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Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study

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Abstract

Purpose: To compare the rates of detection of optic disc hemorrhages by clinical examination and by review of optic disc photographs at the Optic Disc Reading Center (ODRC), to assess the incidence of and the predictive factors for disc hemorrhages in the annual disc photographs of the Ocular Hypertension Treatment Study (OHTS), and to determine whether optic disc hemorrhages predict the development of primary open-angle glaucoma (POAG) in the OHTS.

Design: Cohort study.

Participants: 3,236 eyes of 1,618 participants.

Methods: Both eyes of participants were examined for optic disc hemorrhages every 6 months by clinical examination, with dilated fundus examinations every 12 months, and by annual review of stereoscopic disc photographs at the ODRC.

Main Outcome Measures: Incidence of optic disc hemorrhages and POAG endpoints.

Results: Median follow-up was 96.3 months. Stereophotograph-confirmed glaucomatous optic disc hemorrhages were detected in 128 eyes of 123 participants prior to POAG. Twenty one (16%) were detected by both clinical examination and review of photographs and 107 (84%) only by review of photographs (P <0.0001). Baseline factors associated with disc hemorrhages were older age, thinner corneas, larger vertical cup/disc ratio, larger PSD index on perimetry, family history of glaucoma, and smoking. The occurrence of a disc hemorrhage increased the risk of developing POAG 6-fold in a univariate analysis, (p<0.001; 95% confidence interval 3.6 – 10.1), and 3.7-fold in a multivariate analysis that included baseline factors predictive of POAG (p<0.001; 95% confidence interval 2.1 – 6.6). The 96-month cumulative incidence of POAG in the eyes without optic disc hemorrhage was 5.2% compared to 13.6% in the eyes with optic disc hemorrhage. In eyes with a disc hemorrhage that developed a POAG endpoint, the median time between the two events was 13 months.

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Conclusion: Review of stereo photographs was more sensitive at detecting optic disc hemorrhage than clinical examination. The occurrence of an optic disc hemorrhage was associated with an increased risk of developing a POAG endpoint in participants in the OHTS. However, the majority of eyes (86.7%) that developed a disc hemorrhage have not developed a POAG endpoint to date.

Introduction

The Ocular Hypertension Treatment Study (OHTS) was designed to determine whether lowering intraocular pressure in participants with ocular hypertension (OHT) delays or prevents the development of primary open angle glaucoma (POAG). Results to date have shown an approximate 50% reduction in conversion from OHT to POAG with a 20% reduction in intraocular pressure (IOP).[1] Baseline predictive factors for conversion include higher IOP, larger cup to disc ratio, thinner cornea, higher pattern standard deviation on visual field testing, and older age.[2]

The presence of an optic disc hemorrhage at baseline examination excluded participation in the study while a hemorrhage that developed subsequently was not by itself considered a POAG endpoint.[3] The presence or absence of optic disc hemorrhages was determined by investigators using clinical examination every 6 months and by review of stereo photographs at the Optic Disc Reading Center (ODRC) once per year. The purposes of this report are to compare the detection of glaucomatous optic disc hemorrhages by clinical examination and by review of disc photographs, to assess the incidence of disc hemorrhages in the annual disc photographs of the OHTS participants before and after the development of a POAG endpoint, to identify baseline factors associated with optic disc hemorrhage during follow-up, and to determine whether optic disc hemorrhages predict the development of POAG endpoints in participants of OHTS.

Methods

The design of the OHTS has been described previously.[3] The OHTS data files used in this report include data from February 1994 though November 2003, with 168 eyes that progressed to a POAG endpoint. Over 60% of participants had completed their 96 month visit by the time of this review with the longest follow-up being 108 months. The median follow-up of all participants was 96.3 months.

