow-up. Visual field progression was estimated using all eligible tests via trend analysis. Because of the different scales used, a correction of +1.0 dB was applied to all thresholds measured using the full-threshold algorithm, in an attempt to maintain equivalence when the algorithm changed at the commencement of the second phase of the OHTS.¹ Simple linear regression of the VF data over time was performed to provide a slope (representing the rate of change in decibels per year) and a *P* value (representing the statistical significance of the slope compared with zero). Two types of analyses were performed: (1) regression of the sequence of mean deviation (MD) values to calculate its rate of change (mean deviation rate of change [MDR]); and (2) pointwise linear regression (PLR) in which the sensitivity at each VF location in the 30-2 strategy was regressed over time. A location was considered to be significantly progressing if the sensitivity deteriorated at a rate faster than -0.5 dB/y with *P* < .01.

Three PLR criteria were established for an eye to be considered progressing: (1) at least 1 progressing location; (2) at least 2 progressing locations; and (3) at least 2 neighboring progressing locations in the same hemifield.

DEFINITION OF GLAUCOMATOUS OPTIC DH

Details of how DHs were identified in OHTS have been previously described.⁴ Postdilation stereoscopic optic disc photographs were obtained annually and nondilated clinical examination of the optic nerve was performed at the 6-month interval visits. All stereophotographs were reviewed at the OHTS optic disc reading center. A DH was defined as a flame- or splinter-shaped hemorrhage that was radially oriented and perpendicular to the disc margin. These hemorrhages characteristically extend from within the optic nerve head to the adjacent retina, crossing any peripapillary zone of absent or disrupted retinal pigment epithelium, but need not occupy the entire length of this typical position.⁴

Other causes of optic disc bleeding (eg, posterior vitreous detachment, diabetic or hypertensive retinopathy, and trauma) were excluded. We included only DH detected by the optic disc reading center or those DHs detected by the site investigators that were subsequently confirmed on disc photographs.

POAG END POINTS

Details of how POAG end points were defined in the OHTS have been reported.^{1,2} In summary, confirmed structural and functional change were defined by event analysis. A technically acceptable VF result was considered abnormal if the corrected pattern standard deviation (PSD) or later PSD was abnormal at the *P* < .05 level or if the glaucoma hemifield test result was outside normal limits. Confirmation of a VF abnormality required initially 2 VF test results from 1994 to 1998 and thereafter 3 consecutive test results meeting the earlier-mentioned criteria. Optic disc progression was defined as a generalized or localized thinning of the optic disc rim compared with baseline. Disc hemorrhage, nerve fiber layer dropout, and change in the depth of the cup were not considered grounds for a determination of optic disc change. Each case was then evaluated by the OHTS end point committee, which determined whether the changes were consistent with glaucoma.

Visual field trend analysis included all eligible VF test results regardless of their relationship with the time at which a first DH was detected. Therefore, MDR and PLR end points for DH eyes correspond to rates of VF change during the entire follow-up period for eyes with DH ever detected during their follow-up and not only using the VF sequences after DH detection. This approach was chosen because DHs are transient and often go undetected, even if optic discs are photographed periodically as occurred in OHTS.^{12,13} Also, it is not possible to determine the exact moment at which a DH actually occurred so that the determination of a baseline VF test result based on the date of detection might be imprecise. Therefore, we compared the velocities of VF change between eyes with "hemorrhagic" vs "nonhemorrhagic" optic discs.¹²

STATISTICAL ANALYSES

The generalized estimating equations (GEE) technique¹⁴ was used to account for correlation between the fellow eyes of an individual. Linear and logistic GEE regression were used to assess the association between rates of VF change and different progression end points in patients with and without DH. Given that differences between eyes with and without DH at baseline could affect the progression analysis, variables shown to be independent predictors of glaucoma conversion in OHTS (ie, age, central corneal thickness, baseline IOP, PSD, and vertical cup-disc ratio)^{2,15} were compared between

Table 1. Comparison of Baseline Risk Factors Between DH and Non-DH Eyes

Variable	Mean (SD)		P Value
	Non-DH Eyes (n = 2420)	DH Eyes (n = 187)	
Age, y	55.2 (9.3)	59.0 (9.4)	<.01
Baseline IOP, mm Hg	24.9 (3.0)	25.5 (2.9)	<.01
CCT, μm	574 (38.9)	569 (37.9)	.14
Baseline MD, dB	0.39 (1.22)	0.50 (1.18)	.27
Baseline PSD, dB	1.92 (0.30)	1.97 (0.30)	.05
Baseline VCDR	0.39 (0.20)	0.45 (0.20)	<.01

Abbreviations: CCT, central corneal thickness; DH, disc hemorrhage; IOP, intraocular pressure; MD, mean deviation; PSD, pattern standard deviation; VCDR, vertical cup-disc ratio.

the 2 groups. Variables that were significantly different at baseline between DH and non-DH eyes were entered in a multivariable model to determine whether DH occurrence was independently associated with more rapid rates of VF change.

