The Incidence of Retinal Vein Occlusion in the Ocular Hypertension Treatment Study

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Objective: To determine the incidence of retinal vein occlusion (RVO) in the Ocular Hypertension Treatment Study (OHTS).

Design: Retrospective analysis of data from a randomized clinical trial.

Participants: We included 1636 ocular hypertensive participants with a mean follow-up of 9.1 years. Participants in the medication and observation groups were managed according to their original randomization assignment until June 1, 2002. At that time, the observation participants were offered ocular hypotensive treatment. Data to July 1, 2005, are included in this report.

Methods: Occurrences of RVO in study participants, categorized as branch, central or hemicentral vein occlusion, were documented. Potential RVO events were identified by a keyword search of Adverse Event Reports, the Optic Disc Reading Center database, Endpoint Committee reviews, and by response to a written request for information sent to each clinical site. To confirm a potential RVO, the complete OHTS chart was reviewed. Statistical analyses included *t* tests, chi-square tests and Cox proportional hazards models.

Main Outcome Measures: Incidence of RVO.

Results: Twenty-six RVOs—5 branch, 14 central, and 7 hemicentral RVOs—were confirmed in 23 participants (15 observation and 8 medication). The 10-year cumulative incidence of RVO was 2.1% in the observation group and 1.4% in the medication group ($P = 0.14$; log-rank test). At baseline, participants who later developed a RVO were significantly older (65.1 vs 55.3 years; $P = 0.01$), and had greater horizontal cup-to-disc ratios ($P = 0.0004$).

Conclusions: Although the incidence of RVO was higher in the observation group than the medication group, this difference did not attain significance. Consistent with some previous studies, older age and greater cup-to-disc ratio were associated with the development of RVO.

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The association between ocular hypertension (OHT) or glaucoma and retinal vein occlusion (RVO) has been recognized since the beginning of the 20th century.[1] Most of the studies examining this association, however, have been retrospective.[2–8] Case-control studies have reported that a history of glaucoma or OHT in the fellow eye was significantly more common in patients with central RVO (CRVO) than in controls.[9,10]

In a large series of patients with CRVO and hemicentral RVO (HRVO), Hayreh et al reported the prevalences of glaucoma and OHT were approximately 10% and 16%, respectively, much higher prevalences than found in the general population.[5] The Eye Disease Case-Control Study found that a history of glaucoma was associated with all 3 types of RVO: CRVO, HRVO, and branch RVO (BRVO).[9]

In contrast, a few studies have come to a different conclusion, especially concerning the relationship between BRVO and OHT or glaucoma. The Blue Mountains Eye Study reported 9 cases of CRVO and 25 cases of BRVO during 10 years of follow-up. No significant association was found between incident RVO and intraocular pressure (IOP).[11] The Beaver Dam Eye Study reported 7 incident cases of CRVO and 21 of BRVO during 5 years of follow-up. A detailed risk factor analysis, which was only reported for BRVO, did not find statistically significant associations between BRVO and OHT or glaucoma.[12] However, after 10 years of follow-up, the same study found that participants with incident RVOs were more likely to have had definite or probable glaucoma at baseline.[13]

The Ocular Hypertension Study (OHTS) provides a unique opportunity to examine the incidence of RVO in a large, prospectively followed sample of ocular hypertensive individuals.[14] The OHTS participants were followed closely with IOP measurement, static automated perimetry, and optic disc examination every 6 months, and dilated fundus examination with optic disc photographs annually.

Methods

Study Synopsis

The OHTS is a multicenter, randomized clinical trial to determine the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of glaucoma in individuals with elevated IOP. All participants provided written informed consent for participation in the study. Institutional Review Board approval was obtained at all OHTS clinical sites and the study has been

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conducted in compliance with the Health Insurance Portability and Accountability Act. The protocol for the OHTS is described in detail elsewhere[14] and the manual of procedures for the study is available online at https://vrcc.wustl.edu/mop/mop.htm (accessed August 14, 2009).