During the course of the study, investigators evaluated the optic nerve by means of direct or slit lamp biomicroscopy, noting whether a disc hemorrhage was present in either or both eyes at each examination. The presence of a hemorrhage at the disc margin or within the disc tissue was recorded without making a distinction between splinter hemorrhages typical of glaucoma and hemorrhages due to other concurrent diseases. Clinical examinations were scheduled approximately every 6 months. Annual examinations of the fundus were performed after pupil dilation while those conducted at 6 month interval visits were performed without dilation. At the annual visit, stereoscopic optic disc photographs were taken and reviewed by the ODRC. A minimum of 2 primary readers reviewed each pair of stereo photographs. In addition to other features, readers determined whether a disc hemorrhage was present. If a difference of opinion existed between readers, a third, senior reader (DLB, DRA or RKP) determined whether a disc hemorrhage was present or not. A POAG endpoint was defined as a reproducible optic disc deterioration or a reproducible visual field abnormality attributed to POAG by a masked endpoint committee.[3]

Definition of Glaucomatous Disc Hemorrhage

At the ODRC, the presence of a glaucomatous optic disc hemorrhage was recorded if it was of a type considered typical of glaucoma, specifically a flame- or splinter-shaped hemorrhage,

often with feathered ends, 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. An example of a disc hemorrhage considered typical of glaucoma in an OHTS participant is shown in Figure 1. A splinter or flame-shaped hemorrhage on the disc was not considered related to glaucoma if the disc was swollen or otherwise obviously abnormal from anterior ischemic optic neuropathy, papillitis, or another nonglaucomatous optic neuropathy. Similarly, a hemorrhage within the optic disc was not considered related to glaucoma if multiple nearby retinal hemorrhages suggested diabetic retinopathy, vein occlusion, or another retinal vascular abnormality. In contrast, clinical investigators were asked simply to note the presence or absence of a hemorrhage anatomically located at the disc margin or within the disc tissue without regard to presumed etiology. To avoid potential misclassification of disc hemorrhages, only eyes that satisfied the disc hemorrhage criteria above detected by the ODRC or detected by the clinician and confirmed by disc photographs were included in this report.

Statistical Methods

A McNemar's chi-squared test was performed to determine differences in detection of optic disc hemorrhages by the ODRC and by clinical examination. Only the 128 eyes with optic disc hemorrhages detected or confirmed by the ODRC were included in the analysis of predictive factors. The incidence of disc hemorrhage prior to development of POAG was assessed with Kaplan-Meier methods. A Cox univariate proportional hazards regression, with the robust sandwich variance estimate option to account for the correlation between the two eyes of participants, was performed to determine which baseline characteristics were predictive of disc hemorrhage during follow-up prior to the onset of a POAG endpoint. The incidence of disc hemorrhage after POAG endpoint was estimated with a second Kaplan-Meier analysis. Thirteen eyes of 13 participants were found to have disc hemorrhage at the same visit as an endpoint was reached and were not included in either the pre or post POAG endpoint incidence calculations.

After adjusting for treatment assignment, a Cox multivariate proportional hazards regression model, with the robust sandwich variance estimate option to account for the correlation between the two eyes of participants, was performed to examine whether having a disc hemorrhage, included as a time-dependent covariate during follow-up, was an independent predictive factor for the development of POAG. Other baseline variables in this model included age, vertical cup disc ratio, pattern standard deviation on visual field testing, IOP, and central corneal thickness. Another time dependent Cox survival regression analysis assessed whether of the occurrence of a POAG endpoint increased the risk of a subsequent disc hemorrhage.

Results

Detection of optic disc hemorrhages during clinical examination was compared to detection by review of stereoscopic disc photos at the ODRC in eyes which had not yet reached POAG endpoint through November 2003. 143 eyes were found to have disc hemorrhages by either or both of a clinical examination or review of disc photos. Of these, 107 (74.8%) were reported from photographic evaluation at the ODRC alone, 15 (10.5%) were found during clinical examination alone, and 21 (14.7%) were identified by both ($p<0.001$, McNemar's test). Of disc hemorrhages detected by clinical exam 21/24 (12.5%) were found at annual examinations, possibly due to dilation of pupils at these annual exams. Disc photos of the fifteen eyes with hemorrhages reported only by clinical examination were re-evaluated by two masked independent senior readers at the ODRC (DLB and DRA). In twelve cases the photographs showed a hemorrhage which was not classified as a type considered typical of glaucoma by

