

The Association between Glaucomatous Visual Fields and Optic Nerve Head Features in the Ocular Hypertension Treatment Study

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Purpose: To determine the association between change from baseline in the optic nerve head (ONH) and the visual field (VF) during follow-up of ocular hypertension participants in the Ocular Hypertension Treatment Study.

Design: Longitudinal randomized clinical trial.

Participants: One hundred sixty-eight eyes of 152 ocular hypertensive participants ages 40 to 80 years.

Methods: Cox hazard models were applied to 3232 eyes, which included 81 eyes that reached a study end point by developing a glaucomatous VF (VF end point) and 128 eyes that reached a study end point by developing an optic disc change (optic disc end point).

Main Outcome Measures: Primary open-angle glaucoma end point as determined by changes in the VF or optic disc.

Results: Forty-one eyes reached an end point by both VF and optic disc criteria; 40 eyes reached only a VF end point, and 87 reached only an optic disc end point. Times to reach isolated disc or field end points were similar. Visual field end points were more likely ($P < 0.0001$) in eyes that showed the following ONH features: an ONH hemorrhage, thinning of the optic disc rim, or enlargement of the horizontal cup-to-disc (C/D) ratio. Optic disc end points were more likely ($P < 0.0001$) in eyes that showed the following VF features: some evidence of a nasal step or a partial arcuate VF defect, or an increase in the pattern standard deviation (PSD).

Conclusions: Both the VF and the optic disc must be monitored with equal diligence, because either may show the first evidence of glaucomatous damage. Changes in the ONH based on stereophotographic observation (rim thinning, hemorrhage, or a slight increase in C/D ratio) and VF changes (evidence of a nasal step/partial arcuate defect or an increase in PSD) suggest that these cases have an increased risk of developing glaucoma. Confirmation of such subtle findings should be sought through repeat testing and correlation with other clinical results. *Ophthalmology* 2006;113:1603–1612 © 2006 by the American Academy of Ophthalmology.

The clinical diagnosis of glaucoma and monitoring the course of subjects with glaucoma for progressive change

utilize evaluations of the visual field (VF), optic disc, and retinal nerve fiber layer (RNFL). The logical relationship

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between glaucomatous structural changes in the optic nerve head (ONH) and functional loss in the VF is described in numerous articles.¹⁻⁵ Progressive change or abnormality in the optic disc or the RNFL typically is detected before the VF is recognized as abnormal in the early stages of primary open-angle glaucoma (POAG).⁶⁻¹² Among the structural features that have been reported to precede detectable field loss are notching and thinning of the neuroretinal rim, disc hemorrhage, and localized or diffuse loss of the RNFL.¹³⁻³²

However, as recently reviewed,³³ there is a variable relationship between the manifestations of structural (e.g., ONH and RNFL) and functional (e.g., VF) clinical deficits produced by glaucoma, perhaps because of individual variation in the details of topography or tissue components damaged by the glaucomatous process. In any event, in some eyes, with present clinical methods, structural and functional glaucomatous losses become apparent simultaneously, or functional glaucomatous loss appears without recognition of structural damage.³⁴ Direct comparison across studies is made difficult for various reasons, including retrospective data collection, use of different examination methods, small sample sizes, limited follow-up time, or imprecise inclusion/exclusion criteria.³³⁻⁴³

The Ocular Hypertension Treatment Study (OHTS) provides a unique opportunity to study further the relationship of clinical VF and ONH abnormalities when they first emerge, as each modality was monitored carefully and independently in participants while glaucoma first developed. The OHTS is a randomized clinical trial to evaluate the safety and efficacy of topical hypotensive medication in delaying or preventing the onset of VF loss and/or optic nerve damage in participants with elevated intraocular pressure (IOP) who are at moderate risk for developing POAG. Details of the methods and results of the OHTS have been published.⁴⁴⁻⁴⁸

This report is an analysis of the association of changes at the ONH with VF changes while these participants with ocular hypertension were being monitored.

Materials and Methods

A total of 1636 ocular hypertensive participants without evidence of glaucomatous damage (ages 40-80 years) and with an IOP between 24 mmHg and 32 mmHg in one eye and between 21 mmHg and 32 mmHg in the other eye were enrolled and randomized either to observation or to treatment with commercially available topical ocular hypotensive medications. Institutional review board/ethics committee approval and informed consent were obtained in accordance with the Health Insurance Portability and Accountability Act regulations. Twenty participants (40 eyes) had no follow-up data and thus are excluded from the analysis.

