Original Article

Hypertension and multiple cardiovascular risk factors increase the risk for retinal vein occlusions: results from the Gutenberg Retinal Vein Occlusion Study

Katharina A. Ponto[a,b], Inge Scharrer[c], Harald Binder[d,i], Christina Korb[a], Ann K. Rosner[a,e], Till O. Ehlers[a], Nikola Rieser[a], Nadja C. Grübel[a], Heidi Rossmann[f], Philipp S. Wild[b,g,h], Nicolas Feltgen[i], Norbert Pfeiffer[a], and Alireza Mirshahi[a,j,k]

Objective: Although several risk factors for retinal vein occlusion (RVO) are known, what triggers RVO is unclear in many cases. We aimed to evaluate the relevance of multiple risk factors in patients with RVO.

Methods: The Gutenberg RVO Study is an observational case–control study that assessed thrombophilic, cardiovascular, ophthalmic, and drug-related risk factors in participants with RVO and the same number of matched controls. Conditional logistic regression analysis was chosen to estimate the risk of RVO due to several risk factors.

Results: Of 92 patients with RVO, 46 (50%) had central RVO, 31 (33.7%) had branch RVO, and 15 (16.3) had hemi-RVO. Systemic hypertension was associated with RVO [any RVO: odds ratio (OR): 1.81; 95% confidence interval (CI): 1.14–2.88; branch RVO: OR: 2.56; 95% CI: 1.08–6.10]. The most frequent combinations of risk factors were hypertension with dyslipidemia (33 of 92, 35.9%) and hyperhomocysteinemia and high levels of factor VIII (10 of 92, 10.9%). An increase in the risk sum score by one additional risk factor corresponded to ORs of 1.74 (95% CI: 1.31–2.32) for cardiovascular risk factors, 1.38 (95% CI: 1.04–1.82) for thrombophilic risk factors, and 1.43 (95% CI: 1.20–1.70) for the total number of risk factors for RVO.

Conclusion: Cardiovascular risk factors are more important than other risk factors for the presence of RVO. The risk of RVO increased by approximately 40% with any additional risk factor and by 70% with any additional cardiovascular risk factor.

Keywords: hypertension, retinal vein occlusion, retinal vessels, risk factors, thrombosis

Abbreviations: BRVO, branch retinal vein occlusion; CI, confidence interval; CRVO, central retinal vein occlusion; GHS, Gutenberg Health Study; HRVO, hemiretinal vein occlusion; OR, odds ratio; RVO, retinal vein occlusion

INTRODUCTION

Retinal vein occlusions (RVOs) are a major cause of vision loss and the most common retinal vascular disease second to diabetic retinopathy [1,2]. Obstruction of the retinal venous system may involve the central retinal vein (central RVO, CRVO) or a branch retinal vein (branch RVO, BRVO), whereas hemi-RVO (HRVO) refers to a proximal occlusion that affects half of the retinal drainage area [3,4]. There is a positive association between retinal vascular events and mortality, stroke [5,6], myocardial infarction [7], and (ischemic) heart failure [8–10]. According to a study by Bertelsen *et al.* [11], CRVO is associated with an overall increase in all-cause mortality compared with that of controls, and this increase is attributed to cardiovascular diseases and diabetes. In another study, the event rate for cerebrovascular accidents in patients with RVO was almost two-fold higher than that observed in controls [12].

In a recent German population-based study, we published a prevalence of RVO of 0.4%, in which males were 1.7 times more frequently affected by RVO than females [13]. Cardiovascular disease, some coagulopathies, ophthalmic parameters, and drug-related risk factors have been identified as risk factors for RVO (Table 1). A large proportion of patients with RVO have a history of cardiovascular disease, hypertension, diabetes mellitus, or open-angle glaucoma [3,14,15]. A recent study investigated whether the results of early tests for hypercoagulability were associated with the development of CRVO risk factors later in life and assessed the necessity of these tests in younger patients [16]. In this study, none of the patients demonstrated further clotting or any unusual thrombi during long-term follow-up. A meta-analysis found that there is evidence of an

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[a]Department of Ophthalmology, [b]Center for Thrombosis and Hemostasis, [c]Depart-Department of Medicine III (Hemostaseology), [d]Division of Biostatistics and Bioinformatics, Institute of Medical Biostatistics, Epidemiology and Informatics, [e]Department of Anesthesiology, [f]Institute of Clinical Chemistry and Laboratory Medicine, [g]Preven-Preventive Cardiology and Preventive Medicine, Center for Cardiology, [h]DZHK (German Center for Cardiovascular Research), Partner Site Rhine Main, University Medical Center, Mainz, [i]Faculty of Medicine and Medical Center, Institute of Medical Biometry and Statistics, University of Freiburg, Freiburg im Breisgau, [j]Department of Ophthalmology, University Medical Center Göttingen, Göttingen and [k]Dardenne Eye Hospital, Bonn, Germany

Correspondence to Katharina A. Ponto, MD, Department of Ophthalmology, University Medical Center Mainz, Langenbeckstr. 1, 55131 Mainz, Germany. Tel: +49 6131 17 6038; fax: +49 6131 17 47 6038; e-mail: katharina.ponto@unimedizin-mainz.de

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TABLE 1. Most important risk factors for retinal vein occlusions

Risk factors and diseases	References
Thrombophilic	
Hyperhomocysteinemia	[20,21]
Cardiolipin antibodies	[22]
Lupus anticoagulant	[23]
Activated protein C resistance (factor V Leiden mutation)	[24]
Prothrombin gene mutation (G20210A)	[24,25]
High factor VIII levels	[19]
Antithrombin deficiency	[26]
Hyperviscosity due to high hematocrit	[27,28]
History of thrombosis (RVO, DVT, LE)	[24]
Family history of thrombosis (RVO, DVT, LE)	[24,29]
Cardiovascular	
Systemic hypertension	[30–32]
Diabetes	[33]
Dyslipidemia	[33]
Coronary heart disease	[34]
Smoking	[34]
Obesity	[33]
Ophthalmic	
High intraocular pressure/glaucoma	[35–40]
Drug-related	
Oral contraceptives	[41]
Diuretics	[3,42,43]

The table summarizes the 'traditional' risk factors for retinal vein occlusions and the related references. RVO, retinal vein occlusion.

association only with hyperhomocysteinemia and anticardiolipin antibodies, factors that are known as risk factors for venous thrombosis and arterial vascular disease [17]. Therefore, systematic thrombophilia screening in patients with RVO cannot be recommended [18]. On the other hand, multiple thrombophilic disorders are associated with the development of RVO, especially among patients younger than 65 years of age [19]. Currently, no data (ND) have been published regarding the associations of RVO with the presence of multiple risk factors in the same individual. Furthermore, it is unclear whether cardiovascular or thrombophilic risk factors are more relevant.

The aim of this clinical study was to investigate the relevance of the presence of multiple risk factors in patients with RVO in a case–control setting. We hypothesized an association between the coexistence of several risk factors in individuals with RVO.

