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Incidence of Retinal Vein Occlusion and Its Association with Mortality

Results from the Gutenberg Health Study

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Purpose: To determine the incidence of retinal vein occlusion (RVO) in the general population in Germany and analyze potential associations with ocular and systemic factors as well as with mortality.

Design: Analysis of a prospective population-based cohort study.

Participants: The Gutenberg Health Study is a population-based cohort study, including 15 010 participants 35 to 74 years of age. A total of 12 954 participants were included with a gradable fundus photograph at baseline. A total of 9305 participants at the 5-year-follow-up and 6428 participants at 10-year-follow-up had additional images.

Methods: At baseline and the 5- and 10-year follow-up examinations, fundus photographs of the macula and the optic disc were obtained. At the 5- and 10-year follow-up, infrared images also were obtained. We evaluated these for RVO (branch RVO [BRVO] and central RVO [CRVO]). The cumulative 5-year- and 10-year–incidence was computed on a per-person level. Multivariable logistic regression analysis was conducted to assess associated factors and cox regression was performed to analyze its influence on mortality.

Main Outcome Measures: Five-year and 10-year cumulative incidence of BRVO and CRVO.

Results: The 5-year-cumulative-incidence was 0.35% (95% confidence interval [CI], 0.25%–0.5%; n = 33) for BRVO and 0.043% (95% CI, 0.014-0.12%; n = 4) for CRVO. The 10-year cumulative incidence was 0.64% (95% CI, 0.46%–0.87%; n = 55) for BRVO and 0.14% (95% CI, 0.067%–0.27%; n = 12) for CRVO. Incidence of RVO was associated with older age (odds ratio, 1.05; 95% CI, 1.02–1.09; $P < 0.001$). An increased risk of mortality was noted in patients with RVO (BRVO: hazard ratio, 2.27; 95% CI, 1.08–3.0; $P = 0.023$; CRVO: hazard ratio, 3.83; 95% CI, 1.95–7.9; $P < 0.001$) after adjustment for cardiovascular risk factors.

Conclusions: This study described the incidence of RVO in a large European population–based cohort and is associated with an increased mortality after RVO.

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Retinal vein occlusion (RVO) is the second most common retinal vascular disorder to cause visual morbidity and blindness after diabetic retinopathy.[1] It can be classified as branch RVO (BRVO) or central RVO (CRVO) according to its site of occlusion. Branch RVO typically is located near an arteriovenous intersection promoted by the compression of the vein at the arteriovenous crossing. Degenerative changes of the vessel wall and abnormal hematologic factors play a crucial role both in BRVO and CRVO.[2] Previous studies have described an association of RVO with cardiovascular risk factors like arterial hypertension, family history of stroke, or arterial fibrillation.[3,4]

Branch RVO is more common than CRVO, but data in large population-based studies about their prevalence and especially incidence are rare. Song et al[5] evaluated prevalence and incidence estimates in a meta-analysis that included 17 studies on prevalence (4 studies with 6001–10 000 participants and 3 studied with more than 10 000 participants) and 6 studies reporting incidence of RVO (all studies with < 4000 participants with follow-up ranging between 5 and 15 years). The estimated age-specific prevalence of BRVO and any RVO ranged from 0.23% for BRVO and 0.26% for all RVOs (age range, 30–39 years) to 2.64% for BRVO and 3.39% for all RVOs (age range, 80–89 years), and that of CRVO ranged from 0.03% to 0.75%. The overall prevalence estimates of any RVO, BRVO, and CRVO in those 30 to 89 years of age were 0.77%, 0.64%, and 0.13%, respectively. The pooled 5-year

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and 10-year cumulative incidence calculated of 3 studies was estimated to be 0.86% and 1.63%, respectively, for any RVO. Additionally, the Hisayama Study with 1775 participants reported a 9-year cumulative incidence of any RVO as 3.0% in Japan,[6] and the Beaver Dam Eye Study reported a 15-year cumulative incidence among 2119 participants as 1.8% for BRVO and 0.5% for CRVO in the United States.[7] Park et al[8] reported a yearly incidence in the total Korean population of 0.048% (0.053% for women and 0.043% for men) with a higher incidence in older people and a peak between 70 and 74 years using health claim data. However, because of the study design, a direct comparison is not possible. To date, no data are available on the incidence of RVO in a European population, and large cohort studies are very rare worldwide.