the criteria used by the ODRC outlined above, but included hemorrhages associated with multiple retinal hemorrhages and dilated veins typical of retinal vein occlusion (Figure 1), peripapillary subretinal hemorrhage (Figure 1), or structures that mimicked hemorrhages such as a tortuosity of a vein, baring of choroidal vessels, large retinal vessels crossing the disc, or clumping of the retinal pigment epithelium. In the other three cases, disc hemorrhages were noted only at a semi-annual clinical examination but no disc photos were available for comparison , so there was no way to definitively classify these disc hemorrhages as glaucomatous or non-glaucomatous. Both misclassified and unclassified hemorrhages were excluded from the remainder of the analyses that follow. Therefore, 128 eyes were defined as having glaucomatous disc hemorrhages prior to a POAG endpoint.

Through November 2003, 168 eyes of 159 participants developed a POAG endpoint, 94 (56%) by optic disc criteria alone, 59 (35%) by visual field criteria alone, and 15 (9%) by both. The cumulative incidence of eyes with at least one disc hemorrhage prior to POAG by follow-up years 1 to 8 was 0.3% (9), 0.9% (27), 1.5% (46), 2.1% (65), 2.3% (71), 2.8% (86), 3.3% (98), 4.1% (115); approximately 0.5% per year. Figure 2 shows the cumulative incidence of optic disc hemorrhages in the treated and observation groups over 8 years of follow-up. Disc hemorrhages occurred slightly more often in the observation group but this difference was not statistically significant (Cox proportional hazard regression analysis, P = 0.13). Table 1 displays a frequency distribution of the numbers of pre-endpoint disc hemorrhages detected in 128 eyes of 123 participants. Of these 111 (86.7%) did not develop a POAG endpoint during a median follow-up of 30.7 months after disc hemorrhage occurred. Seventeen eyes (13%) were observed with a disc hemorrhage prior to developing POAG endpoint, eight (47%) by optic disc criteria, eight (47%) by visual field criteria, and one (6%) by both. In eyes with a disc hemorrhage that later developed a POAG endpoint, the median time from optic disc hemorrhage to a POAG endpoint was 13 months.

The association of baseline factors on the incidence of optic disc hemorrhages, determined with univariate Cox proportional hazard regression analysis, is presented in Table 2. Older age, thinner central corneal thickness measurement, greater vertical cup/disc ratio, and greater pattern standard deviation (PSD) index on perimetry were statistically significantly associated with disc hemorrhage. Baseline IOP and assignment to pressure lowering medications were not associated with the development of a disc hemorrhage, although there was a trend in both cases (P = 0.12 and 0.13 respectively). Family history of glaucoma (P = 0.023), and a lifetime history of smoking at least 100 cigarettes (P = 0.027) were also associated with disc hemorrhages.

To assess whether the risk of POAG increased after disc hemorrhage, disc hemorrhage was included as a time-dependent covariate in a Cox survival regression model of time to endpoint. The risk of developing POAG after occurrence of a disc hemorrhage was 6.0 times higher than without a disc hemorrhage (hazard ratio = 6.0, 95% confidence interval = 3.6 to 10.1; P < 0.001). After adjusting for baseline factors previously identified as being predictive of POAG in the OHTS,[2] as well as treatment assignment, the independent contribution of a disc hemorrhage to risk was less (hazard ratio = 3.7, 95% confidence interval = 2.1 to 6.6, P < 0.001). All of the baseline risk factors previously found to be significant prognostic factors for the development of POAG (assignment to observation, older age, higher IOP, thinner cornea, larger cup to disc ratio, higher PSD, no diabetes) remained statistically significant after the inclusion of optic disc hemorrhage in the multivariate model.

Of the 168 eyes that developed POAG, 15 eyes of 15 participants had documented disc hemorrhages after the development of POAG. Of these 15 eyes, 13 (87%) had no documented disc hemorrhages prior to POAG endpoint; one of the two remaining cases had a single pre-POAG disc hemorrhage, and one had two pre-POAG disc hemorrhages. The cumulative

incidence of one or more disc hemorrhages after the date of the development of POAG from 1 to 4 years respectively was 3.1% (5), 5.1% (8), 6.5% (10), and 9.9% (13); approximately 2.5% per year. The occurrence of a POAG endpoint significantly increased the incidence of a first disc hemorrhage ($p<0.001$). The maximum number of POAG disc hemorrhages after reaching endpoint was 5 in a single eye. Table 3 displays the frequency distribution of disc hemorrhages in 168 eyes of 159 participants after a POAG endpoint had been reached. No difference was found in the incidence of disc hemorrhages after endpoint between cases that had reached an endpoint by disc criteria versus field criteria ($P = 0.83$, log-rank test).

