Ten-Year Incidence of Retinal Vein Occlusion in an Older Population

The Blue Mountains Eye Study

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Objective: To assess the 10-year incidence of retinal vein occlusion (RVO) and its predictors in an older population.

Methods: The Blue Mountains Eye Study examined 3654 residents aged 49 years and older (82.4% response) from 1992 to 1994, reexamined 2335 residents (75.1% of survivors) from 1997 to 1999, and reexamined 1952 residents (75.6% of survivors) from 2002 to 2004. Incident RVO was assessed from stereoscopic retinal photographs. Kaplan-Meier cumulative 10-year incidence was calculated.

Results: After excluding 47 residents with RVO at baseline and 171 residents with no photographs at either follow-up examination, 2346 residents were considered at risk of developing RVO. The cumulative 10-year incidence of RVO was 1.6%. Age was significantly associated with the incidence of RVO (P = .03, Mantel-Haenszel χ² test for trend). Factors predicting the incidence of RVO included mean arterial blood pressure (age-adjusted odds ratio [OR], 1.41 per 10-mm Hg increase), ocular perfusion pressure (OR, 1.71 per 10-mm Hg increase), obesity (OR, 2.16), and presence of retinal arteriolar wall signs (focal narrowing: OR, 3.37; arteriovenous nicking: OR, 4.09; and opacification: OR, 4.89).

Conclusions: Older age (≥70 years), increasing mean arterial blood pressure, and atherosclerotic retinal vessel signs were significant predictors of incident RVO.

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Retinal Vein Occlusion (RVO) is an important cause of unilateral vision loss and has been associated with an increased risk of cardiovascular mortality and stroke. Central RVO, even when unilateral, may be associated with reduced vision-related quality of life. Most reported studies of RVO are derived from hospital-based samples, with few population-based studies providing data on the prevalence of RVO and its associated risk factors. The frequency of RVO in a hospital-based sample was 1.5%. The prevalence of RVO among older population-based samples has ranged from 0.3% in the Atherosclerosis Risk in Communities Study (12,642 persons aged 51-70 years) and the Cardiovascular Health Study (2824 persons aged 73 years and older) to 1.6% in the Blue Mountains Eye Study (3654 persons aged 49 years and older). The Beaver Dam Eye Study reported a 0.7% prevalence of RVO. The substantially lower prevalence of RVO among subjects in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study is likely because only 1 single-eye nonmydriatic photograph was taken of each participant in those studies.

In Hiroshima, Japan, the 5-year incidence of RVO was 0.6% at a general outpatient clinic but was 4.2% in the glaucoma clinic. The 4-year incidence of RVO in an Israeli study of persons aged 40 years and older was 2.14 cases (0.2%) per 1000 people. In the Beaver Dam Eye Study population, the 5-year incidence of RVO was 0.8%. In a Japanese cohort study, 245 (19.6%) of 1250 baseline participants 40 years and older were reexamined after 10 years, and 1 patient (0.41%) had developed incident branch RVO; this study had substantial participant losses during follow-up. To our knowledge, there are no other reports of 10-year incidence data of RVO from large well-conducted population-based cohort studies.

Systemic risk factors associated with RVO include hypertension, diabetes mellitus, cerebrovascular disease, cardiovascular disease, increased body mass index, reduced high-density lipoprotein cholesterol levels, smoking, thyroid disorder, and peptic ulcer. Ocular risk factors associated with RVO include glaucoma or ocular hypertension, shorter axial length, and focal arteriolar narrowing and arteriovenous (AV) nicking. A recent meta-
Analysis of RVO and thrombophilic factors indicated that hyperhomocysteinuria and cardiolipin antibodies may be associated with RVO. Other hematologic factors reportedly associated with RVO include elevated erythrocyte sedimentation rates and elevated hematocrits.

A 1.6% prevalence of RVO was previously reported among an older Australian population. The objective of this study was to assess the 10-year incidence of RVO and its predictors in the same older Australian population.

