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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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Abstract

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 (US).

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 were performed to identify socio-demographic factors, ocular and non-ocular conditions that were associated with incident BRVO.

Main Outcome Measure—Hazard of incident BRVO with 95% confidence intervals (CI).

Results—Of the 492,488 enrollees who met the inclusion criteria, 2,283 (0.5%) developed an 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 developing 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 to those with none of these conditions. Disease severity was also important; enrollees with end-organ damage caused by HTN had a 107% increased hazard of developing BRVO compared to enrollees without HTN (aHR=2.07, CI 1.75–2.45, p<0.0001). Although there

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Supplemental materials are provided at the end of the online version of this manuscript. The following should appear online-only: Table 1.

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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 developing BRVO (aHR=1.36, CI 1.18-1.57, p<0.0001) compared to those without DM. Although cerebrovascular disease 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 appear to be major risk factors for BRVO. Ophthalmologists should emphasize to patients and their primary physicians the importance of effectively managing systemic medical conditions that are associated with BRVO.

Over 16 million people worldwide are affected by branch retinal vein occlusions (BRVO).¹ Given that older 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. BRVOs are associated with significant ocular morbidity; over one in ten 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 higher than costs for age-matched controls.³

The concept of Virchow's triad teaches that the following three factors predispose to thrombosis: endothelial damage, abnormal blood flow, and hypercoagulability. In some studies,⁴⁻¹⁵ but not others,^{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 whether hypercoagulability predisposes patients to developing retinal vein occlusions,^{6,17-9} 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 disease (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 the present study we sought to identify independent predictors of incident BRVO after adjusting for socio-demographic factors, 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) codes²⁰ for eye-related diagnoses (360-379.9), 1 Current Procedural Terminology (CPT) codes²¹ 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 non-ocular conditions and socio-demographic information including age, sex, race, education level and household net worth. Additionally, the database has records of all outpatient prescriptions since 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}

Since 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 (Figure 1). Since the outcome of interest was a new diagnosis of BRVO, any individual who had a record of BRVO during their first two years in the plan were omitted from the analysis to exclude non-incident cases. Since 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 visits 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 at least one additional eye visit 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 as 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 Institute, 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, as this was conceivably their last opportunity to receive a diagnosis of BRVO by an eye care provider. Multivariable Cox regression models were adjusted for socio-demographic 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 <http://aaojournal.org>).

Independent predictors in the regression model included markers for the three components of Virchow's triad (Figure 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 *Hypercoagulable State*, for which we included the following systemic diseases: HCS, cancer, deep vein thrombosis/pulmonary embolism (DVT/PE), 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 had ≥ 1 prescription for any such medications during her 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 with one another.

In the model, glaucoma status, CVA, MI, DVT/PE, and use of anticoagulants were treated as time-dependent covariates since 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 if 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 censoring. Other covariates evaluated, such as DM, HTN, PAD, dyslipidemia, CHF, migraine and HCS, were not treated as time-dependent covariates given the chronic, longstanding nature of these diseases and challenges with identifying an exact date of onset of these conditions. Other model covariates included selected chronic systemic diseases (obstructive sleep apnea, dementia, depression), ocular comorbidities (cataract, pseudophakia / aphakia, macular degeneration, primary open-angle glaucoma (OAG), exfoliation syndrome glaucoma, and ocular hypertension (OHTN)), socio-demographic factors (age, sex, race/ethnicity, household net worth, education, and region of the country of home residence) and the Charlson Comorbidity Index, a measure of overall health.²⁹ OAG, OHTN, and exfoliation syndrome were included in the models because these conditions have previously been shown to be associated with BRVO.^{12,13,30} We also tested selected interactions in the model.

To explore the impact of the severity of DM and HTN on the risk of developing BRVO, a second Cox regression model was run, controlling for all of the same covariates as in the initial model, except that DM and HTN in the original model were replaced by “uncomplicated” and “complicated” DM and HTN in the second model. We defined “complicated” HTN or DM as those who had evidence of end-organ damage (e.g. nephropathy, neuropathy) from the condition and “uncomplicated” cases as those with no record of end-organ damage from these specific conditions as was done previously.¹⁹

Finally, to address potential concerns about miscoding known to exist in claims data, a sensitivity analysis was performed to determine whether the association between the predictor variables and BRVO was affected if we changed our definition of BRVO from requiring a single ICD-9-CM code to identify enrollees with BRVO to requiring an initial and 1 confirmatory BRVO diagnosis at a subsequent clinic visit. For all analyses, $p < 0.05$ was considered statistically significant.

