The 15-Year Cumulative Incidence of Retinal Vein Occlusion

The Beaver Dam Eye Study

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Objectives: To describe the 15-year incidence of retinal vein occlusion (central retinal vein occlusion and branch retinal vein occlusion) and associated risk factors.

Methods: A population-based study where branch retinal vein occlusion and central retinal vein occlusion were detected at baseline (n=4068, 1988-1990) and three 5-year follow-up examinations by grading 30° color fundus photographs.

Results: The 15-year cumulative incidences of branch retinal vein occlusion and central retinal vein occlusion were 1.8% and 0.5%, respectively. Using a generalized estimating equation model, incident retinal vein occlusion was related to baseline age (odds ratio [OR] per 10 years, 1.70; 95% confidence interval [CI], 1.36-2.12), history of barbiturate use (OR, 5.30; 95% CI, 2.28-12.31), focal retinal arteriolar narrowing (OR, 2.45; 95% CI, 1.29-4.66), glaucoma (OR, 3.17; 95% CI, 1.50-6.69), serum ionized calcium level (OR per 0.4 mg/dL, 0.43; 95% CI, 0.23-0.79), serum phosphorus level (OR per 0.3 mg/dL, 1.15; 95% CI, 1.01-1.30), and serum creatinine level (OR for ≥ 1.4 vs < 1.4 mg/dL, 1.61; 95% CI, 1.00-2.59). Migraine headache history was associated with branch retinal vein occlusion (OR, 1.99; 95% CI, 1.08-3.67). Diabetes history was associated with central retinal vein occlusion (OR, 6.35; 95% CI, 1.90-21.27).

Conclusions: Incident retinal vein occlusion is not infrequent in the population, especially after age 65 years. The relationships of barbiturate use, serum creatinine level, serum ionized calcium level, and serum phosphorus level with incident retinal vein occlusion require further assessment in other large population-based studies.

Arch Ophthalmol. 2008;126(4):513-518

RETINAL VEIN OCCLUSION (RVO) (branch RVO [BRVO] or central RVO [CRVO]) is a cause of significant loss of vision. In the Beaver Dam Eye Study, 12% of eyes that developed severe visual impairment (best-corrected visual acuity ≤ 20/200) during a 15-year follow-up were due to RVO. Most of the information regarding RVO has come from clinical case series, case-control studies, and clinical trials. To date, information regarding the long-term cumulative incidence of RVO in population-based studies has been limited.

Data from previous studies have shown an association of RVO with hypertension, increased body mass, dyslipidemia, smoking history, atherosclerotic vascular disease, diabetes mellitus, abnormal rheological factors, elevated intraocular pressure (IOP), and open-angle glaucoma, although these associations have not been consistent. The purposes of this report are as follows: (1) to describe the long-term cumulative incidence of RVO; (2) to examine associated risk factors; and (3) to describe the relationship of RVO to subsequent visual changes in the large population-based cohort in Beaver Dam, Wisconsin. Data from this article build on our previous observations in the Beaver Dam Eye Study population regarding the 5-year incidence of RVO.

METHODS

POPULATION

Methods used to identify and describe the population have appeared in previous reports. In brief, a private census of the population of Beaver Dam (99% white) was performed from fall 1987 to spring 1988 in people aged 43 to 84 years. Of the 5924 eligible individuals, 4926 participated in the baseline examination in 1988 to 1990. Of the 4552 surviving participants at the baseline examination, 3684 (81.1%) participated at baseline and in the 5-year follow-up examination in 1993 to 1995. Comparisons between participants and nonparticipants at baseline and the 5-year follow-up examination have appeared elsewhere. Of the 3334 surviving participants at baseline and in the second examination, 2764 (82.9%) participated in the 10-
Comparisons between participants and nonparticipants at baseline and the 10-year examination have been described elsewhere. The mean (SD) and median times between baseline and the 15-year follow-up examination were 14.9 (0.5) years and 14.8 years, respectively.

Comparisons between participants and nonparticipants at the 15-year follow-up have been described elsewhere. In general, persons who did not participate in the 15-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to have fewer years of education completed, higher systolic blood pressure, and more pack-years smoked than persons who participated. After adjusting for age, participants with RVO at baseline were as likely to participate at the 15-year follow-up as those in whom RVO was absent (data not shown).