Discussion

The current analysis of the OHTS data provides evidence that careful review of optic disc photographs detects optic disc hemorrhages more frequently than does clinical examination, at least in the context of this clinical trial. This was true despite the fact that photographs were performed, in general, once per year and clinical examinations twice per year. If optic disc photographs had been taken as often as clinical examinations were performed, the difference would most likely have been even greater. There are several possible explanations for this finding. First, detecting an optic disc hemorrhage from a photograph performed on a dilated eye may be easier than detecting it with the direct ophthalmoscope or condensing lens and slit lamp in an eye that is not stationary and not always dilated. Second, two readers working from photographs may devote more time reviewing photographs compared to the time utilized by a single clinician during a clinical examination. Third, perhaps investigators in the study were relying more on the ODRC to detect disc hemorrhages.

OHTS participants who develop optic disc hemorrhages share baseline characteristics with OHTS participants who develop POAG, including older age, thinner corneas, and larger baseline cup to disc ratio. Some of these predictive factors, such as age, contribute to an increased susceptibility to damage. Some predictive factors, such as an enlarged cup or a disc hemorrhage, may represent the beginning of the actual damage process itself.[4] Any of these predictive factors make it more likely the person will develop glaucoma, and the clinician should realize that patients with one or more of these risk factors are at increased risk. Of note, in the multivariate analysis, when these other factors that correlate with POAG development are taken into account, the occurrence of a disc hemorrhage independently adds additional risk.

Assignment to the treatment arm of the study reduced the incidence of POAG, but was not found to reduce the incidence of splinter hemorrhages on the disc at a statistically significant level, perhaps due to the small number of disc hemorrhages to date. The disassociation that IOP-lowering reduces the incidence of POAG but not of hemorrhages may signify that those who experience hemorrhages are more susceptible to IOP, such that the IOP-lowering achieved in OHTS was not adequate to prevent either the hemorrhages or conversion to fully manifest glaucoma. Another possible explanation might be that those with splinter hemorrhages are “bleeders” due to a different pathogenic factor that causes hemorrhage and axon damage. However, the number of cases in this series is too small to support any particular potential explanation.

In this study, while a participant with an optic disc hemorrhage during follow-up was 6.0 times more likely to develop a POAG endpoint, 86.7% of the participants with an optic disc hemorrhage did not develop a POAG endpoint to date, a mean follow-up period of about 31 months. Thus the occurrence of an optic disc hemorrhage is not synonymous with development of glaucoma, nor a sign that POAG will with certainty soon become manifest. The results of the study also do not suggest that all OHT patients be subjected to photographs annually solely to detect optic disc hemorrhages. They may well be evident on careful clinical examination in

which attention is directed toward their detection, knowing that outside the context of a clinical trial photographs may not be as thoroughly examined.

An additional interesting finding in the current study is that the cumulative incidence of optic disc hemorrhages was 0.5% per year prior to the development of POAG and 2.5% per year in eyes after the development of POAG. This is consistent with findings in several cross sectional studies that found that patients with POAG have an increased prevalence of optic disc hemorrhages compared to patients with ocular hypertension.[5,6] To our knowledge, this is the first report to show a higher incidence of optic disc hemorrhages after the development of POAG in a longitudinal study. It is important to recognize, however, that these incidence rates are underestimates because disc hemorrhages are transient and photographs were taken annually. It is likely that disc hemorrhages occurring between annual photographs might be missed.

Of note, when considering the implications of the present study, one must realize that an optic disc hemorrhage at time of recruitment was an exclusion criterion because of an uncertain relationship between ocular hypertension, disc hemorrhages, and POAG. Thus, we are most likely studying a group of participants who are less likely to have optic disc hemorrhages throughout follow-up than an all inclusive cohort of eyes with ocular hypertension.