Eligibility criteria included age between 40 to 80 years, no evidence of either glaucomatous structural or functional damage by standard clinical measures and IOP between 24 and 32 mmHg in 1 eye and between 21 Hg and 32 mmHg in the other eye. Baseline medical history was by self-report. The IOP was measured by 2 OHTS certified study personnel, an operator and a recorder, using a calibrated Goldmann applanation tonometer. Baseline IOP was defined as the mean of 2 or 3 IOP measurements at the baseline/randomization visit as opposed to IOP measurements taken during the qualifying visits. Every effort was made to perform IOP readings at the same time of day to minimize diurnal fluctuation. The time of day of IOP readings was recorded.

From February 1994 to October 1996, participants (n = 1636) were randomly assigned to treatment with topical IOP-lowering medication or observation. The goal of treatment with topical ocular hypotensive medication was to achieve an IOP of ≤24 mmHg and a minimum 20% reduction from the baseline IOP, except that IOP < 18 mmHg was not required. Humphrey 30-2 visual fields were performed every 6 months and stereoscopic optic disc photography was performed every 12 months. The optic disc was examined every 6 months, with a dilated fundus examination performed every 12 months. After publication of results in June 2002 showing that topical hypotensive medication was safe and effective in preventing or delaying the development of glaucoma, topical medication was offered to participants originally randomized to the observation group.[15]

Ascertainment of Retinal Vein Occlusion

Potential cases of RVO occurring during OHTS follow-up were identified using the following methods.

- Electronic searches of the OHTS database were conducted for any combination of the keywords—"central retinal vein occlusion," "hemiretinal vein occlusion," and "branch retinal vein occlusion" in Adverse Events Forms, the Optic Disc Reading Center database, and the Endpoint Committee Forms. The Endpoint Committee, which is masked as to randomization assignment, determines whether each occurrence of confirmed visual field abnormality or optic disc change is attributable to glaucoma or not.
- The Study Chairman sent letters (July 2005) to clinic principal investigators of each of the 22 OHTS clinical sites asking for the participant identification number and date of diagnosis of any cases of RVO.

Statistical Methods

The analysis data set included data from 1636 participants randomized between February 1994 and October 1996. The data set for this report closed July 1, 2005. The unit of analysis for eye-specific variables was the first affected eye among RVO cases versus 1 eye selected randomly among participants who were controls. The date of diagnosis of RVO was determined by the first affected eye of a participant.

The occurrence of RVO is reported as a percent of all participants randomized, either adjusted or unadjusted for variable follow-up time. The occurrences of RVO during follow-up in the observation and medication groups were plotted using Kaplan-Meier life tables and compared using the log-rank statistic that adjusts for variable duration of follow-up. We used *t* tests and chi-square statistics to compare baseline IOP, demographics, clinical characteristics, and self-reported health history of participants who did or did not develop RVO. A Cox proportional hazards model for the development of RVO included randomization group and baseline variables with *P*-values of ≤0.10 in univariate analyses.

Results

This report includes data from the start of randomization in February 1994 to July 1, 2005. During this reporting period, the mean follow-up for the medication group was 9.1±2.7 standard deviation (SD) years, during which time these participants were treated. The mean follow-up for the observation group was 9.1±2.6 SD years. The observation group participants were treated for an average of 2.9±0.6 years from June 1, 2002, to July 1, 2005. The mean IOP over the entire period for the medication group was 19.0±3.5 mmHg. In the observation group, the mean IOP was 23.6±3.8 mmHg before treatment and 20.0±4.3 mmHg after initiation of treatment.

After identification of potential RVOs and subsequent confirmation through chart review and communication with clinical investigators (when necessary), 26 occurrences of RVO were confirmed in 23 subjects: 5 BRVO, 14 CRVO, and 7 HRVO.

Two participants, both randomized to the observation group, experienced >1 RVO event. One participant was determined to have CRVO in the first eye and 58 months later to have CRVO in the fellow eye. At the same visit, the other participant was found to have BRVO in the right eye and HRVO in the left eye. The left eye of this participant subsequently developed CRVO 50 months later.