Computerized statistical analyses were performed using the R software environment (R Development Core Team, <http://www.R-project.org>). Statistical significance was defined at $P < .05$.

RESULTS

We included 2607 eyes of 1378 participants. Of these, 359 eyes of 276 participants reached an OHTS POAG end point. The mean (SD) number of VF tests per eye was 23.7 (4.9), spanning a mean (SD) of 12.2 (2.0) years of follow-up. The mean (SD) VF MD at baseline was 0.40 (1.2) dB and the mean (SD) VF PSD at baseline was 1.90 (0.3) dB. At least 1 DH was detected in 187 eyes (7.2%). One hundred thirty-five eyes had a single DH and 52 eyes (2%) had recurrent (≥ 2) DH.

Participants with DH were older ($P < .01$) and had higher baseline IOP ($P < .01$), larger baseline vertical cup-disc ratios ($P < .01$), and worse baseline PSD values ($P = .05$) (**Table 1**). Eyes with recurrent DH had thinner corneas and worse baseline MD values than those with a single DH (**Table 2**). In the univariable analysis, the MD deteriorated significantly faster in DH eyes when compared with non-DH eyes (mean [SD], -0.17 [0.27] dB/y vs -0.07 [0.19] dB/y, respectively; $P < .01$, GEE regression). In the multivariable model, DH occurrence remained an independent factor associated with faster rates of VF change even after adjusting for the differences at baseline mentioned earlier ($P < .01$) (**Table 3**). There was a significant association between DH occurrence (yes/no) and whether an eye was considered to be progressing using all 3 PLR criteria described earlier: odds ratio (OR) for at least 1 progressing location, 3.6; $P < .01$; OR for at least 2 progressing locations, 2.8; $P < .01$; and OR for at least 2 neighboring progressing locations in the same hemifield, 2.5; $P < .01$.

Among eyes that reached a POAG end point as determined by the OHTS POAG end point criteria ($n = 359$), 73 (20%) had at least 1 DH. Among these 359 end point eyes, the mean (SD) MDR of eyes with DH was similar

Table 2. Comparison of Baseline Risk Factors for Single and Recurrent DHs

Variable	Mean (SD)		P Value
	Single DH Eyes (n = 135)	Recurrent DH Eyes (n = 52)	
Age, y	58.4 (9.4)	60.7 (9.2)	.14
Baseline IOP, mm Hg	25.3 (2.7)	25.9 (3.3)	.23
CCT, μm	574 (37.2)	557 (37.0)	<.01
Baseline MD, dB	0.54 (1.17)	0.12 (1.45)	.05
Baseline PSD, dB	1.95 (0.31)	2.02 (0.26)	.09
Baseline VCDR	0.39 (0.20)	0.45 (0.20)	.09

Abbreviations: CCT, central corneal thickness; DH, disc hemorrhage; IOP, intraocular pressure; MD, mean deviation; PSD, pattern standard deviation; VCDR, vertical cup-disc ratio.

Table 3. Multivariable Model: Association Between Baseline Variables, DH, and the Global Rate of Visual Field Change (Mean Deviation Rate)

Risk Factors	Coefficient	SE	P Value
DH (yes)	-0.067	0.018	<.01
Age (per 9.4 y from mean)	-0.060	0.005	<.01
Baseline IOP (per 3 mm Hg from mean)	-0.018	0.004	<.01
CCT (per 39 μm from mean)	0.011	0.005	.02
Baseline PSD (per 0.31 dB from mean)	-0.016	0.004	<.01
Baseline VCDR (per 0.2 unit from mean)	-0.013	0.005	<.01

Abbreviations: CCT, central corneal thickness; DH, disc hemorrhage; IOP, intraocular pressure; PSD, pattern standard deviation; VCDR, vertical cup-disc ratio.

to eyes that did not have a DH (-0.30 [0.36] vs -0.25 [0.35] dB/y, respectively; $P = .27$, GEE regression).