PROCEDURES

Similar procedures were used at the baseline and follow-up examinations. Informed consent was obtained and institutional review board approval was granted at the beginning of each examination. A standardized questionnaire that included pertinent questions on diabetes status, cigarette smoking history, hypertension, antihypertensive medication use, and, in women, hormone replacement therapy was administered.

All of the examinations included measuring weight, height, and pulse rate using standardized protocols and have been described in detail elsewhere. Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) and a nonstereoscopic color fundus photograph temporal to but including the fovea were taken in each eye. Additional fundus photographs were taken if an RVO was found outside these fields. Photographs were graded using the Wisconsin Age-Related Maculopathy grading scheme. As part of this scheme, all photographic fields of each eye were examined by the graders (Carol Hoyer, BA, Maria Swift, BS, Andy Ewen, BA, Ellen Hall, BA, and Anne Mosher, BS, SMM) to detect RVO. Old CRVOs were characterized by occluded and sheathed retinal veins, whereas more recent occlusions were characterized by retinal edema, optic disc hyperemia or edema, scattered superficial and deep retinal hemorrhages, and venous dilatation. The BRVOs involved a more localized area of the retina in the sector of the obstructed venule and were characterized by scattered superficial and deep retinal hemorrhages, venous dilatation, intraretinal microvascular abnormalities, and occluded and sheathed retinal venules. When present, the site of the occlusion (superotemporal, inferotemporal, or outside the temporal quadrants) was recorded. In addition, the position of the retinal arteriole in respect to the retinal venule (anterior vs posterior) closest to the site of the occlusion was also recorded. One of us (R.K.) examined all photographs from persons with questionable or definite RVO.

When 2 eyes of a participant were discrepant regarding the presence of a lesion, the grade assigned for the participant was that of the more severely involved eye. For example, in assigning the presence of an RVO, if the RVO was present in one eye but not the other, the participant would be considered to have an RVO. When lesions could not be graded in one eye and the other eye had no lesions present, the participant’s information was set to absent. For BRVOs, this occurred in 92, 99, 123, and 60 subjects during the baseline and 5-, 10-, and 15-year examinations, respectively. For CRVOs, it occurred in 90, 87, 118, and 45 subjects during the baseline and 5-, 10-, and 15-year examinations, respectively.

DEFINITIONS

Current age was defined as the age at the time of the baseline examination. The mean systolic blood pressure was the average of the 2 systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the 2 diastolic blood pressures. Hypertension was defined as a mean systolic blood pressure of 160 mm Hg or higher and/or a mean diastolic blood pressure of 95 mm Hg or higher and/or history of hypertension with use of antihypertensive medication at the time of examination. Cardiovascular disease was defined as a history of angina pectoris, myocardial infarction, or stroke.

STATISTICAL ANALYSIS

We used SAS version 9.1 statistical software (SAS Institute, Inc, Cary, North Carolina) for statistical analysis. The calculations of the cumulative incidence of RVOs allow persons who were right censored (not seen after the baseline, 5-year, or 10-year examination due to death or nonparticipation) to contribute information to the estimates. These estimates also account for the competing risk of death and are interpreted as the probability of an end point occurring before any competing risks such as death. We assume that the competing risk method is the appropriate measure when the burden of incident disease (eg, RVO) is of interest as alternative methods, such as the product-limit method, represent a rate if there were no competing events such as death. A person only needed to have gradable photographs at baseline and the 5-year follow-up examination or die between baseline and the 5-year follow-up to contribute to the estimates. Included in the analyses were data from 4162 persons: 2291 people examined with gradable photographs at baseline and through 15 years of follow-up, 726 examined with gradable photographs at baseline through 10 years of follow-up, 795 examined with gradable photographs at baseline and through 5 years of follow-up, and 350 who died before the 5-year follow-up. The latter group contributes only mortality information for cumulative incidence estimates. The numbers at risk for each RVO outcome (Table 1) vary owing to differences in prevalent disease at baseline.