To qualify for enrollment, VF test results (30-2 full-threshold test with the Humphrey Visual Field Analyzer [Carl Zeiss-Meditec, Inc., Dublin, CA]) were required to be normal (global indices within the 95% age-specific population norms and a glaucoma hemifield test result within the 97% age-specific population norm based on STATPAC 2 analysis) in both eyes, as determined by the Visual Field Reading Center (VFRC).⁴⁹ The ONHs also were evaluated and judged to have an anatomic configuration within normal limits in both eyes on clinical examination and on inspection of stereoscopic optic disc photographs, as determined by the Optic Disc

Reading Center (ODRC).⁵⁰ Participants were not included if VF examination results or photographs of good clarity and stereopsis could not be obtained. Participants who had a visual acuity worse than 20/40 in either eye, previous intraocular surgery, or diabetic retinopathy or other diseases capable of causing VF loss or optic disc change also were excluded.

Follow-up visits were scheduled every 6 months from the date of randomization. Visual fields were tested every 6 months, and optic disc stereophotographs were taken each year or more often when required by the protocol because of suspected development of abnormality. Participants and clinical investigators were not masked to the randomization assignment during follow-up, but the ODRC, VFRC, and End Point Committee were masked to treatment status.

Visual field abnormalities were determined from single-field STATPAC printouts by trained and certified masked readers at the VFRC,⁴⁹ and optic disc change was determined from stereoscopic photographs by trained and certified masked readers at the ODRC.⁵⁰ Throughout the study, readers at each resource center (VFRC and ODRC) were masked not only to all clinical information about the patient, including the arm of the study to which he or she was randomized, but also to any previous assessment of the field or disc at either center, any determinations by the End Point Committee, and current findings at the other reading center.

According to OHTS criteria, a VF was considered to be abnormal if the test was reliable and glaucoma hemifield test (GHT) and/or corrected pattern standard deviation (CPSD) global index results were outside normal limits ($P < 0.01$ and $P < 0.05$, respectively). Borderline GHT results were an indication that the results were suspicious but not clearly abnormal. Thus, borderline GHT results were not included as an abnormal field. An OHTS VF was classified as reliable if none of the reliability indices (false-positive errors, false-negative errors, or fixation losses) exceeded the 33% limit. An optic disc was examined for a change from baseline condition, manifest mainly by a neuroretinal rim that is thinner than before, with corresponding expansion of the cup in any meridian or diffusely around the disc circumference. The reader compared the 2 photographs without knowing which was the baseline and which was the follow-up photograph. Change detection was considered evidence of developing glaucoma only when the later photograph was found to be worse than the earlier photograph.⁵¹ Other abnormalities evident in the photographs, such as the findings of central retinal vein occlusion, were recorded but not considered to represent a glaucomatous change of the optic nerve. Whether or not glaucomatous changes were observed, VF examinations and optic nerve photographs were obtained according to the study protocol, even if the patient had reached a study end point and a change in management occurred. Visual field test results and optic nerve photographs were compared with the baseline, with the readers unaware of the patient's status.

Before the VFRC would ask the End Point Committee to consider an eye for study end point, the OHTS VF abnormality was required on 3 consecutive reliable VFs with the abnormality in the same location and on the same index (GHT and/or CPSD outside of normal limits [$P < 0.01$ and $P < 0.05$, respectively]).⁴⁷ If the follow-up VF was abnormal on 2 consecutive follow-up visits 6 months apart, on the same index and in the same location, confirmation was obtained by an additional third VF test obtained within 1 day to 8 weeks of the second abnormal field. If this third VF was also abnormal, and the defect was in the same location and on the same index, the Coordinating Center was notified. All of the VFs, including the set of 3 consecutive abnormal VFs (the 2 obtained at consecutive 6-month visits plus the confirmatory field obtained promptly after the second abnormal one), were referred to the End Point Committee for review.

Similarly, before the ODRC would send a photograph of the eye to the End Point Committee for study end point consideration, optic disc change was confirmed. Optic disc photographs were taken routinely only once a year (unlike VFs, which were obtained every 6 months). Therefore, if a single routine annual photograph was judged to have changed, a fresh set of confirmation photographs was obtained within 4 weeks or, in some cases in which this was not possible, the next available photographs were used for confirmation. The confirmation photographs were inspected arbitrarily mixed in with other photographs examined that day, so the reader was masked to the fact that the previous photograph had been judged to have changed from baseline. If the change was not confirmed on these photographs obtained on a separate day, the patient was returned to the schedule of photographs annually. If the 2 sets of photographs confirmed optic disc change, the Coordinating Center was notified and the photographs were referred to the End Point Committee for review.