METHODS

The Gutenberg Retinal Vein Occlusion (RVO) Study is an observational case–control study located in Mainz, Germany. The aim of the Gutenberg RVO Study is to investigate the relevance of traditional risk factors for RVO and combinations of these conditions in the same individual to weigh the importance of these risk factors and to identify novel risk factors for RVO.

Study participants

A total of 92 patients with RVO and the same number of age-matched and sex-matched controls were included in this study (Table 2). According to the protocol, 50% of the patient group had CRVO and 50% had other types of RVO. Furthermore, 50% of the CRVO-group and non-CRVO-group (BRVO + HRVO) were aged less than 65 years, and 50% were aged at least 65 years. We chose the cutoff age of 65 years to determine these subgroups, as this cutoff was used in previous studies on RVO [13,19]. The inclusion criteria for the patient group included the occurrence of RVO within the past 60 days, legal age, and informed consent to participate. The exclusion criteria included an uncertain diagnosis, minors under age 18 years, physical or mental illness making participation impossible, acute inflammatory or malignant diseases, and refusal to participate. A control group was recruited and matched by year of birth and sex.

Patients with missing data for the most important variables (Table 1) were excluded from the analyses. In these cases, we recruited additional participants to achieve a sample size of 92 per group.

Study protocol

Between March 2013 and October 2017, patients with RVO who were admitted to the Department of Ophthalmology, University Medical Center Mainz, were screened to participate in the study. The (matched by age and year of birth) controls were patients without RVO who were treated at the same department for other reasons and fulfilled the inclusion criteria. Blood was drawn from all participants to assess standard parameters (blood count, electrolytes, levels of plasma uric acid, liver and renal function, etc.) and thrombophilic parameters. Biobanking was performed to assess novel risk factors for RVO in the future. All patients and controls underwent a standardized interview to obtain information regarding their medical history and family history, including ophthalmic, cardiovascular, endocrine, and thrombophilic diseases and risk factors. The patient group received a thorough ophthalmic investigation, including visual acuity testing, 24-h profiles of intraocular

TABLE 2. Participants of the Gutenberg Retinal Vein Occlusion Study

Patients			Controls		
	Age	*n*		Age	*n*
CRVO, $n=46$	<65 years	23	Matched by year of birth and sex	<65 years	23
	≥65 years	23		≥65 years	23
Non-CRVO, $n=46$	<65 years	16 BRVO 7 HRVO		<65 years	23
	≥65 years	15 BRVO 8 HRVO		≥65 years	23
		$\sum=92$			$\sum=92$

Distribution of the different subgroups according to different types of RVO and age. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion.

pressure, pupillary testing, slit lamp biomicroscopy, fundoscopy, and optical coherence tomography. Furthermore, patients with RVO underwent an extensive, 5-h-long standardized protocol that included an ophthalmic examination and a complete general medical examination focused on cardiovascular parameters in the study center of the population-based Gutenberg Health Study (GHS). The detailed protocol has been described previously [44,45].

The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.554.12). Written informed consent was obtained from participants after an explanation of the nature and possible consequences of the study. This research adhered to the tenets of the Declaration of Helsinki.

For the present analysis, we assessed possible risk factors in patients with CRVO, BRVO, and HRVO and compared the presence of different and multiple risk factors in these patients versus controls. Table 1 summarizes important risk factors for RVO, which were derived from a literature search and the results of our own investigations in the population. The thrombophilic risk factors were defined as follows: hyperhomocysteinemia: level of homocysteine at least 15 μmol/l, cardiolipin antibodies: IgG at least 16.6 IU and IgM at least 46 IU, lupus anticoagulant: diluted Russel Viper venom Time-ratio less than 1.2, factor V Leiden mutation (legacy name: G1691A, R506Q; name according to HGVS: c.1601G>A, p.Arg534Gln; dbSNP: rs6025) of the F5 gene (RefSeq NM_000130.4), which causes activated protein C resistance, prothrombin gene (F2 gene; RefSeq: NM_000506.4) mutation (legacy name: G20210A; name according to HGVS:_ c.*97G>A; dbSNP: rs1799963), p.Arg506Gln, prothrombin mutation: heterozygous or homozygous mutations of the following gene: g.20210G>A, high factor VIII (FVIII) activity: >150%, antithrombin deficiency: activity less than 80%, hyperviscosity due to high hematocrit levels (>44%), and history or family history of thrombosis: self or family history of RVO, deep leg vein and/or arm thrombosis, and pulmonary embolism. The cardiovascular risk factors and diseases were defined as follows: arterial hypertension (AH) was diagnosed if antihypertensive drugs were taken or if the mean SBP was at least 140 mmHg in the 2nd and 3rd standardized measurement after 8 and 11 min of rest or if the mean DBP was at least 90 mmHg in the 2nd and 3rd standardized measurement after 8 and 11 min of rest. Diabetes was diagnosed in individuals with a definite diagnosis and treatment of diabetes by a physician, a blood glucose level at least 126 mg/dl after overnight fasting of at least 8 h or a blood glucose level at least 200 mg/dl after a fasting period of less than 8 h and/or a glycated haemoglobin (HbA1c) level at least 6.5%. Dyslipidemia was defined as a definite diagnosis of dyslipidemia by a physician or an LDL/HDL-ratio at least 3.5. Obesity was defined as a BMI at least 30 kg/m^2. Smoking was dichotomized into nonsmokers (never smokers and ex-smokers) and smokers (occasional smokers and smokers). We also investigated the presence of coronary heart disease and self and/or family history of previous thrombotic events by personal interviews. Furthermore, all medications were listed. We defined the intake of oral contraceptives and/or diuretics as drug-related risk factors for RVO. The presence of glaucoma or ocular hypertension was documented (self-reported diagnosis and/or antiglaucoma medication or history of glaucoma surgery). Intraocular pressure was measured in the framework of a 24-h profile using Goldmann applanation tonometry. Patients were diagnosed as having a high intraocular pressure if maximum values at least 20 mmHg were measured.

Intima–media thickness (IMT) was assessed as previously described [46]: an iE33 ultrasound system (Philips Medical Systems, Best, The Netherlands) with an 11–3-MHz linear-array transducer was used, and evaluation was performed using an automatic computerized system (QLAB; Philips Medical Systems, Böblingen, Germany). Triggering was performed according to the Q wave on electrocardiography to enable measurement in complete relaxation of the ventricle. Mean IMT was recorded 1 cm before the carotid bulb over a length of 1 cm at the far wall of both common carotid arteries (CCAs). Only parts of the CCA without plaques were included in the IMT analysis. Plaques were defined as protrusions into the lumen of 1.5 mm, and screening for plaques was performed for common, internal, and external carotid arteries. A previous analysis in 4814 participants of the population-based Gutenberg health study found that median IMT was 0.62 mm (25th percentile 0.55, 75th percentile 0.70) in women and 0.65 mm (25th percentile 0.57, 75th percentile 0.75) in men [46].