The present longitudinal data and multivariate analysis add to literature that suggests that optic disc hemorrhages are a negative predictive factor in ocular hypertension, as distinct from its already well established predictive value in fully manifest glaucoma. Longitudinal studies have shown this predictive association for both primary open angle[7 - 9] and normal tension glaucoma (NTG).[10 - 12] However, the evidence for an association between optic disc hemorrhage and development of POAG in patients with OHT is less abundant. In a univariate longitudinal analysis, Drance and colleagues[7] studied 29 ocular hypertensive individuals with optic disc hemorrhages compared with 29 ocular hypertensive individuals without optic disc hemorrhages and found that 10 progressed in the optic disc hemorrhage group while only 1 progressed in the group without optic disc hemorrhages over the same follow-up period. The follow-up period was not mentioned in this report. Airaksinen and colleagues[14] retrospectively studied 25 ocular hypertensive patients with optic disc hemorrhage, 8 of whom had developed glaucomatous visual field or optic disc changes one to two years following the development of a disc hemorrhage with an average follow up time of 6 years. No control group was included in this study. In a prospective cohort study, Diehl et al[9] found that glaucoma suspects with optic disc hemorrhages (N = 7) were 14 times more likely to develop worsening nerve fiber layer status than those glaucoma suspects without optic disc hemorrhages (N = 56) after one year of follow-up. Siegner and Netland[15] performed a retrospective study of 17 patients followed for OHT and found that optic disc hemorrhages were associated with glaucomatous changes in the optic disc or visual field compared with OHT control eyes without optic disc hemorrhages, with changes occurring a similar time after optic disc hemorrhage as the current study (1 − 2 years). The OHTS is the largest prospective longitudinal study to show that optic disc hemorrhages are a predictive factor for the development of POAG in patients with OHT.

It is important to note that splinter-shaped optic disc hemorrhages must be evaluated in the context of other clinical findings. Here they are found to be predictive for the development of POAG in the presence of elevated IOP, but hemorrhages of similar location and morphology may be due to other ocular and systemic causes. Disc hemorrhages may occur with posterior vitreous detachment,[16,17] non-glaucomatous optic neuropathies,[18] optic disc drusen,[18] and vascular occlusive diseases of the retina,[18] all of which are readily apparent on dilated fundus examination. Systemic disorders associated with optic disc hemorrhage include diabetes mellitus, systemic hypertension, systemic lupus erythomatosis, and leukemia.[18] If any of these other ocular or systemic conditions are present, it cannot be concluded from the present data

that a patient with OHT is necessarily at a higher risk for future development of POAG or NTG.

The current study does not suggest that all OHT patients with an optic disc hemorrhage should be treated since the majority of patients with optic disc hemorrhage did not develop manifest POAG during the study period. On the other hand, there is evidence from other studies that lowering intraocular pressure in patients with POAG reduces the incidence of future optic disc hemorrhages.[19] The present study suggests that optic disc hemorrhage in the setting of OHT places patients at a higher risk of developing POAG, as does older age, thinner cornea, higher pattern standard deviation on automated perimetry, and larger vertical cup to disc ratio. Thus an optic disc hemorrhage should be included in the decision matrix about initiating treatment in a patient with ocular hypertension. Because optic disc hemorrhages are such a strong predictive factor for the development of POAG in ocular hypertension, we recommend frequent monitoring for optic disc hemorrhages by careful examination of the optic disc through a dilated or undilated pupil and/or optic disc photography.

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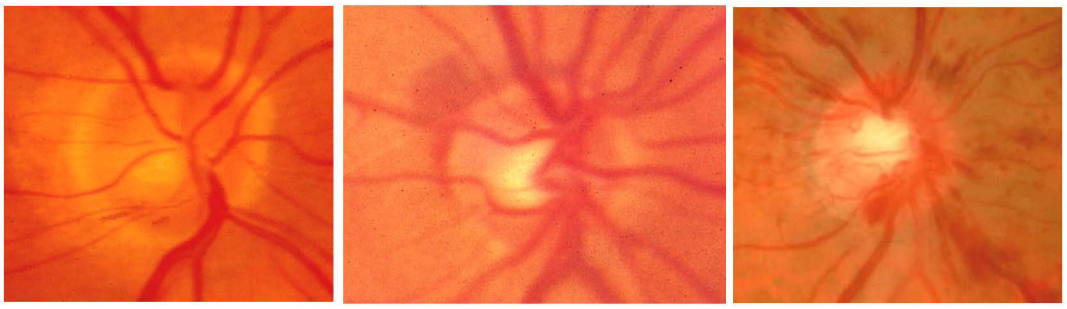