Methods

Study Population

The Gutenberg Health Study was an observational, population-based, prospective, single-center cohort study at the University Medical Center of the Johannes Gutenberg-University Mainz. The study sample of 15 010 participants was drawn randomly from local governmental registry offices and was stratified equally by sex, decade of age, and residence (rural vs. urban). The study design was described in detail elsewhere.[9] In brief, the baseline examination took place from 2007 through 2012 and consisted of an ophthalmologic examination, several cardiovascular and general examinations, as well as interviews and questionnaires. A total of 12 423 participants (82.8%) from the baseline cohort underwent the 5-year follow-up examination, and 9575 participants (63.8%) from the baseline cohort underwent the 10-year follow up examination. All participants gave written informed consent before inclusion in the study. The Medical Ethics Commission of Rhineland-Palatinate and local and Gutenberg-University of Mainz data protection officials reviewed and approved the study (ethics committee review no., 837.020.07(5555)). The research adhered to the tenets of the Declaration of Helsinki.

Ophthalmic Examination Procedure

The ophthalmic evaluation that participants in the Gutenberg Health Study underwent included measurements of distance-corrected visual acuity and objective refractive error. Intraocular pressure was measured by noncontact tonometry (Nidek NT-2000; Nidek). A slit-lamp examination was carried out and fundus images were obtained with a nonmydriatic fundus camera (Visucam PRO NM; Carl Zeiss) from both eyes with physiologic pupils in a darkened room after an adaption phase of 15 minutes. Three fundus photographs per eye were obtained: 30° centered on the macula and 30° und 45° centered on the optic nerve head. At the 5-year and 10-year follow-up visits, all examinations were repeated with additional infrared photography of the macula and OCT examinations.

Investigated Factors and Comorbidities

Participants were asked to undergo fasting and then underwent a 5-hour standardized examination in a predefined sequence. Multiple parameters such as age, sex, height (in centimeters), bodyweight (in kilograms), and body mass index (BMI) were evaluated. Body mass index of $\geq$ 30 kg/m^2 was defined as obese. Systolic and diastolic blood pressure after 3, 8, and 11 minutes of rest was measured using Omron HEM 705-CP II (OMRON). Medication use of antihypertensive drugs, a mean systolic blood pressure of $\geq$ 140 mmHg in the second and third standardized measurement, or a mean diastolic blood pressure of $\geq$ 90 mmHg in the second and third standardized measurement was defined as arterial hypertension. Blood sugar levels (in milligrams per deciliter), hemoglobin A1c levels (in percentage), low-density lipoprotein cholesterol (in milligrams per deciliter), high-density lipoprotein cholesterol (in milligrams per deciliter), and triglycerides (in milligrams per deciliter) were obtained. Use of antidiabetic agents, a fasting blood glucose level of $\geq$ 126 mg/dl at the baseline examination, or a blood glucose level of $\geq$ 200 mg/dL or hemoglobin A1c level of $\geq$ 6.5% were classified as diabetes. Dyslipidemia was defined as a definite diagnosis of dyslipidemia by a physician or a low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio of $\geq$ 3.5. More parameters were evaluated in a computer-assisted interview: smoking status was dichotomized into no smoking (never and former smoking) and smoking (occasional smoking and smoking). History of myocardial insult or stroke for the participant and their family history were obtained. Additionally, mortality updates were performed by quarterly queries to the registry offices and the mortality registry of Rhineland-Palatinate. For death reviews, official death certificates were acquired.

Grading of Fundus and Infrared Photography

All fundus images were graded according to standard operating procedures. The image quality was graded for every fundus photograph as good, fair, poor, and not available. The fundus images were assessed by 2 different trained observers for baseline (H.E.), 5-year follow-up (H.E.), or 10-year follow-up (A.M.V.) examinations as well as infrared photographs of 5-year and 10-year follow-up examinations (A.M.V.). The grading was adjudicated by an experienced clinical grader (T.P., A.K.S.). Results of the baseline examination regarding RVO have been published already as well as the grading criteria for BRVO or CRVO.[3]

Presence of hemorrhages along retinal vessels with abnormal caliber or a congested vein at an arteriovenous crossing site (Fig 1), a localized area of sheathing of the retinal veins, arteriovenous collaterals, or laser marks in a localized area close to the vascular arcades without signs of diabetic retinopathy in the same eye or the other eye was graded as a BRVO. Central RVO was characterized by hyperemia of the optic nerve head with scattered superficial and deep retinal hemorrhages in all 4 quadrants, presence of arteriovenous collaterals, neovascularization at the optic disc, opticociliary shunts (Fig 2), or panretinal photocoagulation without signs of diabetic retinopathy in the other eye. After detecting patients with BRVO or CRVO at the follow-up visits, we reviewed the baseline photographs to evaluate whether the RVO happened within the follow-up period or was present already at baseline. Patients with a new RVO at the 5-year follow-up visit who did not return to the 10-year follow-up or with no more visible RVO signs at the 10-year visit nevertheless were included in the 10-year cumulative incidence.

