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Risk Factors Associated with Developing Branch Retinal Vein Occlusion Among Enrollees in a United States Managed Care Plan

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Purpose: To determine risk factors associated with development of a branch retinal vein occlusion (BRVO) among a large group of managed-care plan beneficiaries in the United States.

Design: Retrospective, longitudinal cohort study.

Participants: All beneficiaries age ≥55 years continuously enrolled for ≥2 years in a managed care network from 2001−2009 who had ≥2 visits to an eye care provider.

Methods: Multivariable Cox regression analyses identified sociodemographic factors, ocular and nonocular conditions associated with incident BRVO.

Main Outcome Measures: Hazard of incident BRVO with 95% confidence interval (CI).

Results: Of the 492 488 enrollees who met inclusion criteria, 2283 (0.5%) developed incident BRVO. After adjustment for confounding factors, blacks (adjusted hazard ratio [aHR], 1.43; CI, 1.19−1.73; $P = 0.0001$) had a 43% increased hazard of BRVO relative to non-Hispanic whites. Enrollees with hypertension (HTN) alone (aHR, 1.78; CI, 1.36−2.32; $P < 0.0001$) or HTN along with other metabolic syndrome components (diabetes mellitus [DM] and hyperlipidemia; aHR, 1.44; CI, 1.12−1.84; $P = 0.005$) had an increased hazard of developing a BRVO compared with those with none of these conditions. Disease severity was important; enrollees with end-organ damage caused by HTN had a 107% increased hazard of developing BRVO compared with enrollees without HTN (aHR, 2.07; CI, 1.75−2.45; $P < 0.0001$). Although there was no association between DM without end-organ damage and BRVO (aHR, 0.92; CI, 0.81−1.04; $P = 0.2$), individuals with end-organ damage from DM had a 36% increased hazard of BRVO (aHR, 1.36; CI, 1.18−1.57; $P < 0.0001$) compared with those without DM. Although cerebrovascular accident was associated with an increased hazard of developing BRVO (aHR, 1.34; CI, 1.19−1.52; $P < 0.0001$), other diseases of the vascular system (deep venous thrombosis/pulmonary embolism, peripheral vascular disease, hypercoagulable state, myocardial infarction) or anticoagulant use did not increase the risk of BRVO ($P > 0.10$ for all comparisons).

Conclusions: Both HTN and end-organ damage from DM contribute to arteriosclerosis, atherosclerosis, and endothelial dysfunction, which seem to be major risk factors for BRVO. Ophthalmologists should emphasize to patients and their primary physicians the importance of effectively managing systemic medical conditions associated with BRVO. *Ophthalmology 2014;■:1−10 © 2014 by the American Academy of Ophthalmology.*

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More than 16 million people worldwide are affected by branch retinal vein occlusions (BRVO).[1] Given that advancing age is a known risk factor for BRVO, with increasing longevity of the population, the prevalence of venous occlusive disease is likely to rise in the coming decades. The BRVO is associated with significant ocular morbidity; >1 in 10 patients who suffer from BRVO are left with ≤20/200 best-corrected visual acuity in the affected eye.[2] Studies reveal that patients who develop BRVO report a decrease in quality of life proportionate to the vision loss in the affected eye, even when good visual acuity is maintained in the uninvolved eye.[2] Furthermore, personal and societal costs associated with BRVO are estimated to be much greater than costs for age-matched controls.[3]

The concept of Virchow's triad teaches that the following 3 factors predispose to thrombosis: endothelial damage, abnormal blood flow, and hypercoagulability. In some studies,[4−15] but not other investigations,[6,7,9,12,13,15,16] systemic disease that raises the risk for endothelial damage or abnormal blood flow—including the components of Virchow's triad: hypertension (HTN), dyslipidemia, diabetes mellitus (DM), and heart disease—has been associated with retinal vascular occlusion. There has also been debate about

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whether hypercoagulability predisposes patients to developing retinal vein occlusions,[6,17–19] and little work has been done to determine whether a hypercoagulable state (HCS) may affect the risk of BRVO differently from that of central retinal vein occlusion (CRVO).

Previously, we studied risk factors associated with CRVO and found that HTN, cerebrovascular accident (CVA), HCS, black race, and end-organ damage from HTN or DM all increased the risk of CRVO.[19] We postulated that risk factors for BRVO may differ some from risk factors associated with CRVO because of the different anatomic relationships among retinal vessels. For example, occlusion of a branch retinal vein may be more likely to be secondary to compression from the adjacent artery at an arteriovenous crossing point resulting from hardening of the artery caused by endothelial damage and plaque accumulation. By comparison, the central retinal artery and vein lie next to each other, and so may be more susceptible to occlusion from a condition such as HCS.[6] In this study, we sought to identify independent predictors of incident BRVO after adjusting for sociodemographic factors and ocular and medical comorbidities, and to determine whether the factors associated with BRVO are similar or dissimilar to those we had previously found to be associated with CRVO.