Figure 1.
Splinter hemorrhage typical of glaucoma (left panel). Non-glaucomatous peripapillary hemorrhage between the neural retina and the retinal pigment epithelium and therefore sharply delimited at the disc margin. This hemorrhage is not in the nerve fiber layer (middle panel). Multiple disc and retinal hemorrhages typical of central retinal vein occlusion (right panel). All images are of subjects in the Ocular Hypertension Treatment Study.

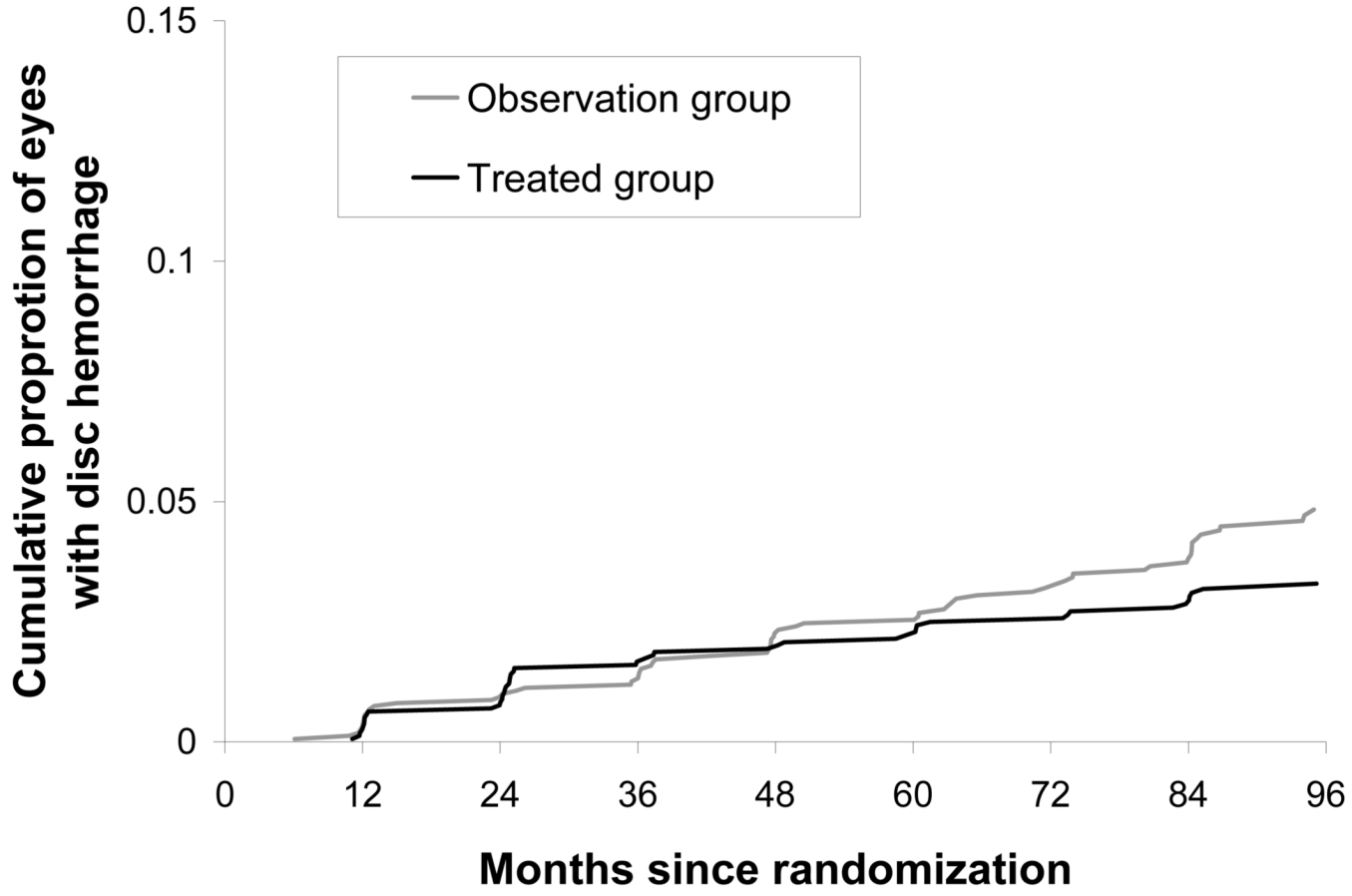

Figure 2.
Cumulative incidence of optic disc hemorrhages in annual photographs of treated and observation groups

Table 1

Number of disc hemorrhages per eye and percent of eyes reaching POAG endpoint

Number of disc hemorrhages per eye	Number of eyes	Number (%) of eyes reaching POAG endpoint N = 168
0	3108	151 (4.9%)
1	112	15 (13.4)
2	12	2 (16.7%)
3	2	0
4	2	0

Table 2

Baseline factors and disc hemorrhage in the OHTS

Baseline Variable	Group sizes (for categorical variables)	Risk Ratio	P-value	95% Confidence Limit on risk ratio Lower	Upper
Pressure lowering therapy					
Yes	1612	0.76	0.13	0.53	1.09
No*	1624				
Age (per decade increase)		1.58	<0.001	1.32	1.88
Corneal thickness (per 40μ decrease)		1.23	0.024	1.03	1.47
Vertical cup/disc ratio (per 0.1 DD increase)		1.14	0.005	1.04	1.25
Pattern Standard Deviation (1 unit increase)		2.51	0.005	1.32	4.78
IOP (per 10 mmHg increase)		1.57	0.12	0.89	2.77
Myopia					
Spherical equivalent ≤ −3, >−6	523	1.22	0.41	0.76	1.98
Spherical equivalent ≤ −6	105	0.59	0.40	0.18	1.98
Spherical equivalent > −3*	2608				