In this way, these 2 modalities (VF and optic disc) were evaluated separately and independently, in masked fashion, by the VFRC and ODRC. If either center recorded a confirmed change, all information from both centers was sent to the End Point Committee, which was masked to the randomized assignment of the individual. The End Point Committee reviewed the participant's ocular and medical history, stereoscopic optic disc photographs, and VF examinations. They determined whether the VF changes were due to POAG and whether optic disc change was a clinically significant magnitude and could not be attributed to differences in photographic technique or to nonglaucomatous disease.⁴⁷ The date of study end point was designated as the test day when the *first* VF or optic disc photograph that suggested development of POAG was noticed, and the remaining confirmation procedure and evaluation by the End Point Committee were conducted simply as a process to assure specificity of the changes. For ethical reasons, an effort was made to detect very subtle change, in an effort not to miss early glaucomatous injury, because one randomized group of participants with ocular hypertension was not receiving treatment. Because of the risk of false judgments of small changes, confirmation was required for scientific reasons to ensure specificity of the end point.

Noting that the optic disc and the VF were evaluated independently, and that independent readings continued at each center even if the other center perceived a change or the End Point Committee had declared the patient to have reached end point, we took the opportunity to examine the time relationship between detectable changes in the 2 modalities. Specifically, we evaluated optic disc and VF characteristics at baseline and at all subsequent visits, before and after reaching an OHTS POAG end point. Importantly, we included evaluations that were judged to show abnormality but that were not confirmed and verified by the End Point Committee, to judge the predictive value of unconfirmed observations.

As a refinement of evaluation of the VFs in the OHTS, a classification system consisting of 17 VF abnormalities was developed to characterize VF defects. This classification system was validated by showing it to be reproducible.⁴⁸ The common defects that turned out to be relevant to the present study included nasal steps and partial arcuate defects. A nasal step was defined as a limited field loss adjacent to the nasal horizontal meridian with at least 1 abnormal point ($P < 0.05$) at or outside 15° on the meridian. The defect could not include >2 significant points (on either plot) in the nerve fiber bundle region on the temporal side. It was possible to have a nasal step defined by a single test point that was sufficiently abnormal along the horizontal meridian. In these instances, caution was employed to avoid the possibility of higher false-positive rates. A partial arcuate defect was defined as VF loss consisting of ≥ 3 adjacent points occupying some portion of the

arcuate nerve fiber bundle region that extended from the blind spot toward the nasal meridian superiorly or inferiorly. The defect was generally contiguous with either the blind spot or the nasal meridian and had to include at least 1 abnormal location in the temporal VF (temporal to the vertical meridian passing through the point of fixation).

As the OHTS study end point represents the development of POAG, the term *POAG end point* was used in the primary outcome reports of Kass et al⁴⁴ and Gordon et al.⁴⁵ We restrict the use of the term *end point* to signify a confirmed change in either the optic disc or VFs that were later verified by the End Point Committee. The committee made its judgment based on all available information, except to which arm of the study the patient had been assigned. A distinction was made between 2 types of end points, depending on whether the case was sent to the End Point Committee for verification from the ODRC based on a confirmed optic disc or from the VFRC based on confirmed VF criteria. These were noted respectively as *disc end point* or *field end point*. For any eye during follow-up, the 2 types of end points might have occurred simultaneously, one center might have initiated an end point review after the other had already done so, or only one of the end points might have been reached to date. For the reported primary analysis of the study determining treatment effect, no distinction was made, and the term *POAG end point*, if not otherwise specified, represents the first of any of these circumstances to occur.

In this report, to make a distinction from *end point*, we will use the term *change* when describing any change in the optic disc or VF compared with the baseline condition, whether or not it later was confirmed or, even if confirmed, ultimately verified as an official study end point by the End Point Committee.

We included data through June 2002 (3232 eyes) and used marginal Cox proportional hazards⁵¹ to study the relationship between observation of equivocal optic disc or VF findings and the development of an end point judged by confirmed VF or optic disc change. These failure time (survival) models for studying POAG onset included corrections for correlations between fellow eyes from the same subject and adjustments for covariates.

It should be noted in the Cox model analysis that all eyes that did and did not reach an end point, as well as all eyes that did and did not show change, were included. In essence, there was a built-in control group from those eyes regardless of change/no change or end point/no end point.