Statistical Analysis

Medians, interquartile ranges, minimums, and maximums were calculated for all primary and secondary continuous variables. For variables distributed normally, means and standard deviations were computed. For dichotomous variables, absolute and relative frequencies were computed. Ocular parameters both for the right and left eye were computed in at least 1 and both eyes. Interobserver reliability was evaluated with Cohen's κ coefficient.

Five-year and 10-year cumulative incidence data for BRVO and CRVO were computed including the 95% confidence

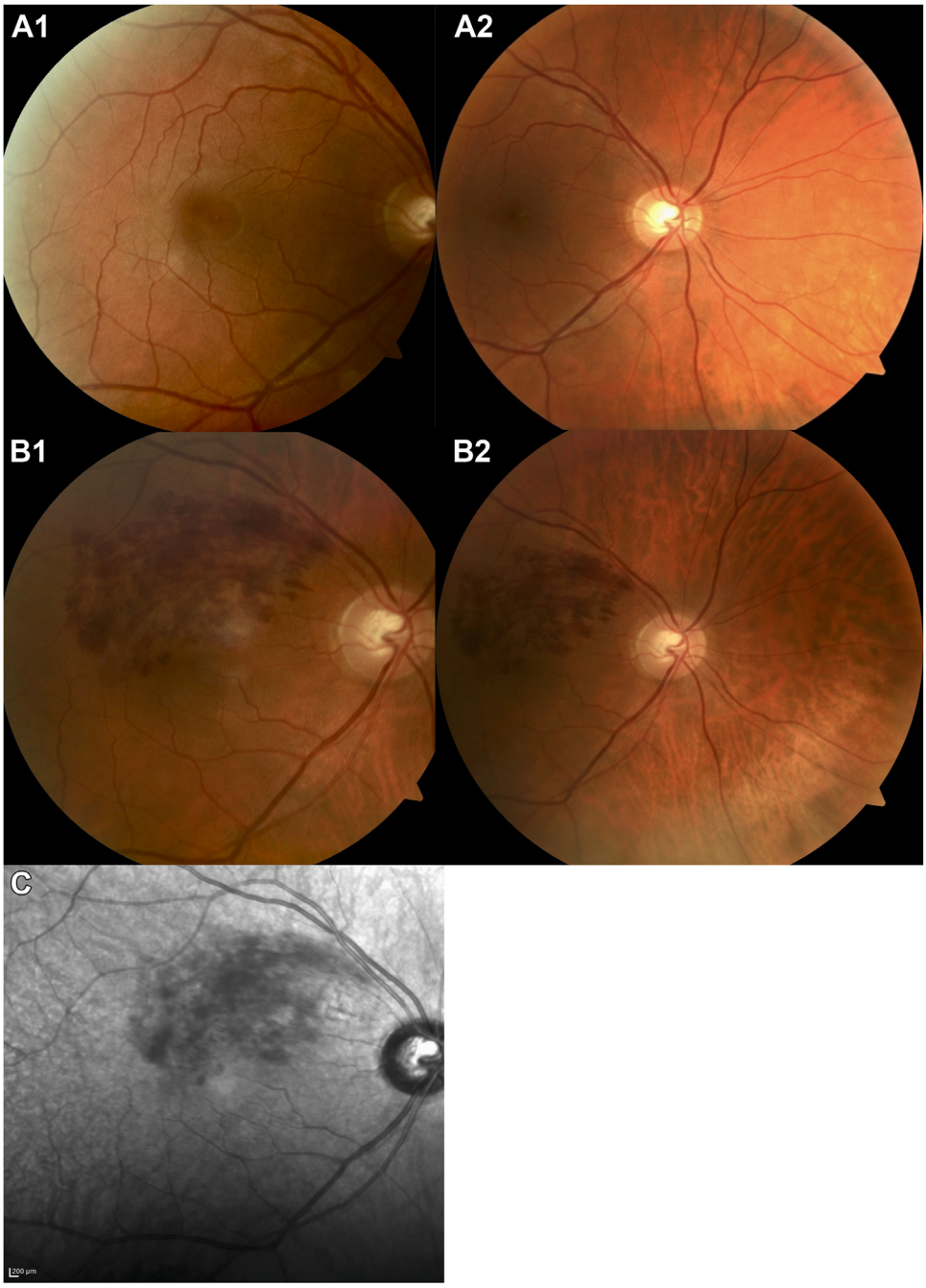

Figure 1. **A1**, **A2**, Fundus photographs obtained at baseline showing no retinal vein occlusion. **B1**, **B2**, Fundus photographs obtained at the 10-year follow-up showing branch retinal vein occlusion. **C**, Infrared image obtained at the 10-year follow-up showing branch retinal vein occlusion. Images from the population-based Gutenberg Health Study.