METHODS

The Blue Mountains Eye Study is a population-based cohort study of a suburban Australian population aged 49 years and older at baseline. The study was approved by the Western Sydney Area Human Ethics Committee and was conducted in accord with the principles of the Declaration of Helsinki. The survey methods and procedures were described previously. Of 4433 eligible residents, baseline examinations (1992-1994) were performed on 3654 individuals (82.4% participation rate). The surviving baseline participants were invited to attend follow-up examinations after 5 years (1997-1999) and after 10 years (2002-2004). At each visit, the participants were examined in the same order as at baseline using the same procedures and equipment.

Face-to-face interviews were conducted and comprehensive eye examinations, including retinal photography, were performed at each visit. Stereoscopic 30° retinal photographs (Zeiss FF3 fundus camera; Carl Zeiss, Oberkochen, Germany) of diabetic retinopathy study fields 1 (optic disc) and 2 (macula) and nonstereoscopic photographs of fields 3 (temporal), 4 and 5 (upper and lower vascular arcades), and 6 (nasal to the optic disc edge) were taken of both eyes. Diabetic retinopathy study fields 4 and 5 were modified slightly to place the vascular arcades slightly closer to the center of the photograph. All photographs were graded for the presence of RVO by a grader who was unaware of any of the clinical diagnoses and were confirmed by a retinal specialist (P.M.).

Central RVO was characterized by widespread scattered superficial or deep retinal hemorrhages with or without optic disc hyperemia or edema, venous dilatation, retinal edema, or occluded or sheathed veins (Figure 1A). Old resolved central RVOs were diagnosed by the presence of anastomotic vessels.
at the disc. For hemispheric RVO, these signs were present in the upper or lower retinal half, corresponding to the branch of the central retinal vein in which the occlusion occurred. Branch RVO was characterized by retinal hemorrhages occurring within the retinal sector corresponding to the blood supply sector of the occluded venule (Figure 1B). Old branch RVO was characterized by the presence of collateral vessels or intraretinal microvascular abnormalities in a retinal sector.\textsuperscript{30–32} Branch RVO occlusions were further subclassified into occlusions occurring in major venules (first order) or macular branches (second order). The affected branch RVO site (superotemporal, inferotemporal, or outside temporal field) and the arteriolar position (above or below the venule) at the crossing closest to the occlusion site were recorded.

Baseline retinal vessel wall signs were assessed using a standard set of retinal photographs, selected by 1 of us (P.M.) from standard photographic sets developed for the modified Airlie House diabetic retinopathy classification\textsuperscript{33} and the Wisconsin Age-Related Maculopathy Grading System.\textsuperscript{34} Focal arteriolar narrowing was graded as absent/queretible or present. Arteriovenous (arteriole to venule) nicking was considered present if the venular diameter decreased on both sides of the arteriole crossing it. It was graded as absent/questionable, mild, or severe. Opacification of the arteriolar wall was defined as an enhancement of the central reflex at the center of the arteriolar wall, associated with an increased width of the reflex. It was graded as absent/questionable or present. Retinal arteriolar narrowing and AV nicking were evaluated for arterioles at least 0.5 disc diameter from the optic disc. The intragrader reliability (k statistic) for detecting focal arteriolar narrowing and AV nicking was 0.80 and 0.87, respectively.\textsuperscript{35} To measure retinal arteriolar and venular diameters, retinal photographs were digitized. All vessels passing through a circumferential zone between 0.5 and 1.0 disc diameter from the optic disc were measured using a retinal analysis software package (Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison). The Parr-Hubbard formula was used to standardize the arteriolar and venular calibers of each eye. These were summarized as central retinal arteriolar and central retinal venular equivalents.\textsuperscript{36}

At baseline, blood pressure (BP) was measured after participants had been seated for 10 minutes. Systolic BP (SBP) and diastolic BP (DBP) were recorded from the first and fifth Korotkoff sounds. The mean arterial BP was calculated as the following: one third SBP + two thirds DBP. Severe hypertension was defined as a previous diagnosis of hypertension with current use of antihypertensive medication or as an SBP of at least 160 mm Hg or a DBP of at least 100 mm Hg at examination. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as a body mass index of at least 30. Participants were classified as smokers if they currently smoked or had stopped smoking less than 1 year before examination and were classified as heavy drinkers if they consumed at least 4 alcoholic drinks per day.