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences, Version 23 (Chicago, Illinois, USA).

All analyses were based on a prespecified statistical analysis plan.

We used the chi-square test to determine univariable associations. Risk factors with P less than 0.05 in univariable analyses were included in a conditional logistic regression. Due to small subgroups, descriptive statistics were performed to compare the frequencies of different combinations of risk factors between patients with various types of RVO at different ages. We calculated the sum of risk factors to assess the relevance of the number of risk factors in each category. Finally, we performed a multivariable logistic regression analysis to assess the associations between the sum of these risk factors and the presence of RVO. Due to the explorative nature of the study, a significance threshold was not defined for P values. Therefore, P values should be interpreted as a continuous measure of statistical evidence.

RESULTS

A total of 121 patients with RVO were screened for the study. Important variables were missing in seven (5.5%) patients initially included in the study (summarized in Table 1). These participants were excluded and subsequently replaced by an equal number of individuals without missing data for the main variables. Of the 128 screened individuals, 29 (22.7%) were not included in the study: 13 (44.8%) were not willing to participate, four (1.7%) did not completely fulfill the inclusion criteria, nine (31.0%) could not participate due to physical and/or mental illness, and three (1.3%) had technical reasons (e.g. study center closed during holidays) for their missing participation.

Of the 92 patients with RVO included in the study, 46 (50%) had CRVO, 31 (16.8%) had BRVO, and 15 (8.2%) had HRVO. Of this sample, 43 (46.7%) were women (CRVO: 23/46 (50%), BRVO: 14/31 (45.2%), HRVO: 4/15 (40%)), and the median age was 64 years (CRVO: 64, range: 22–88 years, BRVO: 63, 38–88 years, HRVO: 65, 37–84 years). Of the matched controls, 40 (43.5%) were women, and the median age was 64 (22–90) years. Five of 43 (11.6%) female patients with RVO had menopause (missing data in $n = 7$; 16.3%). Among patients with RVO, 16 (17.4%) took direct oral anticoagulants (DOAC), and five (5.4%) took vitamin K antagonists (VKA). In comparison, among the controls, nine (9.8%) took DOAC, one (1.1%) had dual antiplatelet therapy and two (2.2%) took VKA ($P = 0.118$). The median levels of plasma uric acid were 5.75 mg/dl (range: 2.6–9.6 mg/dl) in patients (missing data in $n = 1$) versus 5.2 mg/dl (2.1–9.3 mg/dl, $P = 0.045$). Furthermore, the serum uric acid (SUA) levels were 5.85 mg/dl (2.6–9.6 mg/dl) in patients with CRVO versus 5.8 mg/dl (3.6–8.3 mg/dl) in CRVO and 5.4 mg/dl (2.6–6.6 mg/dl, $P = 0.495$).

Association of retinal vein occlusion with various risk factors and diseases

Table 3 summarizes the risk factors and diseases in the various groups of patients and controls at all age groups. Prothrombin gene mutation, a history and family history of a thrombotic event, AH, dyslipidemia, and smoking were associated (all $P < 0.05$) with RVO and/or the different types of RVO. Table 4 summarizes the risk factors and diseases in the various groups of patients and controls aged younger than 65 years at inclusion in the study. In this subgroup, hyperviscosity due to high hematocrit, a history and family history of a thrombotic event, and AH were associated (all $P < 0.05$) with RVO and/or the different types of RVO. Table 5 summarizes the risk factors and diseases in the various groups of patients and controls aged 65 years and older at inclusion in the study. In older participants, antithrombin deficiency, AH, dyslipidemia, and obesity were associated (all $P < 0.05$) with RVO and/or different types of RVO. Conditional logistic regression (Table 4) was performed to assess the association between various risk factors (factors with $P < 0.05$ in the univariable analyses) in patients with RVO versus the matched controls. Note that these estimates may be unreliable due to non-convergence issues. In the matched analysis including all types of RVO (Table 6), a positive association of systemic hypertension [odds ratio (OR): 1.81; 95% confidence interval (CI): 1.14–2.88; $P = 0.012$] with RVO was found. Systemic hypertension was also positively associated with an event if patients with BRVO and their controls were included only (Table 7; OR: 2.56; 95% CI: 1.08–6.10; $P = 0.033$). If only patients with CRVO or HRVO and their

TABLE 3. Frequency of risk factors in patients with retinal vein occlusion (according to different types of retinal vein occlusion) and in controls for participants of all ages

Risk factors and diseases	RVO patients (all ages)				Controls	*P* (chi-square test)		
		CRVO, $n = 46$	BRVO, $n = 31$	HRVO, $n = 15$				
Number of persons, *n*	All RVO, $n = 92$	46	31	15	92	All RVO vs. controls	CRVO vs. BRVO vs. HRVO vs. controls	CRVO vs. BRVO vs. HRVO vs. controls
Thrombophilic, *n* (%)								
Homocysteine	19 (20.7)	9 (19.6)	8 (25.8)	2 (13.3)	13 (14.1)	0.243	0.599	0.470
Cardiolipin antibodies	2 (2.2)	1 (2.2)	0 (0)	1 (6.7)	2 (2.2)	0.311	0.348	0.526
Lupus anticoagulant	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0.316	N/A	0.800
Activated protein C resistance (factor V Leiden mutation)	15 (16.3)	9 (19.6)	3 (9.7)	3 (20.0)	14 (15.2)	0.840	0.471	0.662
Prothrombin gene mutation (G20210A)	9 (9.8)	3 (6.5)	2 (6.5)	4 (26.7)	3 (3.3)	0.073	0.055	**0.009**
High factor VIII levels	26 (28.3)	18 (39.1)	6 (19.4)	2 (13.3)	21 (22.8)	0.398	0.063	0.085
Antithrombin deficiency	2 (2.2)	1 (2.2)	0 (0)	1 (6.7)	8 (8.7)	0.051	0.348	0.197
Hyperviscosity due to high hematocrit	31 (33.7)	12 (26.1)	14 (45.2)	6 (33.3)	23 (25.0)	0.195	0.221	0.177
History of thrombosis (RVO, DVT, LE)	11 (12.0)	7 (15.2)	3 (9.7)	1 (6.7)	3 (3.3)	0.026	0.602	0.091
Family history of thrombosis (RVO, DVT, LE)	16 (17.4)	9 (19.6)	5 (16.6)	2 (13.3)	4 (4.3)	**0.004**	0.836	**0.035**
Cardiovascular, *n* (%)								
Systemic hypertension	63 (68.5)	30 (65.2)	23 (74.2)	10 (66.7)	34 (37.0)	**<0.001**	0.698	**<0.001**
Diabetes	6 (6.5)	3 (6.5)	2 (6.5)	1 (6.7)	3 (3.3)	0.305	1.00	0.789
Dyslipidemia	39 (42.4)	20 (43.5)	14 (45.2)	5 (33.3)	20 (21.7)	**0.003**	0.732	**0.021**
Coronary heart disease	5 (5.4)	3 (6.5)	1 (3.2)	1 (6.7)	5 (5.4)	1.00	0.801	0.931
Smoking	10 (10.9)	1 (2.2)	7 (22.6)	2 (13.3)	13 (14.1)	0.504	**0.018**	0.055
Obesity	26 (28.6)	11 (23.9)	9 (29.0)	6 (42.9)	16 (17.8)	0.085	0.388	0.163
Ophthalmic, *n* (%)								
High intraocular pressure/glaucoma	26 (28.3)	16 (34.8)	6 (19.4)	4 (26.7)	20 (21.7)	0.307	0.333	0.331
Drug-related, *n* (%)								
Oral contraceptives	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0.316	N/A	0.800
Diuretics	16 (17.4)	9 (19.6)	5 (16.1)	2 (13.3)	15 (16.3)	0.844	0.836	0.939

Univariable analysis with *P* according to chi-square test. Bold letters indicate *P* less than 0.05. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion.