interval (CI). Logistic regression analysis on incidence data was computed including age, sex, arterial hypertension, BMI, smoking status, diabetes, family history of stroke or myocardial infarction, and dyslipidemia. Cox regression analysis was used to investigate the influence of RVO on mortality. Two analyses were performed, one including baseline RVO status and a second including time-dependent covariates of all 3 examination time points. As covariates, RVO status, age, sex, arterial hypertension, BMI, smoking status, diabetes, family history of stroke or myocardial infarction, and dyslipidemia were included. Proportion on hazard assumptions were checked, and data met the assumptions. Statistical analysis was performed using R version 4.3.0 using packages ggplot2, tableone, MASS, geepack, epiDisplay, sinaplot, RColorBrewer, tidyverse, and adjusted curves (The R Foundation for Statistical Computing, available at: http://www.r-project.org).

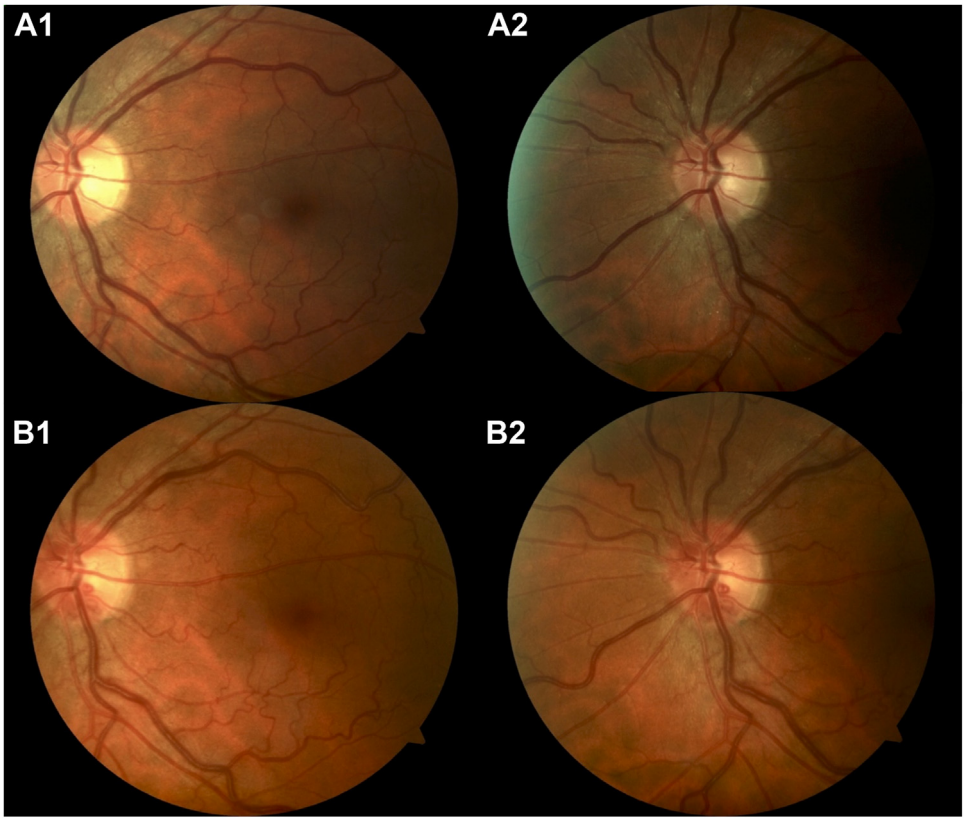

Figure 2. **A1**, **A2**, Fundus photograph at baseline with no retinal vein occlusion. **B1**, **B2**, Fundus photographs at the 10-year follow-up showing increased vessel tortuosity and new opticociliary shunts indicating central retinal vein occlusion. Images from the population-based Gutenberg Health Study.

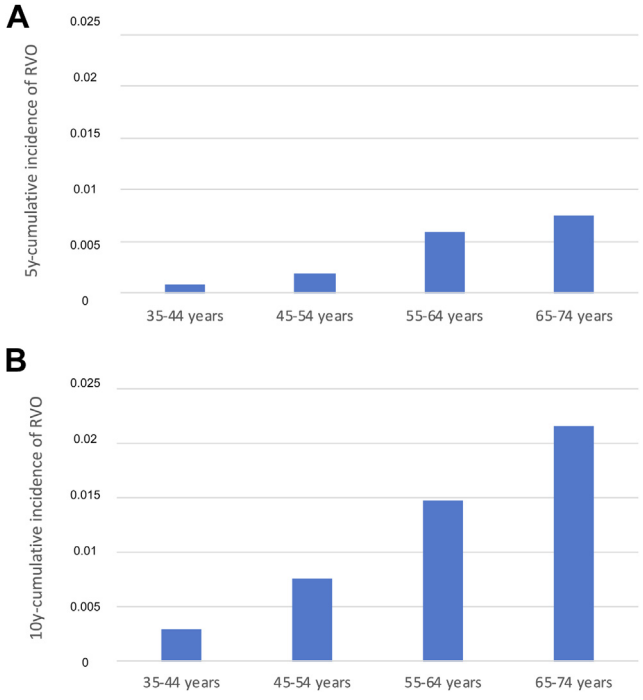

Figure 3. Bar graphs showing 5-year (**A**) and 10-year (**B**) cumulative incidence of any retinal vein occlusion (RVO) per age decade. Data from the Gutenberg Health Study 2007–2022.