Results

Of the 492,488 enrollees who met our inclusion criteria, 2,283 (0.5%) were newly diagnosed with BRVO during the follow-up period (Figure 1). Our study population included 392,718 (79.7%) whites, 23,952 (4.9%) blacks, 16,830 (3.4%) Latinos, 7,949 (1.6%) Asian-Americans, and 3,302 (0.7%) who identified as some “other” race. Race was missing for 47,737 (9.7%) beneficiaries. The mean follow-up from the index date for beneficiaries in our study who developed BRVO was 2.0 ± 1.6 years, which was slightly longer than the mean follow-up for beneficiaries who did not develop BRVO, 1.7 ± 1.5 years ($p < 0.001$). Beneficiaries who did not experience BRVO were younger (65.6 ± 8.1 years) compared to those who developed a BRVO (69.2 ± 8.5 years, $p < 0.001$) (Table 2).

Socio-demographic Factors

Compared to whites, blacks had a 43% increased hazard of receiving a BRVO diagnosis (adjusted hazard ratio (aHR) = 1.43, [95% CI 1.19-1.73], $p = 0.0001$) and Asian-Americans had a 39% increased hazard of receiving a BRVO diagnosis (aHR = 1.39, [95% CI 1.02-1.89], $p = 0.03$), while Latinos had no significant increased hazard (aHR = 1.08, [95% CI 0.85-1.37], $p = 0.54$) (Table 3). There was no significant association between education and the diagnosis of incident BRVO, ($p > 0.05$ for all comparisons). While there was also no association between different levels of household net worth and BRVO, there was a trend to increasing household net worth being associated with a decreased hazard of incident BRVO (p for trend = 0.02) (Table 3).

Components of Virchow’s Triad

Hypercoagulable State—After controlling for potential confounding factors, none of the diseases associated with HCS (cancer, DVT/PE, use of oral anticoagulants or HCS) were found to be significant risk factors for BRVO, ($p > 0.05$ for all comparisons) (Table 3).

Abnormal blood flow / Endothelial damage—Many of the risk factors associated with abnormal blood flow and endothelial damage conferred an elevated BRVO risk.

Enrollees with HTN alone (no DM or dyslipidemia) had a 78% increased risk of BRVO (aHR = 1.78 [95% CI 1.36-2.32], $p < 0.0001$) and those who had a CVA had a 34% increased hazard of developing BRVO (aHR = 1.34 [95% CI 1.18-1.51], $p < 0.0001$). By contrast, the following conditions affecting blood flow were not found to be associated with BRVO: MI, CHF, DM, dyslipidemia, or PAD ($p > 0.05$ for all comparisons, Table 3). Migraine can be associated with vasospasm and could potentially contribute to abnormal blood flow in the retina. In the regression model, migraine did not increase the risk of being diagnosed with a BRVO ($p = 0.66$) (Table 3).

In the multivariable regression, we found that HTN appeared to be the most significant risk factor for developing BRVO, as HTN alone or HTN along with any other components of the metabolic syndrome significantly increased the risk of BRVO. For example, in those with HTN and DM (but no dyslipidemia), the hazard of being diagnosed with incident BRVO increased by 63% (aHR = 1.63 [95% CI 1.16-2.31], $p = 0.006$), by 36% for those with HTN and dyslipidemia (but no DM), (aHR = 1.36 [95% CI 1.07-1.73], $p = 0.01$), and by 44% for those with all three components of metabolic syndrome (aHR = 1.44 [95% CI 1.12-1.84], $p = 0.005$) compared to beneficiaries without any metabolic syndrome components. By comparison, in those with DM alone (no hypertension or dyslipidemia), dyslipidemia alone (no HTN or DM), and dyslipidemia + DM (but no HTN), there was no significant increase in the risk of incident BRVO ($p > 0.05$ for all comparisons) (Table 3).

Severity of Hypertension and Diabetes

In order to evaluate whether the severity of the diabetes or hypertension would impact the risk assessment, we ran a second regression model replacing the various components of metabolic syndrome from the original model with the variables “complicated” and “uncomplicated” DM and HTN, which we defined as those with and without end-organ damage from these diseases. We found that persons with “uncomplicated” hypertension had a 36% increased risk of being diagnosed with BRVO (aHR = 1.36 [95% CI 1.17-1.57], $p < 0.0001$), while those with “complicated” hypertension had a 107% increased risk of being diagnosed with incident BRVO (aHR = 2.07 [95% CI 1.75-2.45], $p < 0.0001$) compared to those without HTN. Those with “uncomplicated” diabetes had no significant increased risk of being diagnosed with BRVO (aHR = 0.92 [95% CI 0.81-1.04], $p = 0.2$), while those with “complicated” diabetes had a 36% increased risk of BRVO (aHR = 1.36 [95% CI 1.18-1.57], $p < 0.0001$), relative to beneficiaries without DM.