Methods

Data Source

The Clinformatics DataMart database (OptumInsight, Eden Prairie, MN) contains detailed records of all beneficiaries who had some form of eye care in a large managed care network with members throughout the 48 continental United States. The dataset contains all individuals with ≥1 *International Classification of Diseases, Ninth Revision-Clinical Modification* (ICD-9-CM) codes[20] for eye-related diagnoses (360−379.9), ≥1 Current Procedural Terminology codes[21] for any eye-related visits, diagnostic, or therapeutic procedures (65091−68899 or 92002−92499), or any other claim submitted by an ophthalmologist or optometrist from January 1, 2001, through December 31, 2009. For each enrollee, we had access to all medical claims for ocular and nonocular conditions and sociodemographic information including age, sex, race, education level, and household net worth. Additionally, the database has records of all outpatient prescriptions because enrollees in the medical plan were also fully enrolled in the pharmacy plan. This database has been used in the past to study patients with several ocular diseases.[19,22–24]

Because all the data were de-identified to the researchers, the University of Michigan Institutional Review Board determined that this study was exempt from requiring its approval.

Participants and Sample Selection

All beneficiaries who were ≥55 years of age and were continuously enrolled in the medical plan for ≥2 years were included. Prior work has demonstrated that BRVO is uncommon among individuals <55 years old,[1] so enrollees who were <55 years old were excluded (Fig 1). Because the outcome of interest was a new diagnosis of BRVO, any individual who had a record of BRVO during their first 2 years in the plan were omitted from the analysis to exclude nonincident cases. Because BRVO can be asymptomatic, to be even more certain that enrollees did not have the outcome of interest (BRVO) during the 2-year look-back period, we also required ≥1 visit(s) to an eye care provider (ophthalmologist or optometrist) during this time frame so that eye care providers would have had an opportunity to identify enrollees with this condition. We also excluded individuals if they did not have ≥1 additional eye visit(s) during the follow-up period so that an eye care provider would have an opportunity to assess for BRVO during this time period. Beneficiaries not continuously enrolled in the plan were also excluded because they could have received a BRVO diagnosis during their time outside of the plan.

Analyses

Statistical analyses were performed using SAS software, version 9.3 (SAS Inc, Cary, NC). Participant characteristics were summarized for the entire sample using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Our outcome of interest was a new diagnosis of BRVO, which was identified if a beneficiary received an ICD-9-CM diagnosis code for BRVO (362.36) after the index date (which we defined as 2 years after entry into the plan). Cox regression with delayed entry was used to estimate the hazard of being newly diagnosed with a BRVO. All beneficiaries were followed in the model from the index date until they were either diagnosed with BRVO or were censored. Censoring occurred at the date of the enrollee's last eye examination, because this was conceivably their last opportunity to receive a diagnosis of BRVO by an eye care provider. Multivariable Cox regression models were adjusted for sociodemographic factors, and ocular and systemic comorbidities. All ocular and systemic disease covariates were identified by the ICD-9-CM codes listed in Table 1 (available at www.aaojournal.org).

Independent predictors in the regression model included markers for the 3 components of Virchow's triad (Fig 2). The first component is endothelial damage, for which we included the following systemic diseases: DM, dyslipidemia, myocardial infarction (MI), congestive heart failure (CHF), CVA, HTN, and peripheral arterial disease (PAD).[25–28] The second component of Virchow's triad is abnormal blood flow, for which we included atherosclerosis secondary to HTN, DM, MI, CHF, CVA, PAD, and migraine as a marker of vasospasm.[26,28] The third component of Virchow's triad is HCS, for which we included the following systemic diseases: HCS, cancer, deep vein thrombosis/pulmonary embolism, and use of oral anticoagulants, which may be a surrogate for previous HCS. The use of oral anticoagulants was obtained from beneficiaries' outpatient pharmacy records. Over-the-counter medication use such as aspirin was unavailable. The oral anticoagulants included in the analysis are listed in Figure 2 and we characterized an enrollee as a user of such medications if she or he had ≥1 prescription for any such medications during her or his time in the plan. Because many people have multiple components of metabolic syndrome—DM, HTN, and dyslipidemia—and the presence of multiple metabolic syndrome components could potentially act in an additive or multiplicative way to increase risk of venous occlusive disease as has been seen with other ocular conditions,[22] we analyzed these factors both individually and in different combinations.

In the model, glaucoma status, CVA, MI, deep vein thrombosis/pulmonary embolism, and use of anticoagulants were treated as time-dependent covariates because we wanted to be certain the exposure occurred before the outcome of interest. For each of these predictors, at every day after the index date, we assessed whether the person had been diagnosed with these time-dependent covariates and updated the value of the predictor in the model accordingly. Thus, we captured the time of exposure to these medications or conditions from the index date to the date of the outcome or