TABLE 4. Frequency of risk factors in patients with retinal vein occlusion (according to different types of retinal vein occlusion) and in controls for participants aged younger than 65 years

Risk factors and diseases	RVO (aged <65 years)				Controls	*P* (chi-square test)		
	All RVO	CRVO	BRVO	HRVO				
Number of persons, *n*	46	23	16	7	47	All RVO vs. controls	CRVO vs. BRVO vs. HRVO	CRVO vs. BRVO vs. HRVO vs. controls
Thrombophilic, *n* (%)								
Homocysteine	42 (91.3)	2 (8.7)	2 (12.5)	0 (0)	4 (8.5)	0.975	0.619	0.809
Cardiolipin antibodies	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	0.320	N/A	0.804
Lupus anticoagulant	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A	N/A	N/A
Activated protein C resistance (factor V Leiden mutation)	9 (19.6)	5 (21.7)	3 (18.8)	1 (14.3)	9 (19.1)	0.959	0.905	0.977
Prothrombin gene mutation (G20210A)	5 (10.9)	2 (8.7)	1 (6.3)	2 (28.6)	2 (4.3)	0.227	0.256	0.154
High factor VIII levels	11 (23.9)	8 (34.8)	2 (12.5)	1 (14.3)	6 (12.8)	0.164	0.224	0.134
Antithrombin deficiency	1 (2.2)	1 (4.3)	0 (0)	0 (0)	2 (4.3)	0.570	0.600	0.797
Hyperviscosity due to high hematocrit	23 (50)	10 (43.5)	10 (62.5)	3 (42.9)	14 (29.8)	**0.046**	0.464	0.135
History of thrombosis (RVO, DVT, LE)	4 (8.7)	3 (13)	1 (6.3)	0 (0)	0 (0)	**0.039**	0.513	0.077
Family history of thrombosis (RVO, DVT, LE)	8 (17.4)	6 (26.1)	2 (12.5)	0 (0)	2 (4.3)	**0.041**	0.229	**0.035**
Cardiovascular, *n* (%)								
Systemic hypertension	24 (52.2)	10 (43.5)	11 (68.8)	3 (42.9)	11 (23.4)	**0.004**	0.259	**0.011**
Diabetes	1 (2.2)	1 (4.3)	0 (0)	0 (0)	0 (0)	0.309	0.600	0.380
Dyslipidemia	14 (30.4)	5 (21.7)	8 (50.0)	1 (14.3)	8 (17.0)	0.128	0.101	0.053
Coronary heart disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A	N/A	N/A
Smoking	7 (15.2)	1 (4.3)	5 (31.3)	1 (14.3)	9 (19.1)	0.615	0.071	0.168
Obesity	12 (26.1)	5 (21.7)	3 (18.8)	4 (57.1)	13 (28.3)	0.815	0.124	0.249
Ophthalmic, *n* (%)								
High intraocular pressure/glaucoma	9 (19.6)	6 (26.1)	1 (6.3)	2 (28.6)	10 (21.3)	0.838	0.248	0.434
Drug-related, *n* (%)								
Oral contraceptives	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	0.320	N/A	0.804
Diuretics	6 (13.0)	2 (8.7)	3 (18.8)	1 (14.3)	3 (6.4)	0.277	0.653	0.515

Univariable analysis with *P* according to chi-square test. Bold letters indicate *P* less than 0.05. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion.

matched controls were included in the model (Tables 8 and 9), no significant associations were found.

Multiple risk factors

The most frequent combination of cardiovascular risk factors was hypertension combined with dyslipidemia (33 of 92, 35.9%). Regarding thrombophilic risk factors the most frequent combination was hyperhomocysteinemia combined with high levels of FVIII (10 of 92, 10.9%; $P = 0.366$). The cumulative number of risk factors in patients with RVO is summarized in Tables 10–12. A higher total number of thrombophilic, cardiovascular, and overall risk factors was found in patients with RVO compared with controls of all ages (Table 10). In the group of patients aged younger than 65 years, a higher rate of thrombophilic risk factors was found in patients versus in controls (Table 11), and in patients aged 65 years and older, more cardiovascular risk factors were found in patients than in controls (Table 12; Fig. 1). Table 13 illustrates the results from multivariable binary logistic regression analysis of the associations between the sum score of the various risk factors with RVO. An increase in the cardiovascular risk sum score by one point corresponded to an OR of 1.74 (95% CI: 1.31–2.32; $P < 0.001$). Pertaining to the number of thrombophilic risk factors, an increase in this risk sum score by one point corresponded to an OR of 1.38 (95% CI: 1.04–1.82; $P = 0.025$). On the other hand, no associations were found between RVO and the number of ophthalmic or drug-related risk factors.

Regarding the total number of risk factors, an increase in the total risk sum score by one point corresponded to an OR of 1.43 (95% CI: 1.20–1.70; $P < 0.001$).

Intima–media thickness

Reliable data on IMT were available from 89 of 92 (96.7%) patients with RVO. The median IMT was 0.71 (range: 0.45–0.91) in patients with CRVO, 0.75 (0.44–0.94) in patients with BRVO and 0.69 (0.59–0.92) in patients with HRVO ($P = 0.162$). Using the normative data (all ages; adjusted for sex) from the previous study by Sinning *et al.* [46], we found that nine (20%) patients with CRVO and three (10%) patients with CRVO had an IMT lower than the 25th percentile, while 19 (42.2%) patients with CRVO, 15 (50%) patients with BRVO, and five (35.7%) patients with HRVO had an IMT higher than the 75th percentile ($P = 0.206$).