Optic disc and VF features were recorded during the follow-up period before but, importantly, also after an end point. Thus, there was opportunity if one reading center prompted an End Point Committee verification to discover whether the other center reported verification later in the study. Moreover, VF or optic disc change on a visit, not later confirmed, could be analyzed with respect to how it might relate to later end point determination initiated by either center. In all analyses discussed in this report, we adjusted for baseline IOP, age, and randomization assignment. The OHTS protocol required participants reaching an end point to receive topical ocular hypotensive medication. For example, if an eye in the observation group developed an optic disc end point before a VF end point, the eye would start to receive treatment at the time of optic disc end point and would be on treatment in the interval before reaching a VF end point. We consequently included treatment as a time-dependent covariate in the failure time model to account for any changes in treatment status, which ultimately may have affected the onset of a change in the other modality.

We report the relationship of the following optic disc changes (during follow-up) with a VF end point: optic disc hemorrhage, rim thinning, and horizontal cup-to-disc (C/D) ratio. We analyzed the existence of an optic disc hemorrhage and rim thinning at any time of or before a VF end point determination. Follow-up horizontal C/D ratio values were recorded at the time of VF end point

Table 1. One Hundred Sixty-Eight Eyes of 152 Ocular Hypertensive Participants with Primary Open-Angle Glaucoma (POAG) End Points

POAG Study End Point	No. of Eyes	% of Eyes
Optic disc, no visual field	87	52
Visual field, no optic disc	40	24
Both visual field and optic disc at same time	12	7
Visual field initially, then optic disc	17	10
Optic disc initially, then visual field	12	7
Total	168	100

onset or the last visit, whichever came first. Vertical C/D ratio data were not recorded until several years after study initiation; hence, we cannot comment on their association with our findings.

We report the relationship of the following VF features (during follow-up) with an optic disc end point: mean deviation (MD), pattern standard deviation (PSD), CPSD, nasal step defect, partial arcuate defect, and the GHT. The follow-up MD, PSD, and CPSD indices were taken at the time of optic disc end point or last visit, whichever came first. An eye was classified as having a nasal step or partial arcuate defect if one of those abnormalities was present at any time on or before an optic disc end point determination. Similarly, we looked for the existence of an abnormal GHT result at or before an optic disc end point determination.

Results

We evaluated a total of 168 eyes (of 152 participants) with (1) both optic disc and VF end points, (2) only a VF end point, or (3) only an optic disc end point (Table 1). A total of 41 eyes reached both VF and optic disc end points to date, either simultaneously or sequentially. Of these, 17 reached a VF end point before reaching an optic disc end point; 12 reached an optic disc before a VF end point; and 12 reached an optic disc and a VF end point at the same visit. There was not a statistically significant difference in the number of eyes in these categories, meaning there was not a greater probability among eyes that achieved both end points for

the VF end point to come before the optic disc end point or vice versa.

Times to optic disc end point and VF end point were essentially the same. Among the 87 eyes that reached an optic disc end point but not a VF end point, the median time to optic disc end point was 1821 days. Among the 40 eyes that reached a VF end point but not an optic disc endpoint, the median time to VF end point was 1801 days.

Among the 87 eyes that reached an optic disc end point, we tabulated (Fig 1) the proportion of visits in which the VF showed change (i.e., the visits in which the eye displayed an abnormal VF [GHT $P < 0.01$ and/or CPSD $P < 0.05$]), even though these abnormalities were not necessarily confirmed subsequently. The visits are categorized temporally as occurring either before or after optic disc end point (Fig 1). Eyes displayed abnormal VFs on some visits before the optic disc produced an optic disc end point (Fig 1). Abnormal VFs, however, became more frequent after an optic disc end point was reached: 25% (22/87) of the eyes displayed abnormal VFs in 30% to 100% of the visits after an optic disc end point, but none of the eyes displayed such a high frequency of abnormal VFs before the optic disc end point ($P < 0.0001$).

In a similar way, we tabulated among the 40 eyes that reached a VF end point the proportion of visits in which the ONH showed a disc hemorrhage and/or rim thinning (Figs 2, 3). Seven of the 40 eyes displayed a disc hemorrhage before VF end point, and 5 of the 40 eyes displayed a rim thinning before VF end point. The proportion of visits in which eyes displayed a disc hemorrhage or rim thinning did not differ significantly before and after VF end points (Figs 2, 3).

There was no significant difference found in the baseline horizontal C/D ratio in a pairwise comparison of the 3 subgroups: (1) the 87 eyes that reached an optic disc end point only, (2) the 40 eyes that reached a VF end point only, and (3) the 41 eyes that reached both VF and optic disc end points, either simultaneously or sequentially.