Age-adjusted rates were computed by the direct method. Tests for differences between rates were conducted by the log-rank test. Multivariate models were constructed by discrete linear logistic regression using the generalized estimating equation approach to account for correlation between eyes when eye-specific risk factors were included. The odds ratio is used as a proxy for the relative risk to access the strength of associations. Time-varying covariates were used as follows. For each separate 5-year follow-up interval, the value of each covariate at the beginning of the interval or the previous value if that value was missing was included in the model. For example, the baseline value was included for the interval between baseline and the 5-year examination. The value at the 5-year examination was included for the interval between the 3- and 10-year examinations, and the value at the 10-year examination was included for the interval between the 10- and 15-year examinations. All of the variables in Table 2 were included in the time-dependent covariate models. However, retinal focal arteriolar narrowing, glaucoma, history of migraine, serum phosphorus level, and serum ionized calcium level were not available at examinations after baseline. Thus, only the baseline values were used. In addition, several variables that were suggestive in previous analyses were added in time-dependent fashion. For BRVO, these were current smoking and cup-disc ratio. For CRVO, they were cup-disc ratio, high blood pressure medications, and IOP. For BRVO or CRVO, they were current smoking, cup-disc ratio, and high blood pressure medications.
RESULTS

INCIDENCE OF RVO

Branch RVO occurred in 64 subjects for a 15-year incidence of 1.8% (95% confidence interval [CI], 1.4%-2.2%); 19 subjects developed CRVO for a 15-year incidence of 0.5% (95% CI, 0.3%-0.8%). Four subjects developed bilateral involvement (1 with BRVO in both eyes, 2 with CRVO in both eyes, and 1 with BRVO in one eye and CRVO in the other) at different intervals of follow-up. The 15-year cumulative incidence of CRVO and BRVO...
While controlling only for age, there were associations of presence of diabetes, glaucoma history, larger cup-disc ratio, higher IOP, and history of current use of antihypertensive medications and barbiturate sedatives at baseline with an increased 15-year cumulative incidence of CRVO (Table 1). There were too few incident cases of CRVO (n=3) to examine the association of factors first measured at the 5-year follow-up.

Relationships of factors associated with either BRVO or CRVO are also shown in Table 1. While controlling for age, in multivariate analyses, glaucoma status and use of barbiturate sedatives were associated with the cumulative incidence of BRVO or CRVO, retinal focal arteriolar narrowing, serum creatinine level, history of migraine, high serum phosphorus level, and low serum ionized calcium level were related to incident BRVO, and history of diabetes and past use of digoxin were related to incident CRVO (Table 2). These models represent the distillation of independent and significant variables remaining of all those considered. No interactions with age or hypertension status were found (data not shown).

Controlling for age and using multivariate models with time-dependent covariates, current smoking (odds ratio, 1.94; 95% CI, 1.04-3.63) and cup-disc ratio (odds ratio per 0.1, 1.24; 95% CI, 1.06-1.46 at the beginning of each 5-year period) were associated with the 5-year incidence of RVO, whereas the serum creatinine level was no longer statistically significant. These changes were found when BRVO was the end point. There were no changes in the CRVO model from those found using a non–time-dependent covariate multivariate analyses model (data not shown).

**RELATIONSHIP OF BRVO TO VISUAL ACUITY**

Of the 61 eyes that developed BRVO and had visual acuity measurements available from before and after the occlusion, the best-corrected visual acuity decreased from 52.8 to 41.1 letters read correctly. Seventeen instances of incident macular edema, 3 of incident retinal new vessels, 8 of incident focal photocoagulation for macular edema, and 3 of incident panretinal photocoagulation for retinal new vessels were found in 25 of these eyes. One eye previously untreated with IOP-lowering drugs was now receiving such medications. Similarly, of the 18 eyes that developed CRVO and had visual acuity measurements available, the best-corrected visual acuity decreased from 54.4 to 31.7 letters. Seven instances of incident macular edema, 3 of incident retinal new vessels, and 2 of panretinal photocoagulation were found in 10 of these eyes.

The Beaver Dam Eye Study provides unique population-based data on the 15-year cumulative incidence of RVO and its association with risk factors and subsequent visual loss using standardized protocols for the recording and grading of these lesions with stereoscopic color fundus photographs. We found an overall 15-year cumulative incidence of 2.3% and associations of RVO with age, use of barbiturates, glaucoma, higher serum creatinine
and phosphorus levels, lower serum ionized calcium level, and retinal focal arteriolar narrowing.

The 15-year cumulative incidences of BRVO (1.8%) and CRVO (0.5%) were not infrequent in the population and increased with age, affecting 2.9% and 1.3%, respectively, of those aged 65 to 74 years or older at baseline before declining. The 15-year cumulative incidence of RVO (BRVO or CRVO) accounting for the competing risk of death was 2.3% in Beaver Dam. This was similar to the 1.6% 10-year incidence in the Blue Mountains Eye Study, which estimated incidence without taking into account the competing risk of death, and higher than that reported in an Israeli study where the estimated 4-year incidence was 2/1000 in persons aged 40 years or older. It was also higher than that found in a 10-year follow-up of a Japanese cohort where the estimated incidence was 0.4% and in a clinic-based study in Hiroshima, Japan, where the estimated 5-year incidence was 0.6%. Comparisons among studies are limited by differences in study design and methods used to estimate cumulative incidence.