Results

Study Population

Of 15 010 participants who took part in the Gutenberg Health Study, 12 954 participants were included with a gradable fundus photograph at baseline (baseline prevalence of BRVO, 0.32%; and baseline prevalence of CRVO, 0.08%). The baseline cohort, prevalence of RVO, and associations with ocular and systemic factors were described in detail elsewhere.[3]

A total of 9305 participants (mean age at baseline, 55.12 years; mean age at 5-year follow-up, 60.52 years; 48.8% female) at the 5-year-follow-up and 6428 participants (mean age at baseline, 52.42 years; mean age at 10-year follow-up, 62.7 years; 48.8% female) at the 10-year-follow-up had a gradable image. The study population is described in detail in Table 1.

Nonresponder item analysis of the baseline visit, and 5-year and 10-year follow-up revealed that baseline participants with and without gradable fundus photography had a comparable age and cardiovascular risk profile, but younger participants at baseline were more likely to participate, have gradable images at the follow-up visits, or both. Furthermore, participants with gradable fundus photography at the follow-up visits had a lower BMI and were less likely to smoke or to have diabetes, arterial hypertension,

Table 1. Description of the Study Population with a Gradable Image at Baseline, 5-Year Follow-up Examination, and 10-Year Follow-up Examination

Features (Baseline)	Study Population with Gradable Images		
	Baseline (n = 12 954)	*5-Year Follow-up (n = 9305)*	*10-Year Follow-up (n = 6428)*
Sex (female)	49.8% (6456)	48.8% (4544)	48.8% (3135)
Age at baseline (yrs)	55.03 ± 11.1	54.12 ± 10.79	52.42 ± 10.19
Age at 5-yr or 10-yr follow-up (yrs)	—	59.12 ± 10.79	62.7 ± 10.2
Body mass index (kg/m^2)	27.35 ± 5.0	27.11 ± 4.78	26.76 ± 4.63
Blood pressure (mmHg)			
Systolic arterial	131.4 ± 17.5	130.69 ± 17.02	129.18 ± 16.3
Diastolic arterial	82.29 ± 9.59	82.28 ± 9.38	82.21 ± 9.22
Arterial hypertension (yes)	49.7% (6438)	47.2% (4389)	43.2% (2778)
Dyslipidemia (yes)	34.7% (4489)	33.3% (3091)	30.4% (1950)
Diabetes (yes)	9.3% (1201)	7.4% (385)	5.7% (367)
Family history of myocardial or cerebral insult (yes)	8.1% (1052)	7.7% (718)	7.3% (469)
Smoking history (yes)	19.6% (2540)	18.5% (1716)	17.8% (1,145)

Data from the population-based Gutenberg Health Study 2007–2022. Data are presented as percentage (no.) or mean ± standard deviation. — = no follow up available for the baseline visit.

dyslipidemia or a family history of stroke or myocardial infarction. More details are provided in Tables S2, S3, and S4 (available at www.aaojournal.org).

Fundus image quality was evaluated in different categories: overall quality was good in 74.38%, fair in 23.11%, and poor in 2.5%. Interrater reliability was high, with a Cohen's κ coefficient of 0.78 for fundus photographs and 0.98 for infrared images.

Cumulative Incidence

The 5-year cumulative incidence was 0.35% (95% CI, 0.25%–0.5%; n = 33) for BRVO and 0.043% (95% CI, 0.014%–0.12%; n = 4) for CRVO. The 10-year cumulative incidence was 0.64% (95% CI, 0.46%–0.87%; n = 55) for BRVO and 0.14% (95% CI, 0.067%–0.27%; n = 12) for CRVO. A detailed description of participants with an incident RVO within the 10-year follow-up is displayed in Table 5.

Univariable analysis revealed an association both of 5-year and 10-year cumulative incidence of RVO with higher age (odds ratio [OR], 1.05; 95% CI, 1.02–1.09; $P < 0.001$; Figure 3) and arterial hypertension (OR, 2.57; 95% CI, 1.43–4.62; $P = 0.002$). This continued to be the case in the 10-year BRVO subgroup analysis (age: OR, 1.05; 95% CI, 1.02–1.08; $P < 0.001$; arterial hypertension: OR, 2.29; 95% CI, 1.21–4.34; $P = 0.01$) but not in the CRVO subgroup (age: OR, = 0.021; $P = 0.57$; arterial hypertension: OR, 1.12; $P = 0.20$), most likely because of the small number of CRVO events in the cohort.