Glaucoma

In our study cohort, 3.8% (18,560) of beneficiaries had OHTN, 14.5% (71,285) had OAG, and 1.2% (5,681) had exfoliation syndrome (Table 2). Those with OHTN had a 31% decreased hazard of BRVO (aHR=0.69 [95% CI 0.52-0.91], $p = 0.01$), relative to those without OHTN. There was no significant association between OAG or exfoliation syndrome and BRVO risk ($p > 0.1$ for both comparisons) (Table 3).

Interaction Analyses

We analyzed whether there were significant interactions between race and certain covariates as race was a significant risk factor for developing BRVO in the main regression model. We

found no significant interaction between education and race ($p>0.05$) on BRVO risk. Likewise, the interaction between race and metabolic syndrome with risk of BRVO was not statistically significant ($p>0.1$).

Sensitivity Analysis

To help address potential concerns about miscoding of BRVO in claims data, we ran a sensitivity analysis requiring a confirmatory diagnosis of BRVO at a separate clinic visit to see whether it would impact the study findings. We found that 1,283 patients (56%) received 1 confirmatory BRVO diagnosis. Using this revised definition of the outcome of interest, nearly all of the above-mentioned findings remained unchanged, except only that Asian-American race was no longer a statistically significant risk factor for BRVO (aHR=1.17 [95% CI 0.75-1.83], $p=0.49$).

Discussion

While some previous population-based and case-control studies identified all the components of metabolic syndrome as risk factors for BRVO, including HTN,^{5, 6,8-11,14,15} DM^{6,16} and dyslipidemia,^{5,10,14} after adjusting for multiple potential confounding factors, including other metabolic syndrome components, in this analysis of nearly 500,000 managed care beneficiaries from across the US, we found that HTN appears to be the main driver of the increased risk for incident BRVO. Moreover, not only did HTN increase the risk of BRVO, those with more severe HTN were at even greater risk. Compared with normotensive patients, the risk of BRVO was 36% higher among those with “uncomplicated” HTN and 107% higher for those with end-organ damage from HTN.

There has been much controversy in the literature as to whether metabolic syndrome components affect the risk of BRVO. Some prior studies did not find an association between DM and BRVO^{4, 9, 10, 12, 15} or dyslipidemia and BRVO,^{4, 15} while other studies found an association between these conditions and BRVO.^{5,6,10,13} In our study, we found no association between dyslipidemia and BRVO. In fact, the presence of dyslipidemia actually attenuated some of the increased risk of BRVO among persons who had multiple components of metabolic syndrome. Whether this reduction in risk is attributable to the condition itself or perhaps to the medications used to treat dyslipidemia, like statins, requires additional study. We also identified that while persons with “uncomplicated” DM had no significant difference in risk of being diagnosed with BRVO, those with end-organ damage from DM had a 36% increased risk of BRVO compared to those without DM. Given our finding that only those with more severe DM seem to be at increased risk of BRVO, this may help explain some of the conflicting findings in the existing literature on the subject as prior studies may have differed from one another in the proportions of patients with more or less severe DM.

The two components of Virchow’s triad that we identified as most important in increasing the risk of BRVO were abnormal blood flow and endothelial damage. HTN contributes to arteriosclerosis. Hardening of the retinal arteries leads to compression of adjacent retinal veins within the adventitial sheath which facilitates venous stasis and predisposes individuals to thrombosis.⁶ DM contributes more to atherosclerosis than arteriosclerosis, but

may also be acting through its role in causing endothelial dysfunction. The worse the glycemic control in a patient with DM, the more reactive oxygen species (ROS) are present in the bloodstream, and ROS are thought to play a major role in the inflammatory component of diabetes-induced atherosclerosis, endothelial damage and, ultimately, cardiovascular disease.³¹ Thus, it is not surprising that it was only enrollees with “complicated” DM who demonstrated an elevated risk of BRVO in our study. If the retinal veins are compromised by endothelial dysfunction that may further add to the risk of thrombosis and occlusion as the atherosclerotic, thickened arteries compress the veins. We did not find that hypercoagulability, the third component of Virchow’s triad, significantly affected the risk of BRVO.