Over a mean follow-up of 9.1 years , the percent of participants who developed RVO in 1 or both eyes was 1.8% (15 of 819 participants) in the observation group and 1.0% (8 of 817 participants) in the medication group unadjusted for follow-up time (chi-square test; $P = 0.14$). The median time to RVO was 7.1 years for the medication group and 5.5 years for the observation group. Of the participants in the observation group who developed RVO, 4 (out of 15) did so after initiation of treatment. Adjusting for follow-up time including loss to follow-up and death, the cumulative proportion of participants who developed RVO in 1 or both eyes was 2.1% in the observation group and 1.4% in the medication group (hazard ratio, 0.53; 95% confidence interval, 0.22–1.24; log-rank $P = 0.14$; Fig 1).

The mean baseline age of participants who later developed RVO was 65.1±8.5 SD years compared with 55.3±9.5 SD years among participants who did not develop RVO (*t* test; $P<0.001$; Table 1). The mean age of participants at the time of RVO diagnosis was 71.6±8.7 years SD. The mean baseline horizontal cup-to-disc ratio (CDR) was significantly higher in participants who developed RVO (0.46) than those who did not (0.36; $P = 0.016$). Participants who later developed RVO also had a more hyperopic baseline spherical equivalent than those who did not (+0.3 vs −0.6 diopters, respectively), although this difference did not achieve significance ($P = 0.067$). There was a nonsignificant trend ($P = 0.083$) for the group that developed RVO to have a lower proportion of females (39.1%) than the group that did not develop RVO (57.2%). No difference in baseline IOP was detected between participants who later developed RVO (24.9±2.5 SD) and those who did not (24.9±3.0 SD; *t* test; $P = 0.94$). Analysis of the last IOPs measured before diagnosis of RVO found a significantly higher IOP among participants from the observation group (22.1±4.0 mmHg) versus the medication group (18.4±3.2 mmHg; $P = 0.035$). The proportion of participants who developed

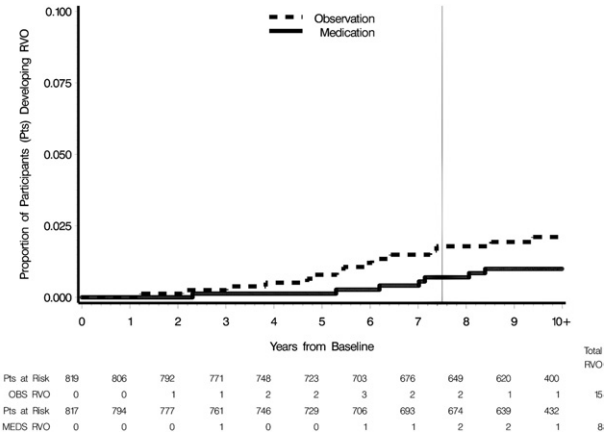

Figure 1. Cumulative proportion of participants in the observation (OBS) group and medication (MEDS) group who developed retinal vein occlusion (RVO). The vertical line indicates the mean follow-up (years) completed when hypotensive medication was offered to the observation group.

RVO by baseline demographic and clinical factors is reported in Table 1.

The Cox multivariate proportional hazards model for the development of RVO included randomization group and baseline variables (age, horizontal CDR, spherical equivalent, and gender) with *P*-values of ≤ 0.10 in univariate analyses (Table 1). Factors in the Cox multivariate proportional hazards regression model that were significantly associated ($P \leq 0.05$) with the development of RVO after adjusting for the correlation among these factors were age (hazard ratio, 3.2 per decade; 95% confidence interval, 1.9–5.4; $P < 0.0001$) and horizontal CDR (hazard ratio, 1.35 per 0.1 units; 95% confidence interval, 1.09–1.67; $P = 0.006$).

Over the course of follow-up, the incidence of progression to primary open angle glaucoma was higher among participants who developed RVO (26.1%, 6 of 23 participants) as compared with participants who did not develop RVO (7.4%, 120 of 1613 participants; Fischer exact test, $P = 0.006$). Of the 6 participants with RVO who also developed primary open angle glaucoma, the RVO date preceded the date of primary open angle glaucoma in 4. All 4 of these participants met endpoint criteria based on optic disc (as opposed to visual field) changes.