Table 5. Description of the Study Population with an Incident Branch Retinal Vein Occlusion and Central Retinal Vein Occlusion within the 10-Year Follow-up

Features	No Retinal Vein Occlusion within the 10-Year Follow-up (n = 6378)	Incident Branch Retinal Vein Occlusion within the 10-Year Follow-up (n = 55)*	Incident Central Retinal Vein Occlusion within the 10-Year Follow-up (n = 12)*
Sex (female)	48.7% (3108)	53% (29)	50% (6)
Age at baseline (yrs)	52.38 ± 10.19	58.6 ± 8.8	59.3 ± 10.5
Body mass index (kg/m^2)	26.75 ± 4.62	27.6 ± 5.0	29.3 ± 3.9
Blood pressure (mmHg)			
Systolic arterial	129.1 ± 16.27	137.6 ± 18.3	141.4 ± 21.9
Diastolic arterial	82.18 ± 9.22	84.3 ± 9.5	84.5 ± 8.8
Arterial hypertension (yes)	43.0% (2745)	66% (36)	75% (9)
Dyslipidemia (yes)	30.3% (1929)	46% (25)	50% (6)
Diabetes (yes)	5.7% (361)	15% (8)	17% (2)
Family history of myocardial or cerebral insult (yes)	7.3% (463)	13% (7)	17 % (2)
Smoking history (yes)	17.9% (1143)	9% (5)	25% (3)

Data from the German population-based Gutenberg Health Study 2007–2022. Data are presented as percentage (no.) or mean ± standard deviation.
*Fourteen patients with an incident branch retinal vein occlusion and 3 patients with an incident central retinal vein occlusion at the 5-year follow-up visit did not complete the 10-year follow-up visit but are included in this description of the study population because we report the cumulative 5- and 10-year incidence cases.

The 5-year cumulative incidence of RVO additionally was associated with dyslipidemia (OR, 2.65; 95% CI, 1.38−5.08, $P = 0.003$), diabetes (OR, 3.51; 95% CI, 1.6−7.71; $P = 0.002$), and a family history of myocardial or cerebral insult (OR, 2.82; 95% CI, 1.23−6.43; $P = 0.014$) in the univariable analysis. Trends for an association of 10-year cumulative incidence of RVO and diabetes (OR, 2.29; 95% CI, 0.97−5.4; $P = 0.059$) and dyslipidemia (OR, 1.67; 95% CI, 0.95−2.94; $P = 0.075$) were still detectable, but not significant. No consistent significant associations of incident RVO and sex, BMI, or smoking status were found. No association with increased incidence for RVO was seen when comparing those who smoke (including former smoking) with those who did not smoke or pack-years of smoking in the analysis. A detailed description of univariable associations to an incident RVO within the 5-year and 10-year follow-up is displayed in Table 6.

The multivariable analysis showed a significant association only with age, but not consistently with any other cardiovascular risk factors. A detailed description of multivariable associations with an incident RVO within the 5-year and 10-year follow-up is displayed in Table S7 (available at www.aaojournal.org).

Retinal Vein Occlusion and Mortality

After follow-up assessment through November 26, 2024, 1743 of 12 940 participants (13.47%) with available mortality data died within a median observation time of 14.68 years. Cox regression analysis showed an increased mortality after RVO after adjusting for cardiovascular risk factors including age, sex, arterial hypertension, BMI, smoking status, diabetes, family history of stroke or myocardial infarction, and dyslipidemia. Participants with CRVO had a nearly 4-fold higher risk of death (CRVO: hazard ratio, 3.83; 95% CI, 1.95−7.9; $P < 0.001$; 12% of those without RVO and 50% [6/12] of those with CRVO died within 15 years), and participants with BRVO had about a 2-fold higher risk of death (BRVO: hazard ratio, 2.27; 95% CI, 1.08−3.0; $P = 0.023$; 29.8% [14/47] of those with BRVO; Table 8; Fig 4).

Discussion

This large population-based cohort study examined the cumulative 5-year and 10-year-incidence of RVO and associated systemic factors as well as differences in mortality rates in Germany. Previous studies regarding the cumulative incidence of RVO with large sample sizes are rare, and, to date, neither data about the incidence in a European population nor any study with > 4000 participants in any population-based cohort study worldwide has been published.