Previously, we performed a similar analysis of risk factors associated with CRVO and found some interesting similarities and differences between risk factors for CRVO and BRVO (Table 4).¹⁹ The two models had only one important difference, and that is for the CRVO analysis we excluded subjects with a record of prior CRVO (non-incident cases) and in the BRVO analysis here we excluded subjects with a record of prior BRVO (non-incident cases). The rest of the inclusion and exclusion criteria and the covariates included in both models were the same for the two analyses. We learned that HTN and CVA were risk factors for both BRVO and CRVO. In contrast, HCS was only a significant risk factor for CRVO.¹⁹ It appears that all of the components of Virchow’s triad, endothelial damage, abnormal blood flow and hypercoagulability, may contribute to CRVO while abnormal blood flow and endothelial damage are the main risk factors impacting BRVO risk in this population.

In our analyses, blacks were found to be at increased risk of developing incident ophthalmic venous occlusive disease, even after controlling for HTN, other metabolic syndrome components, and socio-demographic factors. These results support earlier work by the International Eye Disease Consortium which showed a higher prevalence of BRVO among blacks compared with whites.¹ There are many hypotheses as to why blacks may be at higher risk of end-organ vascular damage, ranging from reduced access to high-quality healthcare, to racism potentially leading to chronic stress, to living in neighborhoods with higher levels of pollution, and to living in unsafe neighborhoods impacting their ability to exercise which can all lead to an increased burden of vascular disease.^{32, 33} It is interesting that there was also a trend in our data showing that after controlling for race, education and underlying comorbidities, there was a trend towards increased household net worth being associated with a decreased BRVO risk (p for trend =0.02). Living in poverty, for some of the reasons mentioned above, increases the burden of systemic vascular disease and may also increase the risk of ocular vascular disease.

Our study has several limitations. First, the data source for this analysis only contains information captured in billing codes. Thus, we were limited in our ability to access clinical data on each enrollee including information from fundus photographs on the location of the vein occlusion, findings on fluorescein angiography capturing the severity of the occlusion, visual acuity, intraocular pressure, blood pressure, body mass index, and smoking status. Providers contributing data to this dataset have different levels of experience in diagnosing BRVO and some may have misdiagnosed this condition. We also did not evaluate persons

<55 years of age so our findings are not generalizable to younger patients, for whom this condition is quite rare. Likewise, all of the persons in our analysis had health insurance, so our results may not be generalizable to the 16% of Americans who lack health insurance.³⁴

The strengths of our study include the ability to study risk factor associated with BRVO in a cohort of nearly 500,000 patients, a sample size which is nearly 10 times larger than existing studies on this topic.¹ The large sample size makes it possible to adjust for multiple ocular and systemic comorbidities and socio-demographic factors and study interaction effects between different variables. Another study strength is that the sample has persons from all over the nation and captures the care of a diverse group of patients by an array of different eye care providers.

This study highlights several key factors that increase the risk of developing BRVO including HTN and end-organ damage from DM. Compared to our prior analysis which identified all three components of Virchow's triad as risk factors for CRVO, in the present study, it appears that only two of the three components, endothelial dysfunction and abnormal blood flow impact the risk of BRVO.