Discussion

Twenty-three OHTS participants had RVOs during a mean follow-up of 9.1 years for a cumulative incidence of only 1.4%. The low number of incident RVO cases limits our ability to compare the observation and medication groups and to identify predictive factors. The incidence of RVO in the OHTS (1.4% over 9.1 years) was comparable with that reported from population-based studies. The Beaver Dam Eye Study found a 5-year incidence of RVO of 0.8%, whereas the Blue Mountains Eye Study reported a 10-year cumulative incidence of 1.6%.[11,12] The diagnosis of RVO was aided by stereoscopic 30° color fundus photographs at the 5-year examination in the Beaver Dam Eye Study and at the 5- and 10-year examinations in the Blue Mountains Eye Study, with RVOs typically identified based on chronic fundus and disc changes associated with the event. Nearly all RVOs in the OHTS population were identified based on acute fundus changes, often accompanied by a change in vision. The relatively frequent follow-up employed in the OHTS study (every 6 months) with dilated fundus examinations (every 12 months), combined with the ongoing documentation of adverse events, made it less likely that a visually significant RVO would go undetected in an OHTS subject. Standardized 2× optic disc photographs were taken every 12 months by certified OHTS photographers and evaluated by an independent reading center, further reducing the possibility of missing the disc changes typically associated with a CRVO or HRVO. It remains possible that

Table 1. Baseline Measures for 23 Participants Who Developed Retinal Vein Occlusion (RVO) and 1613 Control Participants*

	RVO Status		
	Control	*RVO*	***P*-Value**
Baseline age			<0.0001
N	1613	23	
Mean	55.3	65.1	
SD	9.5	8.5	
Gender = female			0.083
N	1613	23	
Percent	57.2	39.1	
Race = African American?			0.72
N	1613	23	
Percent	25.0	21.7	
Baseline spherical equivalent			0.067
N	1613	23	
Mean	−0.6	0.3	
SD	2.4	1.5	
Baseline ETDRS visual acuity (letters correct)			0.66
N	1023	10	
Mean	55.5	54.5	
SD	7.2	3.7	
Baseline intraocular pressure (mmHg)			0.94
N	1613	23	
Mean	24.9	24.9	
SD	3.0	2.5	
Baseline horizontal cup-to-disc ratio			0.016
N	1613	23	
Mean	0.36	0.46	
SD	0.21	0.19	
Baseline vertical cup-to-disc ratio			0.086
N	1613	23	
Mean	0.39	0.46	
SD	0.20	0.23	
Baseline mean deviation (dB)			0.79
N	1613	23	
Mean	0.2	0.2	
SD	1.1	0.9	
Central corneal thickness (μM)			0.41
N	1424	23	
Mean	572.5	565.9	
SD	38.5	38.7	

ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
*Eye-specific measures are reported for a randomly selected eye of controls and for the first affected eye of participants who had >1 RVO. *P*-values are for *t* tests and chi-square tests and are not adjusted for correlation with other measures.

an asymptomatic RVO event, such as a small branch BRVO, which resolved fully, could have gone undetected in the OHTS.

The OHTS was not designed to prospectively identify RVO and the analysis of the incidence of RVO was unplanned. No standardized diagnostic criteria for the diagnosis of RVO were employed. Instead, potential RVOs were identified and documented by OHTS investigators based on clinical findings. Unless annual study photographs were due to be taken at that time, photographic documentation of the RVO was not routinely performed as part of the study. Although many of the participants with potential RVO were ultimately referred to a retina specialist and these evaluations may have contributed to the final diagnosis provided by the OHTS clinical site, review of such documentation was outside of the scope of this analysis. Individual OHTS investigators were free to manage RVOs independently. One exception was the requirement for study approval to initiate topical ocular hypotensive treatment in an observation group participant with RVO.

A focus on the overall incidence of RVO may be misleading in that the role of IOP as a risk factor may differ across RVO subtypes. Although elevated IOP has been repeatedly identified as a risk factor for CRVO and HRVO,[5,16] the results for BRVO have been less consistent. In the Beaver Dam Eye Study, for example, Klein et al[12] did not find an association between BRVO and glaucoma, IOP, or OHT at the 5-year follow-up. A higher frequency of elevated IOP in cases of CRVO as compared with BRVO has been reported in other studies.[4,17] These findings suggested the need to separate the different RVO subtypes in future analyses.[18] In our analysis, the cumulative incidence of CRVO/HRVO (1.3%) was >4 times that of BRVO (0.3%). This lies in stark contrast with the 5-year data from the Beaver Dam Eye Study in which this ratio was reversed: 0.6% for BRVO and 0.2% for CRVO (HRVO not identified separately).[12] Similarly, in the Blue Mountains Eye Study, the 10-year incidence of BRVO was 3 times that of CRVO/HRVO: 1.2% BRVO and 0.4% CRVO (includes HRVO).[11] Given the stronger relationship reported in the literature between elevated IOP and CRVO/HRVO, the reversal of the ratio of BRVO to CRVO/HRVO in the OHTS versus these population-based studies may be related to the requirement for elevated IOP for inclusion into the OHTS.