Recurrent DH eyes had a similar MDR when compared with those with a single DH (mean [SD], -0.20 [0.18] vs -0.16 [0.29] dB/y, respectively; $P = .23$, GEE regression). In contrast to the MDR results, eyes with 2 or more DHs were significantly more likely to display PLR progression than eyes with a single DH for all 3 PLR criteria described earlier: OR for at least 1 progressing location, 4.2; $P = .01$; OR for at least 2 progressing locations, 3.4; $P < .01$; and OR for at least 2 neighboring progressing locations in the same hemifield, 3.6; $P < .01$.

We investigated the relationship between the rate (frequency) of DH detection and the rates of VF progression and found that after controlling for the other covariates (PSD, vertical cup-disc ratio, central corneal thickness, IOP, and age), a greater rate of DH detection was significantly associated with faster MDR ($\beta = -0.70$; 95% CI, -0.30 to -1.09 ; $P < .001$). Of the 52 eyes with 2 or more DHs, 31 eyes (60%) developed recurrence in the same location (within 1 clock hour) and 21 eyes (40%) developed recurrence more than 1 clock hour apart. The location of the recurrent DH (within 1 clock hour or not) did not affect MDR ($P = .68$) or PLR ($P = .52$, $.71$, and $.87$ for the 3 PLR criteria, respectively).

In addition, we investigated whether initial randomization was significantly associated with the likelihood

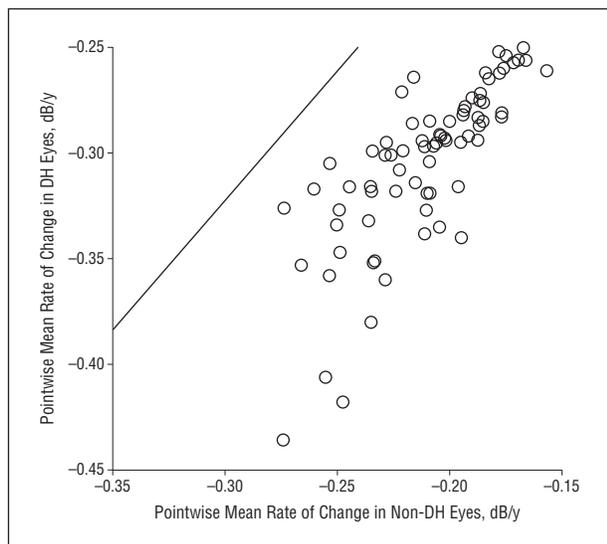


Figure 1. The mean rates of change (from pointwise linear regression) in eyes without disc hemorrhage (DH) (abscissa) plotted against the mean rates of change in eyes with DH (ordinate) for each location in the 30-2 visual field. The black line represents equality.

of DH or its recurrence. Eyes initially randomized to treatment were less likely to have a DH during follow-up (OR, 0.71; $P=.03$). Among eyes with at least 1 DH, there was no significant effect of initial randomization on the likelihood of DH recurrence (OR, 0.90; $P=.76$).

Figure 1 compares the pointwise rates of change at each location in the 30-2 VF, with non-DH eyes (abscissa) plotted against DH eyes (ordinate). All points lie below the unity line ($y=x$, black solid line) indicating that DH eyes showed more rapid decline than non-DH eyes at every location in the VF. **Figure 2** shows the rates of change at all VF locations arranged as a right eye 30-2. Darker shading signifies more rapid rates of deterioration. In DH eyes, the most rapidly deteriorating locations tend to be concentrated in the nasal field, that is, at or outside 15° from the vertical meridian. In non-DH eyes, the rate of change tended to be more rapid at greater eccentricity regardless of meridian.

COMMENT

We investigated the velocity of VF change in the eyes of OHTS participants with and without DH and tested whether DH recurrence or randomization assignment had any effect on progression outcomes using trend analysis. We found that OHTS participants who developed a DH during the study showed more rapid global rates of VF change and were considered to have experienced progression by PLR criteria more often than eyes without DH, even after adjusting for baseline differences. Eyes with recurrent DH had similar global velocities of VF change when compared with eyes with a single DH. However, eyes with recurrent DH were more likely to meet our 3 PLR criteria (ie, at least 1 progressing location; at least 2 progressing locations; and at least 2 neighboring progressing locations in the same hemifield) than those with a single DH.