DISCUSSION

The Gutenberg RVO Study, among others, is a cohort study performed to prospectively investigate the risk factors of venous occlusive disease in the retina. We estimated the relative risk (RR) increase per further risk factor in 92 patients with various types of acute RVO and the same number of matched controls. The risk of RVO increased by

TABLE 5. Frequency of risk factors in patients with retinal vein occlusion (according to different types of retinal vein occlusion) and in controls in participants aged 65 years and older

Risk factors and diseases	RVO (aged ≥65 years)				Controls	*P* (chi-square test)		
	All RVO	CRVO	BRVO	HRVO				
Number of persons, *n*	46	23	15	8	45	All RVO vs. controls	CRVO vs. BRVO vs. HRVO	CRVO vs. BRVO vs. HRVO vs. controls
Thrombophilic, *n* (%)								
Homocysteine	15 (32.6)	7 (30.4)	6 (40.0)	2 (25.0)	9 (20.0)	0.172	0.729	0.461
Cardiolipin antibodies	2 (4.3)	1 (4.3)	0 (0)	1 (12.5)	2 (4.4)	0.135	0.375	0.253
Lupus anticoagulant	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0.309	N/A	0.793
Activated protein C resistance (factor V Leiden mutation)	6 (13.0)	4 (17.4)	0 (0)	2 (25.0)	5 (11.1)	0.777	0.162	0.265
Prothrombin gene mutation (G20210A)	4 (8.7)	1 (4.3)	1 (6.7)	2 (25.0)	1 (2.2)	0.175	0.192	0.076
High factor VIII levels	15 (32.6)	10 (43.5)	4 (26.7)	1 (12.5)	15 (33.3)	0.941	0.229	0.401
Antithrombin deficiency	1 (2.2)	0 (0)	0 (0)	1 (12.5)	6 (16.3)	**0.046**	0.088	0.142
Hyperviscosity due to high hematocrit	8 (17.4)	2 (8.7)	4 (26.7)	2 (25.0)	9 (20.0)	0.750	0.297	0.493
History of thrombosis (RVO, DVT, LE)	7 (15.2)	4 (17.4)	2 (13.3)	1 (12.5)	3 (6.7)	0.192	0.918	0.588
Family history of thrombosis (RVO, DVT, LE)	8 (17.4)	3 (13.0)	3 (20.0)	2 (25.0)	2 (4.4)	0.048	0.706	0.178
Cardiovascular, *n* (%)								
Systemic hypertension	39 (84.8)	20 (87.0)	12 (80.0)	7 (87.5)	23 (51.1)	**0.001**	0.820	0.007
Diabetes	5 (10.9)	2 (8.7)	2 (13.3)	1 (12.5)	3 (6.7)	0.479	0.892	0.855
Dyslipidemia	25 (54.3)	15 (65.2)	6 (40.0)	4 (50.0)	12 (26.7)	**0.007**	0.301	0.021
Coronary heart disease	5 (10.9)	3 (13.0)	1 (6.7)	1 (12.5)	5 (11.1)	0.971	0.816	0.939
Smoking	3 (6.5)	0 (0)	2 (13.3)	1 (12.5)	4 (8.9)	0.672	0.200	0.401
Obesity	14 (31.1)	6 (26.1)	6 (40.0)	2 (28.6)	3 (6.8)	**0.004**	0.655	**0.022**
Ophthalmic, *n* (%)								
High intraocular pressure/glaucoma	17 (37.0)	10 (43.5)	5 (33.3)	2 (25.0)	10 (22.2)	0.124	0.608	0.324
Drug-related, *n* (%)								
Oral contraceptives	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A	N/A	N/A
Diuretics	10 (21.7)	7 (30.4)	2 (13.3)	1 (12.5)	12 (26.7)	0.583	0.359	0.532

Univariable analysis with *P* values according to chi-square test. Bold letters indicate *P* less than 0.05. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion.

approximately 40% with any additional risk factor and by 70% for any additional cardiovascular risk factor. The matched pair analysis identified AH as the only factor that was significantly associated with RVO. The most frequent combination of risk factors was hypertension combined with dyslipidemia.

Cardiovascular risk factors

In the univariable analyses, we found a higher rate of AH in individuals with RVO than in controls. In the multivariable analysis, systemic hypertension was associated with all types of RVO, but it was mainly associated with BRVO. In the matched pair analysis, the chance of a venous occlusion was almost two (all RVO) to 2.5 (BRVO) times higher in persons with hypertension than in those without.

The associations of BRVO with AH are in line with those found in other studies [30,31]. In a recent study, cerebral small vessel disease presented frequently in young patients with RVO, whereas the predominant underlying disease was AH [47]. This finding emphasizes the relevance of hypertension in retinal vascular occlusion, as RVO – in combination with hypertension – seems to be a surrogate

TABLE 6. Conditional logistic regression of risk factors with *P* less than 0.05 in the univariable analyses in patients with retinal vein occlusion (any type) versus matched controls

Covariates	OR	95% CI	*P*
Prothrombin gene mutation (G20210A)	1.60	0.80–3.23	0.187
Antithrombin deficiency	0.37	0.09–1.49	0.160
Hyperviscosity due to high hematocrit	1.26	0.81–1.94	0.306
History of thrombosis (RVO, DVT, LE)	1.44	0.74–2.84	0.287
Family history of thrombosis (RVO, DVT, LE)	1.45	0.82–2.56	0.206
Systemic hypertension	1.81	1.14–2.88	**0.012**
Dyslipidemia	1.24	0.79–1.94	0.355
Smoking	0.84	0.43–1.65	0.610
Obesity	1.15	0.72–1.85	0.556

Bold letters indicate *P* less than 0.05. CI, confidence interval; OR, odds ratio; RVO, retinal vein occlusion.

TABLE 7. Conditional logistic regression of risk factors with *P* less than 0.05 in the univariable analyses in patients with branch retinal vein occlusion versus matched controls

Covariates	OR	95% CI	*P*
Prothrombin gene mutation (G20210A)	2.86	0.59–13.83	0.190
Antithrombin deficiency	0.00	N/A	0.978
Hyperviscosity due to high hematocrit	1.45	0.67–3.14	0.352
History of thrombosis (RVO, DVT, LE)	1.98	0.45–8.77	0.367
Family history of thrombosis (RVO, DVT, LE)	1.21	0.38–3.84	0.744
Systemic hypertension	2.56	1.08–6.10	**0.033**
Dyslipidemia	1.09	0.48–2.48	0.833
Smoking	1.34	0.53–3.37	0.536
Obesity	0.88	0.37–2.09	0.766

Bold letters indicate *P* less than 0.05. CI, confidence interval; OR, odds ratio; RVO, retinal vein occlusion.

TABLE 8. Conditional logistic regression of risk factors with *P* less than 0.05 in the univariable analyses in patients with central retinal vein occlusion versus matched controls

Covariates	OR	95% CI	*P*
Prothrombin gene mutation (G20210A)	1.05	0.31–3.58	0.934
Antithrombin deficiency	0.36	0.05–2.68	0.319
Hyperviscosity due to high hematocrit	1.27	0.63–2.54	0.502
History of thrombosis (RVO, DVT, LE)	1.12	0.47–2.68	0.803
Family history of thrombosis (RVO, DVT, LE)	1.57	0.71–3.46	0.265
Systemic hypertension	1.73	0.75–3.02	0.249
Dyslipidemia	0.13	0.86–3.48	0.126
Smoking	0.29	0.04–2.56	0.292
Obesity	0.97	0.49–2.11	0.965

CI, confidence interval; OR, odds ratio; RVO, retinal vein occlusion.