Not only do these results help us understand how BRVO and CRVO are similar and different from one another, they also reinforce the importance of controlling blood pressure and blood sugar in reducing the risk of this sight-threatening condition. Because HTN and DM cause ocular disease in and of themselves as well as placing patients at risk for vascular occlusions, it is important that ophthalmologists work with primary care providers to educate patients about the importance of controlling the components of metabolic syndrome. Many ophthalmologists and optometrists already educate diabetic patients about the importance of optimal blood pressure and blood sugar control, and this likely heightens patients' sense of the importance of the matter. If a patient is newly diagnosed with a BRVO, this could be used as an opportunity for reviewing a patient's blood pressure and blood sugar records in order to advise patients that diabetes and hypertension, and especially poorly controlled, "complicated" diabetes and hypertension can cause vision loss by a variety of mechanisms but that patients can mitigate this risk by controlling their underlying disease. It could also be used as an opportunity for the ophthalmologist to communicate to the patient's primary care physician (PCP) how the patient's underlying vascular risk factors have put the patient at risk for this devastating ocular disease, the same way in which an ophthalmologist would communicate with the PCP if a patient developed proliferative diabetic retinopathy. The relationship of these epidemic, chronic systemic diseases to ocular vascular occlusion underscores the importance of having all members of the health care team, including specialists and primary care providers, send the same message to all patients about the necessity of excellent control of diabetes and hypertension as well as primary prevention of these diseases through healthy living.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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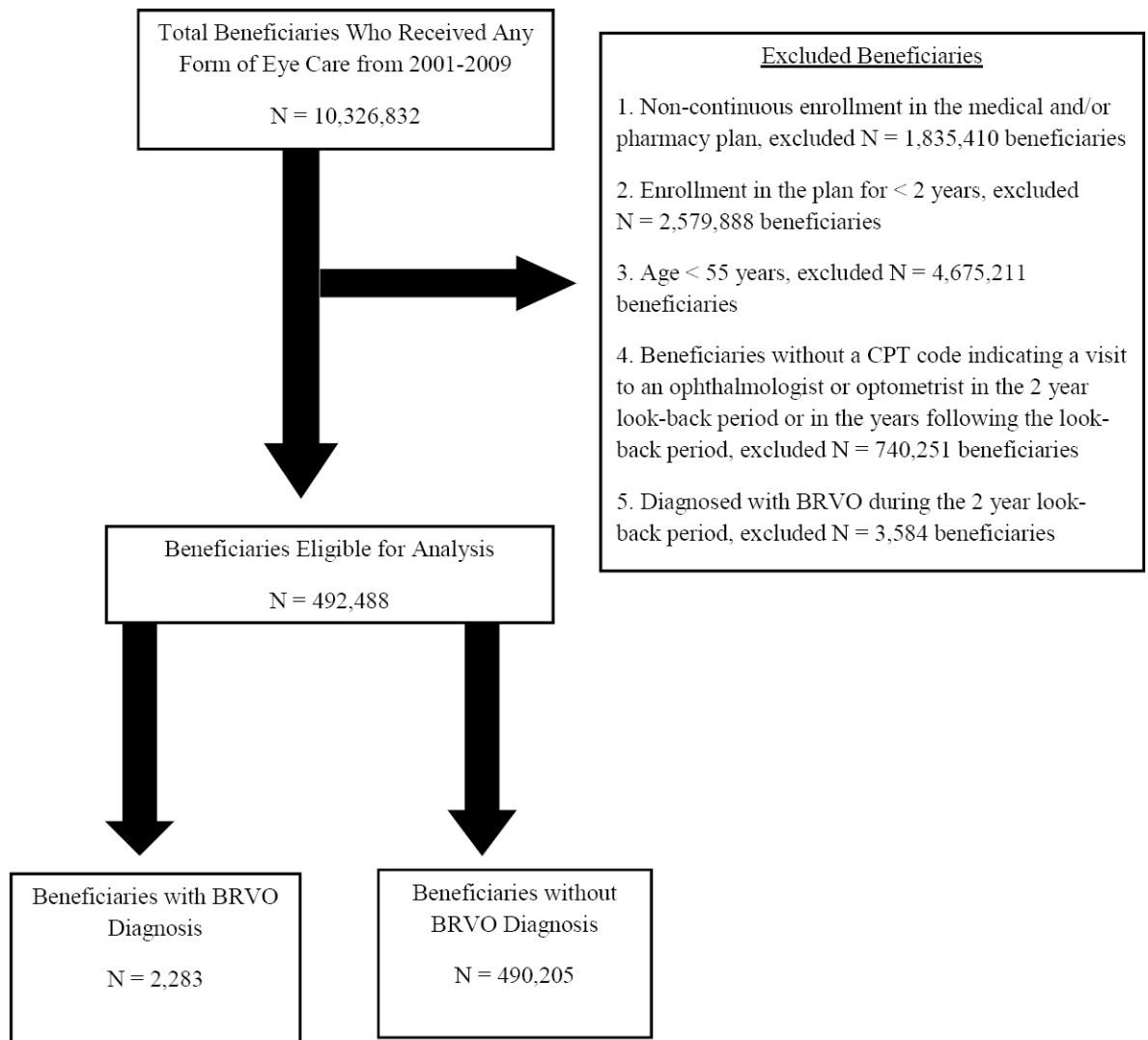


Figure 1.
Selection of Beneficiaries for Analysis
CPT, Current Procedural Terminology; BRVO, Branch Retinal Vein Occlusion