Of baseline participants, 88.1% reattended to provide fasting serum samples at examination. Of 3654 baseline participants, 2335 (75.1% of survivors) returned for the 5-year examination, and 1952 (75.6% of survivors) returned for the 10-year examination. Combining persons seen at either or both follow-up examinations, 2564 (70.2% of baseline participants) were followed up. Of these, 47 had RVO at baseline and 171 had no or ungradable photographs at either follow-up examination and were excluded, leaving 2346 participants who were at risk of developing RVO. Participants who were still alive 10 years after baseline but did not participate in the 10-year examination were older, less likely to own their homes, and more likely to be current smokers compared with nonparticipants (Table 1).

Incident RVO developed in 33 persons. The 10-year cumulative incidence of branch RVO was 1.2% (95% confidence interval, 0.8%-1.7%) and of central RVO was 0.4% (95% confidence interval, 0.1%-0.7%). Central RVO, including hemicentral RVO, developed in 6 participants (18.2%) after 5 years and in 2 additional participants (6.1%) after 10 years. Branch RVO developed in 15 participants (45.5%) after 5 years and in an additional 9 participants (27.3%) after 10 years. One participant (3.0%) developed central RVO in one eye at 5 years and branch RVO in the fellow eye at 10 years. Of 47 participants with RVO at baseline, 3 (6.4%) had a second RVO episode within 5 years: one developed hemicentral RVO, another developed branch RVO in the fellow eye, and the third developed branch RVO at another location in the same eye. Overall, 37 eyes had...
incident RVO, including 10 with incident central RVO and 27 with incident branch RVO.

Incident RVO was more frequent in the left eye (21 [63.6%] of 33 eyes) than in the right eye (12 [36.4%] of 33 eyes). Incident branch RVO occurred equally in the superotemporal and inferotemporal quadrants (11 [42.3%] of 26 eyes for both quadrants) but was infrequent outside the temporal quadrant (4 [15.4%] of 26 eyes). One participant with superotemporal branch RVO at baseline developed incident branch RVO in the inferotemporal quadrant of the same eye. In most eyes (85.2%) with incident branch RVO, the occlusion occurred in the macular (second order) branch, while only 14.8% occurred in a major (first order) branch. Macular edema was present in 5 eyes (18.5%) with incident branch RVO, including 3 eyes (11.1%) with superotemporal branch RVO and 2 eyes (7.4%) with inferotemporal branch RVO. A retinal arteriole crossing the venule near the occlusion site was found in 23 (85.2%) of 27 eyes with incident branch RVO.

Table 2 gives the age-specific 10-year cumulative incidence of RVO, which increased from 0.84% to 2.69% across the age ranges (P = .03 for trend). Figure 2 shows a similar trend for branch RVO (P = .34). Incident central RVO was not observed in any participant younger than 60 years, but among older participants a similar significant age-related increase in incident central RVO was noted (P = .04 for trend). Although incident RVO was more frequent in men (2.0%) than in women (1.3%), this was not significant after age adjustment (P = .24).

Table 3 summarizes how, after age adjustment, increasing SBP, DBP, and mean arterial BP were significantly associated with increasing incidence of RVO. However, previously diagnosed hypertension was not significantly associated with incident RVO. The significant associations between ocular perfusion pressure, obesity, and incident RVO are given in Table 3. Table 4 summarizes how the association between obesity and incident RVO diminished after further adjustment for mean arterial BP.

Retinal vessel wall signs at baseline were strong predictors of incident RVO (Figure 1B and Table 4). Compared with persons without these signs at baseline, persons with these signs were more likely to develop RVO (focal arteriolar narrowing, 4.5% vs 1.2%; mild or severe AV nicking, 2.4% vs 0.6%; and severe arteriolar wall opacification, 6.0% vs 1.2%). After adjusting for age and mean arterial BP or for age and ocular perfusion pressure, all 3 retinal vessel wall signs detected at baseline remained significantly associated with incident RVO. No significant associations were found between baseline generalized arteriolar or venular calibers and incident RVO or branch RVO.

No significant associations were found between incident RVO and IOP, hematologic factors, or fasting serum glucose, creatinine, total cholesterol, or high-density lipoprotein cholesterol levels (Table 3), nor was there any association between incident RVO and smoking, baseline refraction, alcohol consumption, or history of cardiovascular disease or stroke. Separate analyses that were repeated for incident branch RVO showed associations that were similar to those for all incident (central and branch) RVO. A separate risk factor analysis for incident central RVO was prohibited by the small sample size.