TABLE 9. Conditional logistic regression of risk factors with *P* less than 0.05 in univariable analyses in patients with hemiretinal vein occlusion versus matched controls

Covariates	OR	95% CI	*P*
Prothrombin gene mutation (G20210A)	2.32	0.49–10.99	0.288
Antithrombin deficiency	0.35	0.03–4.57	0.420
Hyperviscosity due to high hematocrit	2.01	0.41–9.98	0.393
History of thrombosis (RVO, DVT, LE)	3.47	0.30–39.57	0.317
Family history of thrombosis (RVO, DVT, LE)	3.20	0.41–24.94	0.267
Systemic hypertension	1.30	0.35–4.89	0.693
Dyslipidemia	0.90	0.26–3.10	0.868
Smoking	0.33	0.04–2.76	0.308
Obesity	2.92	0.72–11.75	0.132

CI, confidence interval; OR, odds ratio; RVO, retinal vein occlusion.

marker for cerebral small vessel disease. Pesin *et al.* [32] found that almost 70% of patients with RVO had hypertension according to 24-h blood pressure (BP) monitoring, but 42% of this population had no history of hypertension. Another recent study analyzed risk factors associated with the development of BRVO among a group of managed-care plan beneficiaries in the United States [48]. In this study, enrollees with hypertension had an increased hazard of developing BRVO. In addition, individuals with end-organ damage from diabetes mellitus compared with those without diabetes had a 36% increased hazard of BRVO. The authors concluded that both hypertension and end-organ damage from diabetes mellitus contribute to arteriosclerosis and endothelial dysfunction, which seem to be risk factors for BRVO. Nevertheless, the relevance of the presence of several risk factors (e.g. hypertension and diabetes) was not assessed.

Carotid IMT is increasingly used as an indicator of early atherosclerosis and a predictor for cardiovascular events [46]. The IMT and its association with RVO will be assessed in detail in another substudy of the Gutenberg RVO Study where we will compare these parameters of the RVO cohort with participants of the whole GHS cohort ($n = 15.010$ at baseline). Nevertheless, we did compare the IMT between patients with different types of RVO in the current study. Although the results were not statistically significant, a relevant proportion had an IMT higher than the 75th percentile, especially in those patients with BRVO who had a higher IMT, again highlighting the relevance of BRVO for cardiovascular disease.

TABLE 10. Cumulative number of risk factors in patients with retinal vein occlusions of all ages

Sum of risk factors	RVO (all ages), *n* (%)				Controls, *n* (%)	*P*		
	All RVO	CRVO	BRVO	HRVO				
N	92	46	31	14	92	All RVO vs. controls	CRVO vs. BRVO vs. HRVO	CRVO vs. BRVO vs. HRVO vs. controls
Thrombophilic								
No	21 (22.8)	12 (26.1)	6 (19.4)	3 (20.0)	33 (35.9)	**0.045**	0.076	**0.012**
1	34 (37.0)	14 (30.4)	16 (51.6)	4 (26.7)	35 (38.0)			
2	20 (21.7)	8 (17.4)	5 (16.1)	7 (46.7)	18 (19.6)			
≥3	17 (18.5)	12 (26.1)	4 (12.9)	1 (6.7)	6 (6.5)			
Cardiovascular								
No	18 (19.6)	13 (28.3)	3 (9.7)	2 (13.3)	40 (43.5)	**<0.001**	0.275	**0.002**
1	28 (30.4)	10 (21.7)	12 (38.7)	6 (42.9)	29 (31.5)			
2	23 (25.0)	13 (28.3)	6 (19.4)	4 (28.6)	17 (18.5)			
≥3	23 (25.0)	10 (21.7)	10 (32.3)	3 (21.4)	6 (6.5)			
Ophthalmic								
No	66 (71.7)	30 (65.2)	25 (80.6)	11 (73.3)	72 (78.3)	0.307	0.333	0.331
Yes	26 (28.3)	16 (34.8)	6 (19.4)	4 (26.7)	20 (21.7)			
Drug-related								
No	75 (81.5)	37 (80.4)	26 (83.9)	13 (86.7)	76 (82.6)	0.848	0.704	0.939
1	17 (18.5)	10 (21.7)	5 (16.1)	2 (13.3)	16 (17.4)			
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
Total								
No	4 (4.3)	2 (4.3)	0 (0)	2 (13.3)	15 (16.3)	**<0.001**	0.393	**0.006**
1	11 (12.0)	7 (15.2)	3 (9.7)	1 (6.7)	20 (21.7)			
2	10 (10.9)	4 (8.7)	5 (16.1)	1 (6.7)	19 (20.7)			
≥3	67 (72.8)	33 (71.7)	23 (74.2)	11 (73.3)	38 (41.3)			

Univariable analysis with *P* according to chi-square test. Bold letters indicate *P* less than 0.05. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion.

TABLE 11. Cumulative number of risk factors in patients with retinal vein occlusions younger than 65 years

	RVO (<65 years), *n* (%)				Controls (<65 years), *n* (%)	*P*		
	All RVO	CRVO	BRVO	HRVO				
N	**46**	**23**	**16**	**7**	**47**	**All RVO vs. controls**	**CRVO vs. BRVO vs. HRVO**	**CRVO vs. BRVO vs. HRVO vs. controls**
Thrombophilic								
No	9 (19.6)	5 (21.7)	2 (12.5)	2 (28.6)	20 (42.6)	**0.004**	0.218	**0.005**
1	22 (47.8)	8 (34.8)	11 (68.8)	3 (42.9)	15 (31.9)			
2	6 (13.0)	3 (13.0)	1 (6.3)	2 (28.6)	11 (23.4)			
≥3	9 (19.6)	7 (30.4)	2 (12.5)	0 (0)	1 (2.1)			
Cardiovascular								
No	13 (28.3)	11 (47.8)	1 (6.3)	1 (14.3)	21 (44.7)	0.212	0.096	0.105
1	16 (34.8)	5 (21.7)	7 (43.8)	4 (57.1)	17 (36.2)			
2	10 (21.7)	5 (21.7)	4 (25.0)	1 (14.3)	6 (12.8)			
≥3	7 (15.2)	2 (8.7)	4 (25.0)	1 (14.3)	3 (6.4)			
Ophthalmic								
No	37 (80.4)	17 (73.9)	15 (93.8)	5 (71.4)	37 (78.7)	0.838	0.248	0.434
Yes	9 (19.6)	6 (26.1)	1 (6.3)	2 (28.6)	10 (21.3)			
Drug-related								
No	39 (84.4)	20 (87.0)	13 (81.3)	6 (85.7)	43 (91.5)	0.317	0.885	0.728
1	7 (15.2)	3 (13.0)	3 (18.8)	1 (14.3)	4 (8.5)			
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
Total								
No	3 (6.5)	2 (8.7)	0 (0)	1 (14.3)	9 (19.1)	**0.035**	0.246	0.107
1	7 (15.2)	5 (21.7)	1 (6.3)	1 (14.3)	12 (25.5)			
2	7 (15.2)	1 (4.3)	5 (31.3)	1 (14.3)	10 (21.3)			
≥3	29 (63.0)	15 (65.2)	10 (62.5)	4 (57.1)	16 (34.0)			

Univariable analysis with *P* according to chi-square test. Bold letters indicate *P* less than 0.05. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion.