The 5-year cumulative incidence in this study was 0.35% for BRVO and 0.043% for CRVO, whereas the 10-year cumulative incidence was 0.64% for BRVO and 0.14% for CRVO. This is below reported RVO incidence estimates for the United States or the Western Pacific region, which range between 0.78% and 0.98% for 5 years and between 1.41% and 1.82% for 10-year cumulative incidence estimates.[5] Even higher estimates were published in the

Table 6. Univariable Associations with Any Retinal Vein Occlusion, Branch Retinal Vein Occlusion, and Central Retinal Vein Occlusion

	Cumulative Incidence at 5-Year Follow-up								Cumulative Incidence at 10-Year Follow-up							
	Any Retinal Vein Occlusion			*Branch Retinal Vein Occlusion*			*Central Retinal Vein Occlusion*		*Any Retinal Vein Occlusion*			*Branch Retinal Vein Occlusion*			*Central Retinal Vein Occlusion*	
Features	*Odds Ratio*	*95% Confidence Interval*	*P Value*	*Odds Ratio*	*95% Confidence Interval*	*P Value*	*Odds Ratio*	*95% Confidence Interval*	*Odds Ratio*	*95% Confidence Interval*	*P Value*	*Odds Ratio*	*95% Confidence Interval*	*P Value*	*Odds Ratio*	*95% Confidence Interval*	*P Value*
Sex (female)	0.89	0.47−1.7	0.72	0.87	0.44−1.73	0.70	1.05	.015−7.44	0.96	1.23	0.71−2.15	0.46	1.22	0.66−2.25	0.53	1.31	0.35−4.89	0.69
Age at baseline (yrs)	**1.07**	**1.03−1.1**	**< 0.001**	**1.06**	**1.02−1.1**	**0.001**	**1.21**	**1.01−1.44**	**0.036**	**1.05**	**1.02−1.09**	**< 0.001**	**1.05**	**1.02−1.09**	**< 0.001**	1.05	0.98−1.11	0.18
BMI (kg/ m^2)	1.03	0.96−1.09	0.43	1.03	0.96−1.1	0.40	1.0	0.81−1.23	0.99	1.05	1−1.11	0.052	1.04	0.98−1.1	0.19	1.12	0.99−1.21	0.07
Arterial hypertension (yes)	**2.65**	**1.31−5.38**	**0.007**	**2.58**	**1.23−5.43**	**0.012**	3.37	0.35−32.4	0.29	**2.57**	**1.43−4.62**	**0.002**	**2.29**	**1.21−4.34**	**0.011**	4.63	0.96−22.3	0.06
Dyslipidemia (yes)	**2.65**	**1.38−5.08**	**0.003**	**2.42**	**1.22−4.81**	**0.012**	6.06	0.63−58.24	0.12	1.67	0.95−2.94	0.08	1.63	0.88−3.05	0.12	1.85	0.5−6.88	0.36
Diabetes (yes)	**3.51**	**1.6−7.71**	**0.002**	**2.83**	**1.16−6.88**	**0.022**	**12.7**	**1.79−90.5**	**0.01**	2.29	0.97−5.4	0.06	**2.88**	**1.2−6.88**	**0.018**	—	—	0.99
Family history of myocardial or cerebral insult (yes)	**2.82**	**1.23−6.43**	**0.014**	**2.68**	**1.1−6.52**	**0.029**	4.02	0.42−38.72	0.23	1.75	0.74−4.13	0.20	1.18	0.42−3.36	0.75	3.67	0.76−17.7	0.10
Smoking history (yes)	0.86	0.36−2.05	0.73	0.61	0.21−1.74	0.35	4.42	0.62−31.4	0.14	0.57	0.07−4.58	0.60	**0.11**	**0.02−0.83**	**0.032**	0.57	0.07−4.58	0.60

Data from the German population-based Gutenberg Health Study 2007−2022.
Boldface indicates statistical significance.
— = not available.

Table 8. Association of Mortality and Branch Retinal Vein Occlusion and Central Retinal Vein Occlusion

Model	Branch Retinal Vein Occlusion			Central Retinal Vein Occlusion		
	Hazard Ratio	*95% Confidence Interval*	*P Value*	*Hazard Ratio*	*95% Confidence Interval*	*P Value*
1	**3.7**	**1.57–4.34**	**< 0.001**	**5.59**	**3.63–14.54**	**< 0.001**
2	**2.02**	**1.02–2.81**	**0.043**	**3.16**	**1.53–6.14**	**0.0016**
3	**2.27**	**1.08–3.0**	**0.023**	**3.83**	**1.95–7.9**	**< 0.001**

Data from the German population-based Gutenberg Health Study 2007–2024. Model 2 is adjusted for age and sex. Model 3 is adjusted for age, sex, arterial hypertension, body mass index, smoking status, diabetes, family history of stroke or myocardial infarction, and dyslipidemia. Cox regression analysis with time-dependent covariates at baseline, the 5-year examination, and the 10-year examination was conducted. Boldface indicates statistical significance.

