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.

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Method 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 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-
Comparison between participants and nonparticipants at baseline and in the 5- and 10-year follow-up examinations, 2119 (85.4%) participated in the 15-year follow-up examination between March 31, 2003, and April 30, 2005. 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 dilation. 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 dilation, 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 pressure determinations. 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, 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 event 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 5 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 5- 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
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 glaucoma, migraine, retinal focal arteriolar narrowing, and diabetes, 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 arteriosclerotic mechanisms 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. The failure to find a relation with baseline smoking status may have been a result of selective survival or inaccurate reporting of the exposure.

The higher frequency of BRVO found in the superotemporal quadrant compared with other quadrants and the high frequency of the retinal arteriole found lying anterior to the vein toward the vitreous cavity are consistent with earlier findings from Beaver Dam and elsewhere. Others have speculated that the consistent finding of arterioles anterior 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 quadrant 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.

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REFERENCES