TABLE 12. Cumulative number of risk factors in patients with retinal vein occlusions aged 65 years and older

	RVO (≥65 years), *n* (%)				Controls (≥65 years), *n* (%)	*P*		
	All RVO	CRVO	BRVO	HRVO				
N	**46**	**23**	**15**	**8**	**45**	**All RVO vs. controls**	**CRVO vs. BRVO vs. HRVO**	**CRVO vs. BRVO vs. HRVO vs. controls**
Thrombophilic								
No	12 (26.1)	7 (30.4)	4 (26.7)	1 (12.5)	13 (28.9)	0.168	0.488	0.248
1	12 (26.1)	6 (26.1)	5 (33.3)	1 (12.5)	20 (44.4)			
2	14 (30.4)	5 (21.7)	4 (26.7)	5 (62.5)	7 (15.6)			
≥3	8 (17.4)	5 (21.7)	2 (13.3)	1 (12.5)	5 (11.1)			
Cardiovascular								
No	5 (10.9)	2 (8.7)	2 (13.3)	1 (12.5)	19 (42.2)	**0.001**	0.835	**0.017**
1	12 (26.1)	5 (21.7)	5 (33.3)	2 (25.0)	12 (26.7)			
2	13 (28.3)	8 (34.8)	2 (13.3)	3 (37.5)	11 (24.4)			
≥3	16 (34.8)	8 (34.8)	6 (40.0)	2 (25.0)	3 (6.7)			
Ophthalmic								
No	29 (63.0)	13 (56.5)	10 (66.7)	6 (75.0)	35 (77.8)	0.124	0.608	0.324
Yes	17 (37.0)	10 (43.5)	5 (33.3)	2 (25.0)	10 (22.2)			
Drug-related								
No	36 (78.3)	16 (69.6)	13 (86.7)	7 (87.5)	33 (73.3)	0.583	0.359	0.483
1	10 (21.7)	7 (30.4)	2 (13.3)	1 (12.5)	12 (26.7)			
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
Total								
No	1 (2.2)	0 (0)	0 (0)	1 (12.5)	6 (13.3)	**0.007**	0.178	0.071
1	4 (8.7)	2 (8.7)	2 (13.3)	0 (0)	8 (17.8)			
2	3 (6.5)	3 (13.0)	0 (0)	0 (0)	9 (20.0)			
≥3	38 (82.6)	18 (78.3)	13 (87.5)	7 (87.5)	22 (48.9)			

Univariable analysis with *P* according to chi-square test. Bold letters indicate *P* less than 0.05. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion.

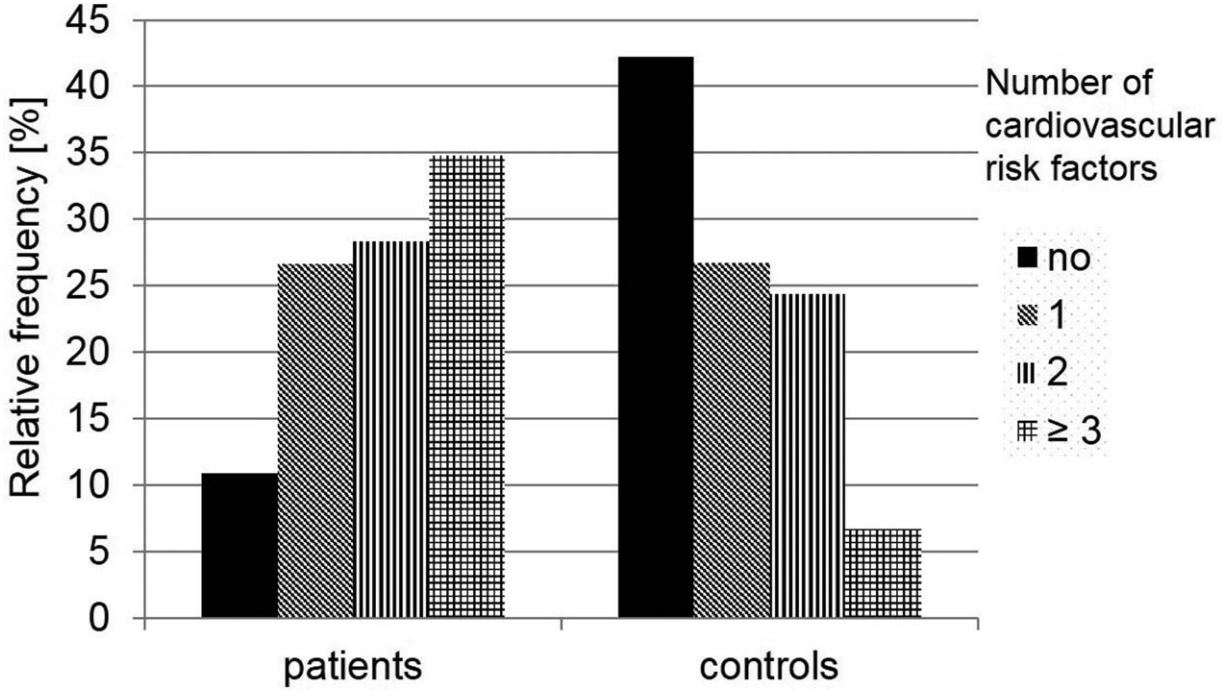

FIGURE 1 Sum of cardiovascular risk factors in patients with retinal vein occlusions versus in controls (all aged 65 years and older). Of patients with retinal vein occlusions, 34.8% had three or more, 28.3% had two, 26.1% had one and 10.9% had no cardiovascular risk factors. In contrast, of the controls, only 6.7% had three or more, 24.4% had two, 26.7% had one and 42.2% had no cardiovascular risk factors ($P < 0.001$). For exact numbers, please refer to Table 12.

Thrombophilic risk factors

In the current study, the univariable analyses revealed a higher frequency of prothrombin gene mutation, high levels of FVIII, and antithrombin deficiency and a positive history and family history of previous thrombotic events. No significant differences between the frequency of other thrombophilic risk factors and the different types of RVO were found.

Conditional regression was performed for the matched analysis. In this model, the chance of RVO was 28 and 14 times higher in persons with a history or family history of a thrombotic event, respectively, than in those without.