We utilized univariate Cox proportional hazard analyses to study the relationship between particular follow-up observations of optic disc features and subsequent VF end points, adjusting for baseline IOP, treatment, age, and correlation between fellow eyes (Fig 4). Both optic disc hemorrhage and rim thinning were related significantly ($P < 0.0001$) to a VF end point with an odds ratio

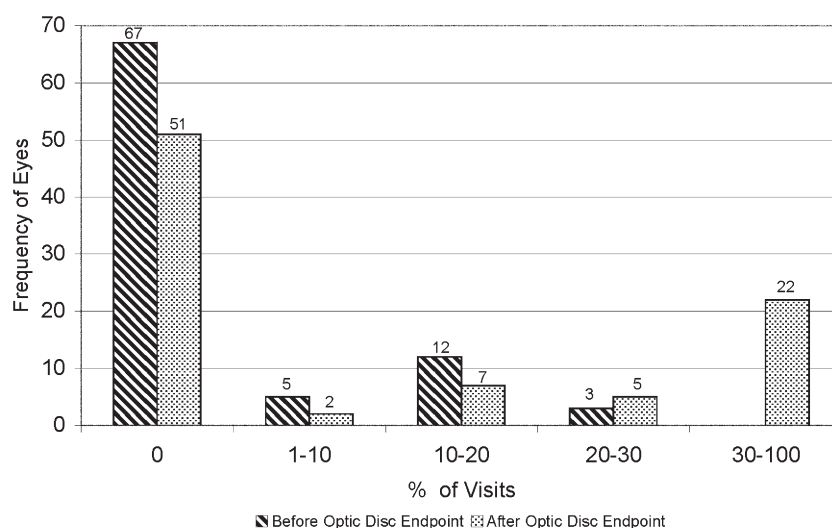


Figure 1. Percentage of visits during follow-up with abnormal visual fields (VFs) (glaucoma hemifield test and/or corrected pattern standard deviation are outside normal limits with $P < 0.01$ and $P < 0.05$, respectively) before and after the optic disc end point among 87 eyes that have not yet developed a VF end point ($P < 0.0001$).

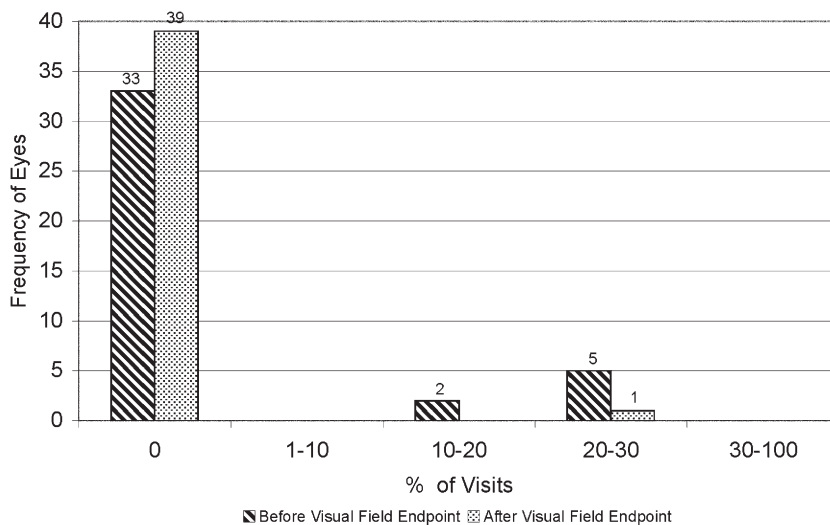


Figure 2. Percentage of visits during follow-up with an optic disc hemorrhage before and after the visual field end point among 40 eyes that have not yet developed an optic disc end point.

(OR) near 2.25. Follow-up horizontal C/D ratio (treated in the model as a continuous variable with 0.1 increments) also was related significantly to a VF end point ($P < 0.0001$), with an OR of 1.37. The average horizontal C/D ratio for eyes reaching a VF POAG end point was 0.50; for eyes not reaching a VF POAG end point, the average horizontal C/D ratio was 0.39.