Smoked at least 100 cigarettes					
Yes	1252	1.53	0.027	1.05	2.24
No*	1532				
Lens Status					
Aphakic or Pseudophakic**	25	2.61	0.19	0.63	10.8
Phakic*	3211				
Gender					
Female	1842	0.72	0.062	0.51	1.02
Male*	1394				
Ethnicity					
Black	798	0.67	0.094	0.42	1.07
Hispanic	112	1.46	0.37	0.64	3.35
White, non-Hispanic*	2264				
Family history of glaucoma					
Yes	1106	1.59	0.023	1.07	2.38
No*	2130				
History of asthma					
Yes	224	0.33	0.057	0.11	1.03
No*	3006				
History of cancer					
Yes	188	1.58	0.15	0.85	2.93
No*	3048				
History of diabetes mellitus					
Yes	382	1.17	0.57	0.69	1.97
No*	2848				
History of high blood pressure					
Yes	1222	0.98	0.91	0.68	1.40
No*	2004				
History of low blood pressure					
Yes	142	0.87	0.76	0.36	2.11
No*	3088				
History of heart disease					
Yes	202	1.91	0.028	1.07	3.38
No*	3030				
History of lung disease					
Yes	78	1.06	0.92	0.34	3.34
No*	3152				
History of stroke					

Baseline Variable	Group sizes (for categorical variables)	Risk Ratio	P-value	95% Confidence Limit on risk ratio Lower	Upper
Yes	38	0.89	0.91	0.13	6.34
No*	3198				
History of other systemic condition					
Yes	910	0.95	0.81	0.65	1.40
No*	2322				
Migraine Headaches					
Yes	356	0.85	0.60	0.47	1.54
No*	2844				

* Reference Group

** None of the 16 eyes of the eight aphakic cases experienced a disc hemorrhage

Table 3

Frequency of disc hemorrhages per eye following POAG endpoint

Frequency of disc hemorrhages per eye	Number (%) of eyes N = 168
0	153 (91)
1	11 (7)
2	2 (1)
3	1 (1)
4	0
5	1 (1)