Determining the long-term incidence of RVO and the risk factors associated with its development is important, as RVO is a potentially blinding eye disease. Although the 4-year and 5-year incidences of RVO have been reported in some studies, ours is the first population-based study (to our knowledge) with suf-
representative of a generalized older population, differing eye). Compared with that study, our study is representing 2 years and 2.5% during 4 years for second episodes in the fellow eye was 6.4% in our study, somewhat lower than the probabilities previously reported in a large clinic case series (0.9% during 2 years and 2.5% during 4 years for second episodes in the same eye and 7.7% during 2 years and 11.9% during 4 years for second episodes in the fellow eye). Compared with that study, our study is representative of a generalized older population, differing from a clinical case-series.

Table 3. Association of Systemic and Ocular Risk Factors With the 10-Year Incidence of Branch and Central Retinal Vein Occlusion

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Age-Adjusted Odds Ratio (95% Confidence Interval)</th>
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<tbody>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
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<tr>
<td>Blood pressure, per 10-mm Hg increase</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.19 (1.03-1.38)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>1.49 (1.08-2.06)</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>1.41 (1.09-1.82)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.12 (0.56-2.27)</td>
</tr>
<tr>
<td>Ocular perfusion pressure, per 10-mm Hg increase</td>
<td>1.71 (1.15-2.53)</td>
</tr>
<tr>
<td>Fasting serum glucose level, per mmol/L increase</td>
<td>0.83 (0.54-1.29)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.05 (0.98-1.12)</td>
</tr>
<tr>
<td>Obesity*</td>
<td>2.16 (1.02-4.56)</td>
</tr>
<tr>
<td>Serum levels, per mmol/L increase</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.96 (0.68-1.34)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>1.05 (0.47-2.37)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.15 (0.89-1.49)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>Hemoglobin level, per g/L increase</td>
<td>1.00 (0.97-1.03)</td>
</tr>
<tr>
<td>Hematocrit, per 10% increase</td>
<td>0.77 (0.27-2.20)</td>
</tr>
<tr>
<td>Fibrinogen level, per mg/dL increase</td>
<td>0.96 (0.68-1.35)</td>
</tr>
<tr>
<td>White, per 10/L increase</td>
<td>0.87 (0.68-1.11)</td>
</tr>
<tr>
<td>Red, per 10/L increase</td>
<td>1.20 (0.51-2.81)</td>
</tr>
<tr>
<td>Platelets, per 10/L increase</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
<td></td>
</tr>
<tr>
<td>Intraocular pressure, per mm Hg increase</td>
<td>0.99 (0.87-1.12)</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>3.37 (1.40-8.13)</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>4.09 (1.80-9.50)</td>
</tr>
<tr>
<td>Mild</td>
<td>3.78 (1.60-9.00)</td>
</tr>
<tr>
<td>Severe</td>
<td>5.70 (1.90-17.18)</td>
</tr>
<tr>
<td>Arteriolar wall opacification</td>
<td>4.89 (2.00-12.07)</td>
</tr>
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</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

*Obesity is defined as a BMI of 30 or higher.

Findings from most studies including a previous prevalence study, have suggested that branch RVO more frequently involves the superotemporal quadrant. This is supported by the incidence data from the Beaver Dam Eye Study, which reported involvement of the superotemporal quadrant in 45.5%, the inferotemporal quadrant in 36.4%, and the nasal quadrants in 18.2% of eyes that developed branch RVO. In our study, an equal proportion (42.3%) of eyes with incident branch RVO occurred in the superotemporal and inferotemporal quadrants, while 15.4% of incident cases occurred outside the temporal quadrants. However, it is possible that superotemporal vein occlusions may cause greater macular edema than RVOs elsewhere and be more symptomatic, leading to presentation bias. Macular edema was more frequent in superotemporal branch RVO than in inferotemporal branch RVO. Anatomical differences suggesting a more nasal distribution of the inferotemporal compared with the superotemporal venules have been considered a possible reason for the more frequent asymptomatic presentation of inferior RVO. This could, in part, explain the proportional differences in the 2 RVO locations observed between clinic-based and population-based samples.