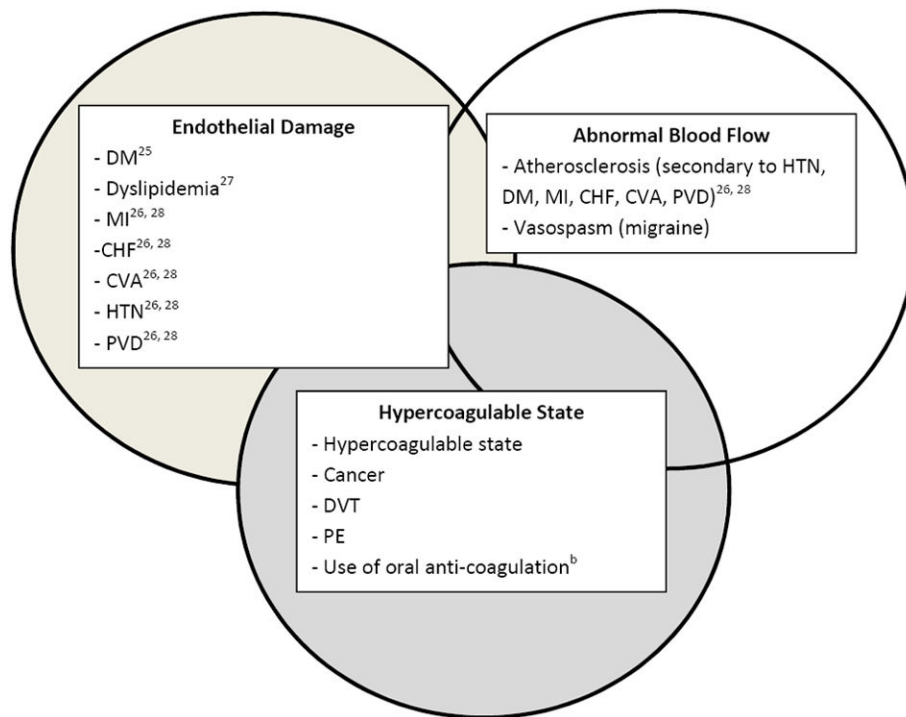


Figure 2.

Virchow's Triad: Medical co-morbidities that may increase the risk of BRVO

^aDM = diabetes mellitus; MI = myocardial infarction; CHF = congestive heart failure; CVA = cerebrovascular attack; HTN = hypertension; PVD = peripheral vascular disease; DVT = deep vein thrombosis; PE = pulmonary embolism; BRVO = branch retinal vein occlusion.

^bUse of oral anti-coagulation was obtained from pharmacy records and included the following medications: Marevin, Jantoven, Coumadin, Warfarin, Heparin, Clopidogrel, Ticlopidine, Plavix, Miradon, Dicumarol, Enoxaparin, Acenocoumarol, Anisinsione, Sintrom

Table 2

Demographic Characteristics

Covariate	No BRVO, n, (%)	Incident BRVO, n, (%)	P Value
Age , mean years \pm SD, [range]	65.6 \pm 8.1 [55-86.9]	69.2 \pm 8.5 [55-86]	
Sex			0.14
Male	204,594 (41.7)	1,295 (43.3)	
Female	285,611 (58.3)	988 (56.7)	
Race			0.02
White	390,914 (79.8)	1,804 (79.0)	
Black	23,812 (4.9)	140 (6.1)	
Latino	16,749 (3.4)	81 (3.6)	
Asian -American	7,902 (1.6)	47 (2.1)	
Other/Missing	50,828 (10.4)	211 (9.2)	
Education			0.06
Less than High School	5,173 (1.1)	27 (1.2)	
High School	166,310 (33.9)	796 (34.9)	
Some College	181,865 (37.1)	883 (38.7)	
College Diploma	113,456 (23.1)	491 (21.5)	
Advanced Degree	1,268 (0.3)	3 (0.1)	
Household Net Worth			<0.0001
<\$ 25,000	23,814 (4.9)	144 (6.2)	
\$ 25-75,000	22,261 (4.5)	130 (5.7)	
\$ 75-150,000	48,633 (9.9)	250 (11.0)	
\$ 150-500,000	206,857 (42.2)	965 (42.3)	
>\$ 500,000	152,222 (31.1)	652 (28.6)	
Systemic Risk Factors			
Arteriosclerosis			
CVA	79,676 (16.3)	712 (31.2)	<0.0001
MI	39,539 (8.1)	293 (12.8)	<0.0001
CHF	72,562 (14.8)	566 (24.8)	<0.0001
Metabolic Syndrome			<0.0001
Only HTN	41,911 (8.6)	244 (10.7)	
Only DM	2,699 (0.6)	10 (0.4)	
Only CHOL	61,121 (12.5)	136 (6.0)	
DM+HTN	11,617 (2.4)	71 (3.1)	
CHOL+HTN (no DM)	178,916 (36.5)	898 (39.3)	
DM+CHOL (noHTN)	9,738 (2.0)	34 (1.5)	
DM+CHOL+HTN	141,284 (28.8)	805 (35.3)	
Complicated ^d DM	74,342 (15.2)	535 (23.4)	