There is relatively good evidence for the relevance of hyperhomocysteinemia in RVO; a meta-analysis showed that plasma homocysteine is associated with an increased risk of RVO [20]. On the other hand, levels of homocysteine are not immediately elevated after CRVO, but they increase in the convalescent period [21]. Therefore, it is possible that elevated homocysteine levels may be caused by the disease process itself.

SUA has been largely addressed in the past as a possible risk factor for coronary artery disease, with a possible association with platelet hyperreactivity [49]. Therefore, we also assessed the levels of SUA between patients and controls and between the different types of RVO. In the current study, higher levels of SUA were observed in patients with RVO than in controls. As it was the aim of this study to assess the relevance of traditional risk factors for RVO and the presence of several of these risk factors, we did not further assess associations between SUA and RVO. This will be performed in a further substudy of the Gutenberg RVO Study.

TABLE 13. Multivariable binary logistic regression analysis of associations between the sum score of various risk factors and retinal vein occlusion

Number of risk factors	Odds ratio	*P*	95% CI
Cardiovascular	1.74	**<0.001**	1.31–2.32
Thrombophilic	1.38	**0.025**	1.04–1.82
Ophthalmic	1.34	0.426	0.66–2.72
Drug-related	0.66	0.342	0.29–1.55

Bold letters indicate *P* less than 0.05. CI, confidence interval.

Ophthalmic risk factors

In the current study, no associations of glaucoma or ocular hypertension with RVO were found. This result can be explained by the following limitation of the study: a large proportion of the controls were recruited at the Dept. of Ophthalmology, Mainz. In addition to other diseases – glaucoma is a special field of interest at this clinic. Therefore, the prevalence of glaucoma/ocular hypertension was almost 30% in controls versus 30% in patients with CRVO or HRVO and approximately 20% in patients with BRVO (compared with controls). This finding is in contrast with previous studies, which demonstrated that persons with increased intraocular pressure and/or glaucoma have a higher prevalence of RVO than persons with no history of elevated intraocular pressure [35,50–54]. Due to the selection of controls with a high proportion of glaucoma, the current study is strongly limited in this matter.

Drug-related risk factors

The role of contraceptives and diuretics as risk factors for RVO has been suggested previously [41]. Nevertheless, in

the current study, no associations of drug-related risk factors with RVO were found. Only one person in the control group and no patients in the RVO group took oral contraceptives, which is explained by the median age of 64 years in both groups.

Relevance of multiple risk factors

In the current study, more than one-third of the patients with RVO had systemic hypertension combined with dyslipidemia. This finding is in line with the results of a previous study by Lam *et al.* [33], where systemic hypertension, hyperlipidemia, and increased BMI were identified as important risk factors for RVO, especially in young patients with BRVO. Nevertheless, this study did not assess the relevance and associations of several risk factors in one individual as we do in the Gutenberg RVO Study.

Regarding thrombophilic risk factors, combinations were less frequently found in general. Nevertheless, in any type of RVO, the most frequent combination was hyperhomocysteinemia combined with high levels of FVIII and/or a positive family history of venous thrombosis.

We calculated sum scores for cardiovascular, thrombophilic, ophthalmic, and drug-related risk factors to assess the relevance of the cumulative number of risk factors for RVO.

There was a significant association between the number of cardiovascular risk factors and the presence of RVO. One-quarter of all patients with RVO and almost one-third of patients with BRVO had three or more cardiovascular risk factors. The relevance of the number of cardiovascular risk factors was confirmed by a multivariable logistic regression model: an increase in the cardiovascular risk sum score by one point (one additional factor) corresponded to an OR of 1.74, roughly corresponding to a RR increase of 70% in a population with low overall incidence.

Regarding the number of thrombophilic risk factors, there was a trend for more risk factors in patients than in controls. No difference was found between the different types of RVO and the number of thrombophilic risk factors. In the multivariable logistic regression analysis, there was only a statistical trend that an increase in the thrombophilic risk sum score by one point corresponded to an OR of 1.38.

Regarding the total number of risk factors, an increase in the total risk sum roughly corresponded to a RR increase of 40%. There are ND from previous studies on combinations of cardiovascular risk factors in patients with RVO. Pertaining to thrombophilic risk factors, Kuhli-Hattenbach *et al.* [19,55] retrospectively assessed the thrombophilia data of 128 patients with RVO aged younger than 65 years to estimate the prevalence of multiple thrombophilic disorders. In this study, multiple thrombophilic defects were significantly more prevalent among RVO patients than among controls. The current study was not able to confirm these results because the median age of our cohort was older than that in the study by Kuhli-Hattenbach. In the latter study, mean age was approximately 45 years, and therefore a higher rate of thrombophilic diseases and combinations of these diseases were found. We assume that thrombophilic risk factors are important in a smaller subgroup of very young patients without thrombophilic risk factors but not in the majority of patients.

Limitations

The main weaknesses of the study are the relatively small number of affected individuals and the selection of controls (e.g. high rate of patients with glaucoma in the control group). The main strength of the study is that each participant was assessed in a comprehensive and rigorous fashion. Furthermore, other observational studies that have also shown that RVO primarily is associated with hypertension and cardiovascular disorders [30–32,46,47] did not address the relevance of the presence of several risk factors in one individual.

In the current study, it was not possible to test for the effects of menopause on the prevalence of RVO as information about this variable was missing for the control group. The same holds true for differences in the IMT: here, we also were not able to test for differences between patients and controls due to missing data in the control group. Instead, the proportions of patients with IMT values lower or higher than the 25th and 75th percentiles were assessed.

In the current study, no protective effect of DOAC or VKA on RVO was observed. This might have been due to the relatively young study population, which had a low rate of overall intake of DOAC/VKA.

Conclusion

The Gutenberg RVO Study demonstrated the relevance of cumulative risk factors for RVO. The risk of an RVO increased by approximately 40% per additional risk factor (any type) and by 70% per additional cardiovascular risk factor. The most frequent combination of risk factors was hypertension combined with dyslipidemia.

The present results indicate that hypertension is a key factor in the development of RVO. Furthermore, there is an increased risk of RVO with each additional (especially cardiovascular) risk factor.

Given that RVO patients generally present to ophthalmologists, their high cardiovascular risk should result in a referral for cardiovascular assessment as part of their management protocol. We recommend obtaining a complete blood count, reviewing the medical history, and evaluating the patient for systemic hypertension (including 24-h BP monitoring), hyperhomocysteinemia, obesity, and hyperlipidemia as part of the initial workup. If no risk factors are found, a more extensive workup can be considered. Thrombophilic disorders should be screened selectively, focusing on young individuals, individuals without additional cardiovascular risk factors, or individuals with a self or family history of thrombosis.

Finally, future studies, as a follow-up to the Gutenberg RVO Study, should assess the effect of RVO treatment and modifiable risk factor reduction on the rate of recurrence and complications in these patients.

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Conflicts of interest

There are no conflicts of interest.

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