Similar univariate analyses were undertaken of the relationship between follow-up VF features and the likelihood of reaching an optic disc end point, adjusting for baseline IOP, treatment, age, and correlation between fellow eyes (Fig 4). Both nasal step and partial arcuate defects were related significantly ($P < 0.0001$) to an optic disc end point, with an OR of 2.41. The follow-up PSD also was related significantly ($P < 0.0001$) to an optic disc end point, with an OR of 1.31 per unit decibel. Similar results were obtained with CPSD. In addition, the follow-up MD was related significantly ($P < 0.0001$) to an optic disc end point, with an OR of 1.10 when MD is expressed as decibel units lower than the mean normal

value of 0 decibels. However, an abnormal GHT result was not related significantly to an optic disc end point ($P = 0.07$).

In a multivariate model that included MD and PSD, MD no longer was related significantly to an optic disc end point onset ($P = 0.92$).

Discussion

In this study, we found that a definite abnormality in either the disc or the VF may occur before the other, and they are less often detected simultaneously. If one defines the clinical onset of glaucomatous optic neuropathy as either a recognized progressive change in the structure of the optic nerve or an abnormality in visual function by standard perimetry, presumed to be driven by a diminished number

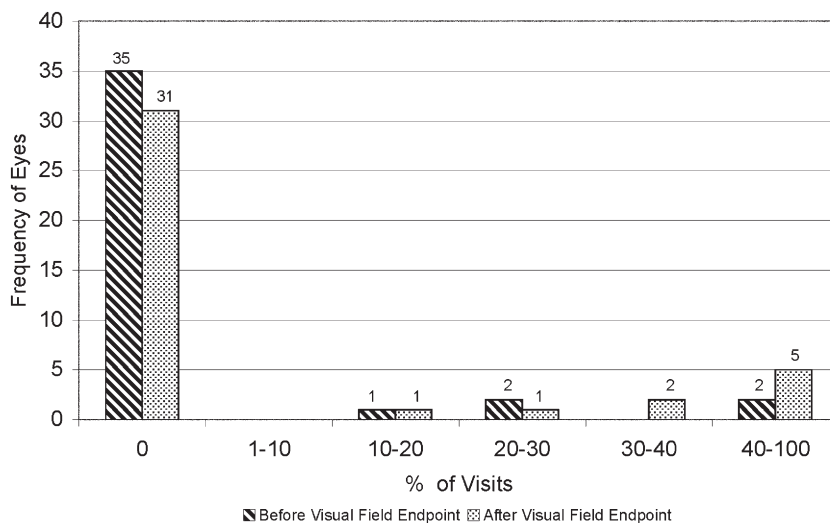


Figure 3. Percentage of visits during follow-up with optic disc rim thinning before and after the visual field end point among 40 eyes that have not yet developed an optic disc end point.

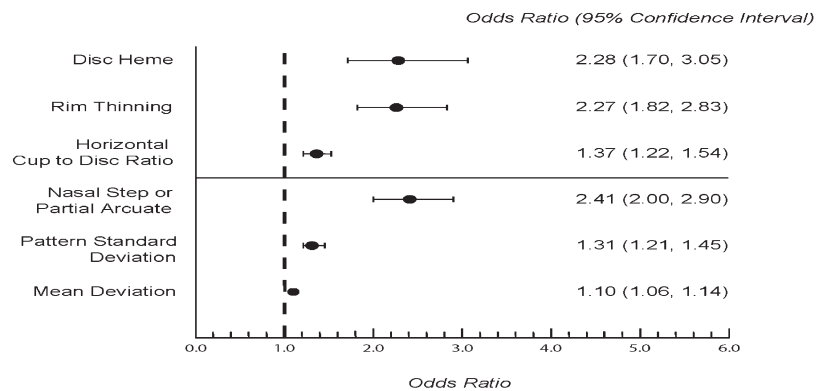


Figure 4. Odds ratios and corresponding 95% confidence intervals from Cox proportional hazard analyses implying a significant relationship between particular optic disc changes (disc hemorrhage, rim thinning, and horizontal cup-to-disc ratio) and end point determination of primary open-angle glaucoma prompted by observation of visual field (VF) change and the significant relationship between particular VF features (nasal step or partial arcuate, pattern standard deviation, mean deviation) and the optic disc end point. All analyses are adjusted for baseline intraocular pressure, treatment, age, and correlation between fellow eyes.

of retinal ganglion cells, then our results suggest that with present methods both modalities must be monitored to detect glaucoma most sensitively. More cases of emerging glaucoma are detected by noting a change in the disc configuration by comparison of stereoscopic photography of the optic disc than by noting the change using automatic perimetric statistical parameters. Often, either the optic disc change or the VF change is confirmed definitively, whereas the other parameter fails to reveal that glaucoma has developed or has uncertain findings. Only future research will show whether both optic disc and VF changes will still be needed after newer methods are developed, refined, and come into common use for testing visual function and for quantifying structures.