Covariate	No BRVO, n, (%)	Incident BRVO, n, (%)	P Value
Complicated ^a HTN	77,300 (15.8)	692 (30.3)	
Endothelial Damage			
Peripheral Vascular Disease	94,506 (19.3)	716 (31.4)	<0.0001
Hypercoagulable State			
DVT/PE	12,820 (2.6)	86 (3.8)	0.0006
Hypercoagulable state	1,772 (0.4)	15 (0.7)	0.02
Oral anti-coagulation	91,653 (18.7)	647 (28.3)	<0.0001
Cancer	93,402 (19.1)	546 (23.9)	<0.0001
Vasospasm			
Migraine	27,541 (5.6)	127 (5.6)	0.91
Ocular Risk Factors			<0.0001
Ocular hypertension	18,499 (3.8)	61 (2.7)	
Open-angle glaucoma	70,824 (14.5)	461 (20.2)	
Exfoliation Syndrome	5,640 (1.2)	41 (1.8)	

Abbreviations: BRVO, branch retinal vein occlusion; SD, standard deviation; CVA, cerebrovascular accident; MI, myocardial infarction; CHF, congestive heart failure; HTN, hypertension; DM, diabetes mellitus; CHOL, dyslipidemia; DVT/PE, deep vein thrombosis/pulmonary embolism

^a“Complicated” refers to disease including end-organ damage caused by DM or HTN

Table 3

Risk Factors for Developing Incident BRVO

Covariates	Unadjusted Hazard Ratio [95% Confidence Interval], P Value	Adjusted Hazard Ratio^d [95% Confidence Interval], P Value
Race^b		
Black	1.59 [1.34-1.89], <0.0001	1.43 [1.19-1.73], 0.0001
Latino	1.18 [0.94-1.48], 0.15	1.08 [0.85-1.37], 0.54
Asian-American	1.43 [1.07-1.91], 0.02	1.39 [1.02-1.89], 0.03
Education^c		
High School Diploma	0.84 [0.57-1.23], 0.36	1.00 [0.66-1.51], 0.99
Some College	0.77 [0.53-1.14], 0.19	0.96 [0.63-1.46], 0.85
College Degree	0.70 [0.47-1.03], 0.07	0.97 [0.63-1.49], 0.90
Advanced Degree	0.38 [0.12-1.25], 0.11	0.42 [0.10-1.79], 0.24
Household Net Worth^d		
\$ 25-75,000	1.00 [0.79-1.27], 0.99	1.04 [0.82-1.33], 0.75
\$ 75-150,000	0.90 [0.73-1.10], 0.30	0.89 [0.72-1.11], 0.30
\$ 150-500,000	0.80 [0.67-0.95], 0.01	0.86 [0.72-1.04], 0.12
>\$ 500,000	0.73 [0.61-0.88], 0.0008	0.82 [0.66-1.01], 0.06
Sex^e		
Female	0.96 [0.89-1.05], 0.39	1.00 [0.91-1.09], 0.92
Systemic and Ocular Risk Factors^f		
Charlson Comorbidity Index	1.05 [1.04-1.07], 0.006	1.04 [1.01-1.06], 0.002
Cerebrovascular Accident	1.56 [1.41-1.73], <0.0001	1.34 [1.18-1.51] <0.0001
Myocardial Infarction	1.20 [1.04-1.39], 0.01	1.00 [0.85-1.18], 0.98
Congestive Heart Failure	1.31 [1.19-1.44], <0.0001	1.07 [0.94-1.21], 0.31
Only HTN	1.99 [1.56-2.56], <0.0001	1.78 [1.36-2.32], <0.0001
Only DM	1.63 [0.85-3.14], 0.14	1.49 [0.74-2.97], 0.26
Only CHOL	0.98 [0.75-1.29], 0.90	0.95 [0.71-1.27], 0.71
DM + HTN	2.10 [1.53-2.88], <0.0001	1.63 [1.16-2.31], 0.006
CHOL + HTN	1.60 [1.28-2.00], <0.0001	1.36 [1.07-1.73], 0.01
DM + CHOL	1.55 [1.04-2.31], 0.03	1.37 [0.90-2.10], 0.15
DM + CHOL + HTN	1.88 [1.50-2.35], <0.0001	1.44 [1.12-1.84], 0.005
Peripheral Vascular Disease	1.25 [1.14-1.37], <0.0001	1.02 [0.91-1.13], 0.80
DVT/PE	1.15 [0.85-1.55], 0.36	0.98 [0.71-1.35], 0.91
Hypercoagulable State	1.57 [0.94-2.61], 0.08	1.43 [0.84-2.44], 0.19
Oral Anticoagulation	1.29 [1.17-1.43], <0.0001	1.11 [0.98-1.25], 0.10
Cancer	1.01 [1.04-1.07], <0.0001	0.88 [0.77-1.00], 0.06
Migraine	1.00 [0.84-1.20], 1.0	0.96 [0.79-1.17], 0.66
Ocular Hypertension	0.92 [0.68-1.26], 0.61	0.69 [0.52-0.91], 0.01