Our findings are consistent with a previous OHTS publication demonstrating the importance of DH as a risk

factor for conversion from ocular hypertension to POAG using event analysis, which revealed an OR of 3.7 in a multivariate analysis.⁴ In our analysis, initial randomization to treatment significantly decreased the likelihood of developing a DH compared with eyes in the observation group, while the OHTS previous report investigating this association found no statistical significance ($P=.13$).⁴ Given the strong relationship between DH and VF progression,^{4,12,13,16,17} our findings are in consonance with Kass et al,¹⁸ who recently reported that early treatment was beneficial in preventing VF progression using event-based end points in the OHTS population.

To our knowledge, this is the first report of a randomized clinical trial exploring the rate of VF change in ocular hypertensive eyes with comparisons between eyes with and without DH. The Collaborative Normal-Tension Glaucoma Study¹⁶ did not find a difference in MDR between eyes with and without DH in a group of patients with established glaucoma (with baseline VF damage, unlike OHTS participants) and statistically normal IOP. However, the mean survival time of untreated eyes without an initial DH was 2159 days, which was significantly longer than the 1187 days for the untreated eyes with a DH at baseline. Even though the Early Manifest Glaucoma Trial¹⁷ showed no association between treatment and the incidence of DH, Medeiros et al¹⁹ recently showed that IOP-lowering therapy slows the velocity of VF progression in eyes that have had a DH. Also, substantial IOP reduction following trabeculectomy decreases the incidence of DH in patients with established glaucoma.²⁰ The beneficial effect of IOP reduction on the likelihood of having a DH in the present study suggests that DH may be partially IOP dependent or, at the very least, IOP sensitive.

The fact that we found no significant difference in MDR between eyes with single vs recurrent DH has at least 4 potential explanations. First, the classification of eyes into “recurrent vs nonrecurrent bleeders” is rather arbitrary, since DHs are often missed or undetected if the optic disc is infrequently photographed.¹⁸ Airaksinen¹² proposed that classifying eyes into “bleeders vs nonbleeders” may be more appropriate than “recurrent vs nonrecurrent.” Second, despite being sufficient to prevent VF progression,² IOP reduction in OHTS may have been insufficient to prevent DH recurrence. Third, DH could be seen as the result (or the by-product) of active structural progression,²¹ and structural change has been reported to predict future VF deterioration.^{11,22} A recurrent DH could be a sign of ongoing structural collapse rather than an additional acute event leading to more rapid VF deterioration. Consistent with this finding, in a retrospective study, de Beaufort et al²¹ demonstrated that glaucomatous eyes with single and recurrent DH had similar global rates of VF change and risk of deterioration using PLR criteria. Finally, because of the localized nature of DH, the use of VF MDR (which summarizes all VF data) may not detect localized VF progression. This hypothesis is supported by our finding that recurrent DH eyes reached our PLR criteria more often than eyes with a single DH.

The group with DH had more risk factors at baseline for progression than the group without DH. We tried to minimize this confounding effect by performing a mul-