Among the newer methods are advances in the detection of both functional and structural manifestations of glaucomatous damage. These may allow both earlier identification of abnormality of change and any alteration in the relationship between ganglion cell integrity and various components of visual function. New methods showing promise include short-wavelength automated perimetry,⁵²⁻⁵⁶ frequency doubling technology,⁵⁷⁻⁵⁹ multifocal visual evoked potentials,⁶⁰⁻⁶² and flicker perimetry.⁶³ New anatomic methods to study the optic disc and retinal nerve fiber more quantitatively also are evolving.⁶⁴⁻⁶⁸ Budenz et al recently showed excellent sensitivity and specificity of measurements of the RNFL with Stratus optical coherence tomography (Carl Zeiss Meditec, Inc., Dublin, CA) in glaucoma participants with established VF defects,⁶⁹ and further study is needed to show whether such measurements can detect damage before abnormalities are detected by perimetry. Zangwill et al examined the predictive ability of confocal scanning laser ophthalmoscopy optic disc topographic measurements for the development of POAG in OHTS participants, showing that topographic optic disc factors alone or when combined with central corneal thickness, IOP, and age helped predict the development of POAG in participants with ocular hypertension.⁷⁰

Apart from which is more easily recognized in clinical practice with methods available at a particular time in

history, it would be incorrect to conclude that at a fundamental level structural change always occurs before or without functional changes, or the other way around. In principle, when axons are lost there is some corresponding loss of some component of visual function simultaneously, but the detection of either structural loss or functional loss depends on the sensitivity of the methods available for their measurement. The sensitivity to recognizing abnormality depends on the range of normal of either the global quantity of axons or visual function, and also on recognizing disease superimposed on individual variation in the normal arrangement or pattern of neural anatomy or visual functions in various locations. Histological studies do confirm that present methods of perimetry may fail to show abnormality where there are demonstrably fewer axons.^{71,72} Visual field change also may be less obvious at the beginning because visibility seems to have a direct linear relationship to the number of axons and ganglia,⁷³ but in clinical testing, the visual thresholds are recorded on a logarithmic scale (decibels). The result is that the decibel change in threshold for a loss of the same number of axons is smaller in the beginning stages of disease than in later stages.

The present analysis in fact confirms that when a defined definitive criterion is met in either disc findings or VF change, often there is some kind of evidence that the other modality has changed, even if not specific and definitive. Specifically, the occurrence of VF end point as defined for the OHTS was associated statistically with optic disc findings that were not considered definitive end point criteria with the methods then available and still in common use. Optic disc hemorrhage or rim thinning (including readings that were not confirmed) was associated with a 125% increase in the risk of developing reproducible VF defects ($P < 0.0001$). Interestingly, 7 of 40 eyes had a disc hemorrhage before the VF POAG end point, and 5 of 40 eyes had rim thinning before the VF POAG end point. In addition, eyes with a larger horizontal C/D ratio were more likely to develop a VF end point (37% greater risk for a 0.1-unit C/D; $P < 0.0001$). It is also interesting to note that the average horizontal C/D ratio for eyes reaching the VF POAG end

point is 0.50; for eyes not reaching the VF POAG end point, the average horizontal C/D ratio is 0.39.

Conversely, certain VF abnormalities that were not sufficiently definitive to meet our criteria for developing glaucoma based on confirmed and reconfirmed abnormality of the GHT or PSD were sometimes seen in eyes that underwent confirmed disc change. These included the presence of a nasal step or a partial arcuate defect, as previously defined (OR, 2.41; $P < 0.0001$). We have shown that partial arcuate or nasal step VF abnormalities are more likely to become an OHTS VF end point (Association for Research in Vision and Ophthalmology abstract 2134/B945, 2004). The degree of PSD abnormality expressed in decibels also is related to the risk of an optic disc end point ($P < 0.0001$).

Although we have identified these warning signs, the magnitude of risk for any parameter, expressed as an OR, cannot be used to gauge which factor is a stronger predictor than another. The variables under consideration were measured on different scales/units and not standardized. Efforts to relate ORs to each other are further confounded in this study by the fact that the ordering of the parameters in Figure 4 was based on grouping the variables (disc hemorrhage, rim thinning, and horizontal C/D ratio) in relation to VF POAG, whereas a nasal step/partial arcuate defect, PSD, and MD are studied in relation to optic disc POAG. The present analysis considered only one end point modality at a time, either an optic disc or a VF end point. One implication of the findings is that if uncertain findings are observed in either the optic disc or the VF, the other modality should be examined, as it may show more definitive evidence of glaucoma.