Hisayama Study in Japan, with 1775 participants reporting a 9-year cumulative incidence of any RVO as 3.0%.[6] However, Park et al[8] reported the mean yearly incidence in the 12-year follow-up in the Korean population of 0.048% using health claim data, suggesting a 10-year cumulative incidence of around 0.5%. A direct comparison of those estimates is inadequate and is not possible because of data collection differences. In addition, only symptomatic patients may visit an ophthalmologist, who must have included the correct *International Classification of Diseases, Tenth Revision*, code to be included in the analysis later. The lower incidence of RVO in the European population matches the reportedly lower prevalence of RVO in Europe of 0.7% in those $\geq$ 55 years of age based on the meta-analysis of Li et al[10] compared with the estimated global prevalence of 0.74% to 3.36% in those 50 to 89 years of age.[5]

Age was associated significantly with the incidence of RVO in the present cohort. Other common cardiovascular risk factors like dyslipidemia, diabetes, or a positive family history of stroke or myocardial infarction showed a significant univariable association with the 5-year cumulative incidence of RVO. Trends for an association of 10-year cumulative incidence of RVO and diabetes and dyslipidemia were still detectable, but not significant. One possible explanation is the known higher mortality rate of patients with a high cardiovascular risk profile. According to this, comparatively healthier participants experience an RVO at an older age. We did not find an association with sex, BMI, or smoking. However, multivariable analysis detected a significant association of incident RVO only with age but not with any other cardiovascular risk factors. This is most likely because of the limited number of patients with new-onset RVO in our study. An underestimation also might have occurred because of selection bias of participants with gradable fundus photographs, infrared images, or both who were younger and had fewer cardiovascular comorbidities and better image quality. Additionally, far peripheral RVO or previous RVO without clinically visible residues such as hemorrhages, shunt vessels, arteriovenous collaterals, or laser marks could not be detected. This is most likely the case for all other cohort studies and CRVO and severe previous BRVO are most likely to have visible residues. A further limitation of our study is the mainly White racial background of participants, the recruitment efficacy proportion of 55.6% at study inclusion, and the age range from 35 to 74 years at study inclusion. Thus, we cannot make any statements about the incidence of RVO in, for example, elderly participants. Association analysis between incident RVO and glaucoma or pseudoexfoliation was not conducted because of low numbers in the respective categories.

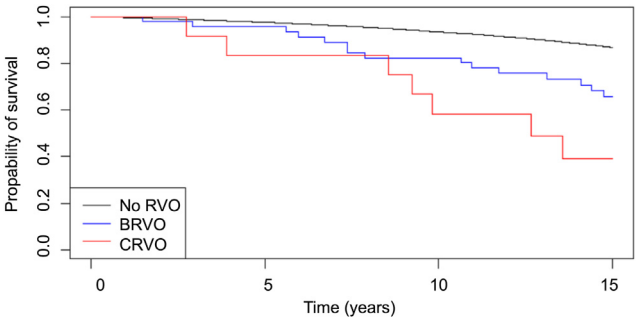

Figure 4. Kaplan-Meier curve showing the probability of survival after branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) at baseline examination. Data from the Gutenberg Health Study. RVO = retinal vein occlusion.

Previous studies reported conflicting findings on the association of RVO and mortality. Although some studies did not find an increased risk,[11–13] others have reported such. However, studies reporting an association either did not differentiate between BRVO and CRVO or showed increased mortality only after CRVO.[4,14–16] Furthermore, sufficient adjustment for cardiovascular risk factors is lacking in some studies, which makes interpretation even more difficult. This study demonstrated a significantly increased risk of mortality in both subgroups: CRVO and BRVO. The association for CRVO was stronger than for BRVO. Further, an association of cardiovascular risk factors and the prevalence of RVO have been demonstrated various times, which may explain the increased risk of mortality. However, in our study, the increased risk of mortality was still significant after adjusting for major cardiovascular risk factors including age, sex, arterial hypertension, BMI, smoking, diabetes, family history of stroke or myocardial infarction, and dyslipidemia.

In summary, this study showed a 5-year cumulative incidence of 0.35% for BRVO and 0.043% for CRVO, whereas the 10-year cumulative incidence was 0.64% for BRVO and 0.14% for CRVO, in a large European-based cohort. Participants with BRVO and CRVO have an increased mortality after RVO independently of major cardiovascular risk factors.

Footnotes and Disclosures

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Analysis and interpretation: Voigt, Schuster

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Abbreviations and Acronyms:
BMI = body mass index; **BRVO** = branch retinal vein occlusion; **CI** = confidence interval; **CRVO** = central retinal vein occlusion; **OR** = odds ratio; **RVO** = retinal vein occlusion.

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