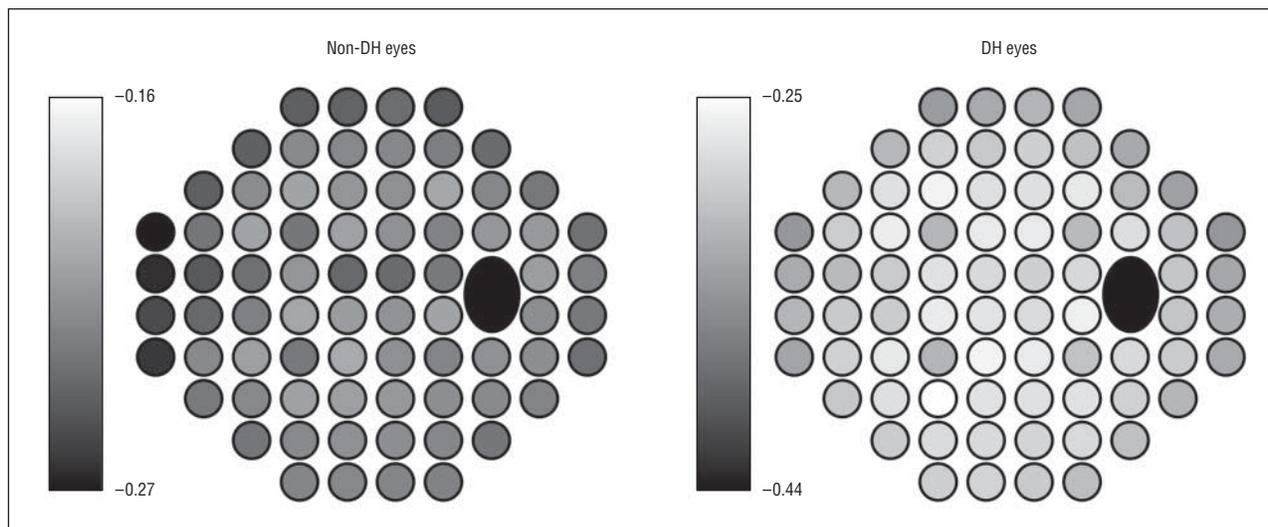


Figure 2. Gray scale representation of the pointwise rates of change, arranged as a right eye 30-2 visual field, in disc hemorrhage (DH) (right) and non-DH (left) eyes. In each case, the locations are shaded according to their average rate of change, from black (most rapid change) to white (least rapid change). Average rates are as shown in the key in each case, in decibels per year.

tivariate analysis including the previously reported risk factors for POAG conversion² as covariates. This analysis confirmed a statistically independent effect of DH on rapid VF progression.

Mean deviation was used in the present study because PSD and VF index fail to detect the diffuse, generalized reduction of sensitivity that may occur in early glaucoma.^{23,24} Linear regression of PSD rather than MD values also seems to show no benefit regarding sensitivity and specificity to detect progression.²⁵ Also, PSD behaves non-monotonically with disease progression, which invalidates the assumptions of linear regression a priori. The VF index is also subject to a “ceiling effect” whereby very early or peripheral damage is not well detected,²⁴ making it less suitable for use in eyes with early VF change such as those encountered in the OHTS.

At first glance, the β coefficients in Table 3 seem to suggest little effect of DH development on rates of VF progression. Pooled data, however, do not take into account differences in the distribution of slopes between the 2 groups (DH vs non-DH). Moreover, we included all usable VF tests performed during the entire OHTS follow-up, and not only those immediately after DH detection, which would tend to mask the more rapid slopes after DH and ignore the focal nature of glaucoma progression. For instance, the ORs for all 3 PLR criteria were very high (OR for at least 1 progressing location, 3.6; $P < .01$; OR for at least 2 progressing locations, 2.8; $P < .01$; and OR for at least 2 neighboring progressing locations in the same hemifield, 2.5; $P < .01$), that is, having at least 1 DH increased the odds of pointwise progression by more than 250% when compared with eyes without DH. This is a very strong effect that we believe justifies more aggressive therapy for these eyes. Additionally, all patients included in our analysis eventually began ocular hypotensive therapy (transition from OHTS phase 1 to phase 2), which may have veiled a more meaningful effect of DHs if no treatment had been initiated. Finally, a more detailed analysis of Table 3, which includes risk fac-

tors reported in the OHTS,² reveals that the role of DH on MDR was approximately 6 times stronger than baseline IOP, central corneal thickness, vertical cup-disc ratio, and PSD.

A different way of analyzing our results regarding the importance of DH on global rates of VF progression is to compare the effect of DH with other known risk factors. For instance, in our study, having a DH during follow-up had as deleterious an effect on MDR as (1) being 10.5 years older than average at baseline; (2) having an 11.4-mm Hg higher baseline IOP than average; (3) having a 23.1- μ m thinner cornea than average; (4) having a 1.3-dB worse baseline PSD than average; or (5) having a 0.1-unit worse baseline vertical cup-disc ratio than average. Clinicians should be aware of these comparisons when assessing the risk of glaucoma conversion among patients with ocular hypertension in practice.

In summary, ocular hypertensive eyes with DH display rates of VF deterioration that are more than twice as rapid as eyes without DH. Recurrent DH does not appear to affect the global rate of VF change as captured by MDR but may impact localized rates as captured via PLR. Assuming linearity of VF change, DH eyes will take half as long to reach VF sensitivity values consistent with meaningful visual impairment. New models for risk calculation in patients with ocular hypertension might benefit from inclusion of DH as a covariate. The presence of DH affects clinical outcomes and should alert the physician to an increased patient risk profile that may require more aggressive therapy.

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