It has been reported before that borderline or variable (unconfirmed) clinical observations may point to the later development of definitive change. Hart and Becker, for example, described some time ago that glaucomatous VFs go through 3 transitional phases⁷⁴ before becoming permanently abnormal. The initial phase has no defect demonstrable despite the fact that early damage is occurring. The second phase is a period in which shallow defects are often transient and barely detectable. In the third phase, VF defects progress at an uneven pace to become very dense. Given variations in photographic technique from one time to another, the same variable interpretation of photographs likely occurs before there is a consistent and certain judgment that change has occurred. Other investigators also have reported that increased short-term fluctuation is an early harbinger of glaucomatous VF loss.^{75–80}

It is important to recognize that whereas these borderline and nonreproducible findings have a statistical correspondence, they are not specific enough to be diagnostic. Even though partial arcuate and nasal step abnormalities increase the likelihood that glaucomatous damage has started, it is also true that 86% of the eyes with these unconfirmed abnormalities did not reach an OHTS VF end point during follow-up to date.⁴⁷ Any new VF finding, especially a subtle one, needs to be confirmed before it is accepted. In fact, we recently found that 66% of subsequent follow-up VFs were normal in eyes that had 2 consecutive, abnormal, reliable VFs. Even eyes that reached a VF end point in the OHTS based on 3 consecutive, abnormal, reliable VFs were normal

on subsequent testing 12% of the time. Thus, a criterion of 3 consecutive, abnormal, reliable VFs was necessary to reach an adequate specificity for the determination that POAG has developed for a clinical trial like the OHTS,⁴⁶ but is still imperfect. The need for repetition of VF testing to be certain that a VF has changed has been shown in other studies as well.^{81–83}

It should be noted that in the OHTS participants were recruited from tertiary-care glaucoma sites and do not necessarily typify the general population of glaucoma suspects. The average results for this group may not always apply to those in a different practice setting, with different underlying or preexisting anatomic or physiologic features. However, we know of no particular relevant features of participants enrolled in the OHTS that would make them unrepresentative for the issues under analysis here.

Another caution in applying the results of the present analysis is that it was designed to separate the evaluation of 2 different components of glaucomatous change (optic disc and VF) when evaluated without either the bias or the help of knowing anything of the other clinical features. Thus, the OHTS ODRC and VFRC evaluated changes independently and were masked to each other's end points. In clinical practice, the clinician should compare disc and field findings to determine if their features logically correspond (e.g., upper rim thinning and inferior VF defect). Knowledge of the findings on one modality influences the significance attached to borderline findings in the other modality—findings that might by independent masked (unbiased) inspection be regarded as nonspecific. However, the finding of corresponding abnormalities in 2 different clinical manifestations serves the same purpose as repeating one of the observations to improve specificity in a clinical study. In clinical practice, the combination of confirming or nonconfirming findings probably leads to more astute diagnostic and therapeutic decisions than can be made on the basis of a single test or observation.

Therefore, clinicians need to pay attention to both VF test findings and optic disc features in ocular hypertensive subjects to avoid missing early recognition of glaucoma. It is unadvisable to depend on use of only one modality, unless clinical circumstances (media imperfections or mental state) prevent both from being accomplished adequately. At present, ophthalmologists do not adhere sufficiently to suggested practice patterns for disc and field documentation. For example, of 395 working-age participants enrolled in 6 managed care plans who were being monitored for glaucoma between 1997 and 1999, only 53% had ONH photography or drawings, and only 66% had VF tests performed during their initial evaluation.⁸⁴ In another review, only 23% of the 193 surveyed participant charts had an ONH drawing or photograph within 15 months of the most recent visit. In addition, only 38% of the 193 participant charts had an ONH drawing or a photograph documented at any time after the initial visit.⁸⁵

In summary, either optic disc or VF parameters may be the first to reveal the development of features defined as typical for POAG in participants with ocular hypertension. Equivocal and nonreproducible changes in the disc or VF deserve attention, as they are signs of an increased chance of

developing fully manifest POAG, even though the majority with these findings do not develop POAG, at least within the time frame of the present study. If either the disc or the field has uncertain glaucomatous features, the other modality needs attention, as it may show the presence of glaucoma definitively or confirms that there is reason to be suspicious.

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