Advancing age and elevated BP or ocular perfusion pressure were the principal baseline systemic variables predicting incident RVO, consistent with previous findings. Adequate control of elevated BP may be important in preventing RVO. The Beaver Dam Eye Study found a significant association of baseline ocular perfusion pressure with the prevalence of RVO but not with its 5-year incidence. However, we confirmed that ocular perfusion pressure is a modest predictor of long-term incident RVO.

Our finding that retinal arteriolar signs indicating established microvascular disease (focal narrowing, AV nicking, or wall opacification) were independent predictors of RVO risk is consistent with earlier data. Sclerotic arteriolar walls may compress underlying venules at AV crossings, leading to reduced blood flow, which in turn could facilitate the development of a thrombus and downstream venular occlusion. Based on this mechanism, sheathotomy at AV crossings has been proposed as a treatment option for branch RVO with macular edema.

Some authors have noted hematologic abnormalities associated with RVO, but we did not. However, we did not collect baseline data for other thrombophilic factors (hyperhomocysteinemia, factor V Leiden mutation, protein C and S deficiency, and antithrombin or anticoagulant antibodies) that are associated with RVO. We failed to find a significant association between incident RVO and elevated fasting glucose or cholesterol levels; the scarcity of incident RVO cases could have contributed to this negative finding.

Although the presence of acquired optociliary (anastomotic) shunt vessels generally indicates old central RVO, this could indicate other conditions, including optic nerve sheath meningioma, papilledema, chronic glaucoma, or diabetes. In our sample, only 1 participant was diagnosed as having old central RVO based on the presence of optociliary shunt.
Table 4. Multivariate Association of Risk Factors With the 10-Year Incidence of Branch and Central Retinal Vein Occlusion (RVO)*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% [No./Total] Developing RVO</th>
<th>Adjusted for Mean Arterial Blood Pressure</th>
<th>Adjusted for Ocular Perfusion Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.44 [10/409]</td>
<td>1.85 (0.86-3.95)</td>
<td>1.85 (0.87-3.95)</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>4.52 [7/155]</td>
<td>2.67 (1.07-6.62)</td>
<td>2.61 (1.05-6.50)</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>2.37 [26/1096]</td>
<td>3.81 (1.64-8.87)</td>
<td>3.84 (1.65-8.93)</td>
</tr>
<tr>
<td>Arteriolar wall opacification</td>
<td>6.00 [6/100]</td>
<td>4.26 (1.71-10.64)</td>
<td>4.19 (1.68-10.49)</td>
</tr>
</tbody>
</table>

*Data are given as age-adjusted odds ratio (95% confidence interval) unless otherwise indicated.

vessels in photographs from the 5-year examination; ever, the optic disc was not pale, and the participant had neither diabetes nor symptoms or signs suggesting optic nerve compression. At 10 years, this participant had developed branch RVO in the fellow eye.

Our study has other limitations. Almost 30% of the baseline participants were not reexamined at the 5-year or the 10-year examinations. Most participants who were lost to follow-up had died; therefore, the incidence of RVO could have been underestimated. It is possible that there are unmeasured predictors of incident RVO that we did not adjust for. The association between cardiovascular risk factors and incident RVO may have been underestimated because of selective survival, a bias arising from the higher risk of dying during follow-up among persons with cardiovascular risk factors. Estimates of the incidence of RVO in our older white population can only be applied to other populations with similar age and characteristics. Nevertheless, our study has many strengths, including its representative population-based sample, the use of 6-field stereoscopic retinal photographs, and the detection of RVO from masked photographic grading, with confirmation by a senior clinician.

In summary, the 10-year incidence of RVO in this older Australian population was 1.6%. Elevated BP and retinal vessel wall changes reflecting chronic hypertension and arteriosclerosis were long-term predictors of incident RVO. Monitoring and adequate control of elevated BP in patients with these signs could be a useful strategy in preventing RVO.

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REFERENCES


Announcement

Calendar of Events: A New Web Feature. On the new Calendar of Events site, available at http://pubs.ama-assn.org/cgi/calendarcontent and linked off the home page of the Archives of Ophthalmology, individuals can now submit meetings to be listed. Just go to http://pubs.ama-assn.org/cgi/cal-submit/ (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.