One consistent finding over a follow-up period of nearly 10 years was that observation group participants had a higher incidence of RVO than those in the medication group, although this difference did not achieve significance. This analysis, however, is not a definitive test of the relationship between elevated IOP and risk for RVO, because there are several factors that might have undermined such a relationship. The OHTS inclusion criteria limited IOP elevation to 32 mmHg in either eye at entry, with the average overall IOP at baseline being 24.9 mmHg.[14] Individual OHTS investigators were allowed to request IOP-lowering treatment for observation group participants with markedly elevated IOPs if deemed necessary for the safety of the participant. Observation group participants were treated with IOP-lowering topical medications during roughly one third of the analysis period (2.9 of 9.1 years), although the last measured IOP before RVO was still significantly higher in participants from the observation group than the medication group. Given the low number of RVOs and relative risk, the study would have needed >6000 participants to detect a difference between the observation and medication groups with statistical power of 80%.

Older age at baseline was a statistically significantly predictive factor for the development of RVO in OHTS. Although average age at enrollment of all OHTS participants was 55.4 years, those developing RVO were considerably older at baseline (65.1 vs 55.3 years). Indeed, RVO occurred at an average of 5.9 years from entry into OHTS (range, 1.2–10.6). The Beaver Dam Eye Study enrolled subjects 43 to 86 years old and had an average age at baseline of 62.0, almost 7 years older than OHTS subjects.[12] The Blue Mountains Eye Study also reported an increase in RVO incidence with age. Participants <60 years of age had a 10-year incidence of RVO of 0.8%; those 60 to 69, 1.6%; and patients ≥70, 2.7%.[11]

At baseline, OHTS participants who later developed RVO had a mean horizontal CDR of 0.46 compared with 0.36 in those who did not, a difference that reached significance ($P = 0.016$). The literature on CDR and RVO is contradictory. In 1 case-control study, the CDR of the fellow eye of 55 CRVO patients was nearly identical to that found in the control group.[19] Mansour et al[20] compared 45 unilateral CRVO eyes that did not have disc edema or a history of OHT or glaucoma in either eye with 27 control subjects and found a greater (0.37 vs 0.26) but not significantly different horizontal CDR. In contrast, while controlling for baseline variables such as age and IOP, the Beaver Dam Eye Study found that participants with higher CDRs at baseline were more likely to develop RVO (predominantly BRVO) within 10 years (40% increase per 0.1 increment in CDR).[13] Beaumont and Kang[21] also reported a significant association between enlarged CDR and RVO, when the RVOs were subdivided according to the putative site of the vascular occlusion.

The only other baseline attribute which approached significance as a risk factor was refractive error. The mean spherical equivalent of RVO subjects was +0.3 diopters compared with −0.6 diopters for those who did not have a RVO. Several studies have associated hyperopia with BRVO.[17,22,23] Given the small number of RVOs detected in our analysis, the importance of refractive error as a baseline risk factor could not be adequately assessed.

In summary, the OHTS cohort provided an opportunity to examine prospectively the incidence of RVO in participants with the risk factor of elevated IOP. Our retrospective analysis found that development of RVO was a relatively infrequent occurrence in OHTS participants, with an incidence of 1.4% cases of RVO (23 of 1636) over a mean follow-up of 9.1 years. Although RVO was more frequent in the observation as compared with the medication group, consistent with previous studies implicating elevated IOP as a risk for RVO, this difference did not achieve statistical significance. Consistent with some previous studies, older age and larger horizontal CDR at baseline were found to be statistically significant predictive factors for the development of RVO.

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