Chance, unadjusted confounding, and bias must be considered when interpreting our findings regarding associations of RVO with risk factors reported herein. We have examined a large number of possible risk factors and conducted multiple tests of significance. Therefore, some of our findings that are statistically significant may be the result of chance alone. This possibility is of particular concern for associations that have not previously been reported, such as with serum ionized calcium and phosphorous levels and history of barbiturate use. Chance is less of a possibility for findings of serum ionized calcium and phosphorous levels, lower serum ionized calcium level, and retinal focal arteriolar narrowing, which have been found to be associated with RVO in earlier studies and where there is a plausible biological rationale.

We found an association of history of receiving blood pressure–lowering medications with incident CRVO and an association of the 5-year increase in systolic blood pressure with incident BRVO, which is consistent with our earlier findings of a relation of hypertension with prevalent BRVO. We did not find a relation of a history of cardiovascular disease with RVO. High blood pressure, cardiovascular disease, and their risk factors have been previously shown to be related to BRVO. Hypertension and atherosclerotic cardiovascular disease have been postulated to cause retinal arteriolar changes, especially at the arteriovenous crossings, resulting in RVO through endothelial cell damage and thrombosis. Others have postulated arterioscleroses resulting in arteriolar insufficiency as the underlying pathogenetic factor resulting in BRVO. Not finding a relation of a history of cardiovascular disease with RVO in Beaver Dam may be owing in part to selective survival, that is, it is possible that persons with a history of cardiovascular disease who developed BRVO were more likely to die before follow-up, possibly underestimating its association with incidence. It is also possible that cardiovascular disease is not associated with the incidence of this condition.

Using time-varying covariate multivariate analyses that show the odds of developing BRVO in 5-year intervals according to smoking status at the beginning of each interval, we found a relation of a history of current cigarette smoking to incident BRVO in Beaver Dam. This association with smoking and incident BRVO is consistent with data from some studies but not others. The association of incident BRVO with cigarette smoking may in part be explained by the inflammatory stimulus of smoking, although the role of inflammation in the pathogenesis of BRVO is not certain. Others have speculated that the consistent finding of arteriolar narrowing to venules at arteriovenous crossings associated with BRVO supports a possible mechanical obstructive role in the pathogenesis of BRVO. The higher frequency in the superotemporal quadrant has been attributed to a larger number of arteriovenous crossings in that quadrant or possibly to relative quadratic differences in the type of direct contacts of the arterioles to the venules. While there are many strengths to this study, conclusions regarding estimates of prevalence and incidence of BRVO and associations described herein must be made with caution. Misclassification may have resulted from not identifying signs of BRVOs in eyes with minimal retinopathy in persons without diabetes or in eyes with moderate retinopathy in persons with diabetes when there was no obvious occlusion of a retinal venule in the fundus photographs. The photographs were taken only of Diabetic Retinopathy Study fields 1, 2, and modified 3 and so were only a sample of the retina; we would have missed more peripheral vein occlusions. In addition, some of the characteristics that we did identify as risk indicators were infrequent, perhaps occurring by chance (type I error). Like many other epidemiological studies of this relationship, we had limited information concerning clotting mechanisms and did not collect information regarding factor V Leiden mutation, antithrombin or anticardiolipin antibodies, or other thrombophilic factors. It is possible that defects in that clotting system could be more important indicators of incidence of RVO than those we did evaluate. We are unable to assess this possibility.

In summary, incident RVOs are not infrequent in the general population older than 65 years. A strong association of retinal arteriolar disease as manifest by focal arteriolar narrowing was found with BRVO. Data from other populations are needed to further confirm associations found herein between risk factors and the incidence of RVOs.

Submitted for Publication: March 13, 2007; final revision received June 29, 2007; accepted July 9, 2007.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by grant EY06594 from the National Institutes of Health (Drs R. Klein and B. E. K. Klein) and in part by Senior Scientific Investigator Awards from Research to Prevent Blindness (Drs R. Klein and B. E. K. Klein).