<u>Covariates</u>	<u>Unadjusted Hazard Ratio [95% Confidence Interval], P Value</u>	<u>Adjusted Hazard Ratio^a [95% Confidence Interval],P Value</u>
Open-Angle Glaucoma	1.11 [1.00-1.24], 0.04	1.08 [0.97-1.21], 0.17
Exfoliation Syndrome	0.69 [0.54-0.89], 0.89	0.94 [0.67-1.32], 0.72

Abbreviations: BRVO, branch retinal vein occlusion; HTN, hypertension; DM, diabetes mellitus; CHOL, dyslipidemia; DVT/PE, deep vein thrombosis/pulmonary embolism

^a Adjusted for age, race, sex, education, household net worth, region of the country, glaucoma ocular hypertension, exfoliation syndrome, cataract, pseudophakia, macular degeneration, obstructive sleep apnea, dementia, mood changes, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, cancer, hypercoagulable state, the use of oral anti-coagulation medications, deep vein thrombosis/pulmonary embolism, migraine, metabolic syndrome (includes hypertension, diabetes mellitus, dyslipidemia alone and in combination), and the Charlson Co-Morbidity Index.

^b Compared to Whites

^c Compared to < High School Diploma, p for trend = 0.61

^d Compared to <\$25,000 Household Net Worth, p for trend = 0.02

^e Compared to Male

Table 4

Comparison of Risk Factors for BRVO and CRVO

Risk Factor	Adjusted HR for BRVO [95% Confidence Intervals], p-value	Adjusted HR for CRVO [95% Confidence Intervals], p-value
Artery Compressing Vein (Arteriosclerosis)		
Cerebrovascular Accident	1.34 [1.18-1.51], <0.0001	1.45 [1.24-1.70], <0.0001
Myocardial Infarction	1.00 [0.85-1.18], 0.98	0.73 [0.57-0.92], 0.01
Congestive Heart Failure	1.07 [0.94-1.21], 0.31	0.98 [0.83-1.15], 0.79
Metabolic Syndrome		
Only HTN	1.78 [1.36-2.32], <0.0001	1.65 [1.13-2.41], 0.01
Only DM	1.49 [0.74-2.971], 0.26	0.95 [0.29-3.08], 0.93
Only CHOL	0.95 [0.71-1.27], 0.71	1.03 [0.68-1.54], 0.90
DM + HTN	1.63 [1.16-2.31], 0.0006	1.83 [1.16-2.90], 0.01
CHOL + HTN	1.36 [1.07-1.73], 0.01	1.45 [1.04-2.04], 0.03
DM + CHOL	1.37 [0.90-2.10], 0.15	1.52 [0.86-2.71], 0.15
DM + CHOL + HTN	1.44 [1.12-1.84], 0.005	1.57 [1.11-2.23], 0.01
Endothelial Damage		
Peripheral Vascular Disease	1.02 [0.91-1.13], 0.80	1.16 [1.00-1.34], 0.04
Hypercoagulable State		
DVT/PE	0.98 [0.71-1.35], 0.91	0.86[0.55-1.34], 0.50
Hypercoagulable State	1.43 [0.84-2.44], 0.19	2.46 [1.41-4.29], 0.002
Oral Anticoagulation	1.11 [0.98-1.25], 0.10	1.04 [0.89-1.22], 0.63
Cancer	0.88 [0.77-1.00], 0.06	0.95 [0.80-1.13], 0.59

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HTN, hypertension; DM, diabetes mellitus; CHOL, dyslipidemia; DVT/PE, deep vein thrombosis/pulmonary embolism; HR = hazard ratio

Bold indicates statistically significant at $p < 0.05$

Models were run with the same covariates as follows: age (as the time axis), race, sex, education, household net worth, region of the country, glaucoma, ocular hypertension, exfoliation syndrome, cataract, pseudophakia, macular degeneration, obstructive sleep apnea, dementia, mood changes, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, cancer, hypercoagulable state, the use of oral anti-coagulation medications, deep vein thrombosis/pulmonary embolism, migraine, metabolic syndrome (includes hypertension, diabetes mellitus, dyslipidemia alone and in combination), and the Charlson Comorbidity Index. Models were run using the same inclusion/exclusion criteria except that non-incident cases of CRVO were excluded in the CRVO analysis¹ and non-incident cases of BRVO were excluded from the BRVO analysis.