Dissertation

Genetic Polymorphism in Retinal Vein Occlusion

Submitted by

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Table of Contents

Abbreviations and Definitions

A	Adenine
BMI	Body Mass Index
BRVO	Branch Retinal Vein Occlusion
C	Cytosine
CI	Confidence Interval
CME	Cystoid Macular Edema
CRP	C-Reactive Protein
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
ELM	External Limiting Membrane
EZ	Ellipsoid Zone
FA	Fluorescein Angiography
G	Guanine
HDL	High-Density Lipoprotein
HMOX	Heme Oxygenase (Gene)
HO	Heme Oxygenase (Enzyme)
HRVO	Hemi-Retinal Vein Occlusion
IOP	Intraocular Pressure
LDL	Low-Density Lipoprotein
LPA	Lipoprotein(a) (Gene)
Lp(a)	Lipoprotein(a) (Lipoprotein)
MMP	Matrix Metalloproteinase (with hyphen when discussing the protein and without hyphen when discussing the gene polymorphism)
NVD	Neovascularisation of the Disc
NVE	Neovascularisation Elsewhere
NVI	Neovascularisation of the Iris or Angle
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography Angiography
ONL	Outer Nuclear Layer

OR	Odds Ratio
PON	Paraoxonase (with hyphen when discussing the protein and without hyphen when discussing the gene polymorphism)
RVO	Retinal Vein Occlusion
SAA	Serum Amyloid A
SNP	Single Nucleotide Polymorphism
T	Thymine
TA	Triamcinolone Acetonide
TIMP	Tissue Inhibitors of Metalloproteinases (with hyphen when discussing the protein and without hyphen when discussing the gene polymorphism)
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolism

1. Abstracts

1.1 Abstract English

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder. The exact pathomechanism remains unclear. In most cases, a crossing branch retinal artery or the central retinal artery at the lamina cribrosa seems to compress the relevant vein. However, it is suggested that other factors, particularly inflammatory ones, also contribute to the development of RVO.

In this exploratory study, we investigated possible association between certain single nucleotide polymorphisms (SNPs) and RVO. Some of these SNPs have already been studied in relation to RVO, while others have not yet been investigated. We aim to identify genetic factors associated with RVO, which would improve our understanding of its underlying pathomechanism.

Methods

This case-control study included RVO patients and control subjects. Medical history was obtained for all subjects, and ophthalmological examinations, including slit lamp, indirect ophthalmoscopy and optical coherence tomography, was performed. Blood samples were taken from all study participants and genotyped for the following SNPs: rs27071746 (HMOX-1), rs243865 (MMP2), rs4789936 (TIMP2), rs1501299 (Adiponectin), rs2241766 (Adiponectin), rs854560 (PON1), rs662 (PON1), rs12218 (SAA), rs10455872 (LPA), rs3798220 (LPA), rs8176719 (AB0) and rs8176746 (AB0).

Results

This study included 485 RVO patients and 295 control subjects. Baseline covariables such as age, selected comorbidities and medications were well balanced between the study groups except that RVO patients were more likely to have a history of stroke and venous thromboembolism and less likely to take lipid-lowering agents.

The HMOX-1 rs2071746 polymorphism was similarly distributed in both study groups (p=0.44). The MMP2 polymorphism rs243865 and the TIMP2 polymorphism rs4789936 had both similar distributions between RVO patients and control subjects (p=0.69, respectively

p=0.59). However, in patients aged 55 years and younger, the C allele at the MMP2 polymorphism was significantly associated with an increased risk for RVO (OR 16; CI 95% 2-100; p=0.012). The adiponectin polymorphism rs1501299 showed a significantly different distribution (p=0.023). Here the T allele was associated with a decreased risk for having an RVO (OR 0.74; 95% CI 0.55-0.99, p=0.041). The other adiponectin polymorphism rs2241766 showed no significant difference in allele distribution between both groups (p=0.73). The two PON1 polymorphism rs854560 and rs662 were similarly distributed between the two groups (p=0.45, respectively p=0.47). At the SAA polymorphism rs12218, the T allele was significantly associated with a lower risk of having a RVO, but only after multivariable adjustment (OR 0.60; CI 95% 0.39-0.92, p=0.020). The LPA polymorphism rs3798220 was similarly distributed in RVO patients and controls (p=0.25). The blood groups were similar distributed between the groups, in detail 31% of RVO patients and 32% of control subjects had blood group 0 (p=0.53).

Discussion

We found for RVO the T allele at the rs1501299 SNP (+ 276 G/T) in the adiponectin gene to be protective. The T allele at the rs12218 SNP in the SAA1 gene was also protective after multivariable adjustment. For patients aged 55 years and younger, the C allele at the rs243865 polymorphism in the promotor region of the MMP2 gene was a significant risk factor for RVO.

1.2 Abstract German

Einleitung

Retinale Venenverschlüsse (RVV) sind die zweithäufigsten Netzhautgefäßerkrankungen. Der genaue Pathomechanismus ist noch nicht vollständig geklärt. In den meisten Fällen scheint eine kreuzende retinale Astarterie oder die zentrale retinale Arterie auf Höhe der Lamina cribrosa die Vene zu komprimieren. Es wird jedoch angenommen, dass auch andere Faktoren, insbesondere entzündliche Prozesse, eine Rolle spielen.

In dieser explorativen Studie untersuchten wir mögliche Zusammenhänge zwischen bestimmten Einzelnukleotid-Polymorphismen (SNPs) und RVV. Einige dieser SNPs wurden bereits im Zusammenhang mit RVV untersucht, während andere bislang unerforscht waren. Ziel war es mögliche neue Risikofaktoren für RVV zu identifizieren.

Methoden

Diese Fall-Kontroll-Studie umfasste Patient*innen mit RVV und Kontrollpersonen. Bei allen Proband*innen wurde eine Anamnese erhoben und ophthalmologische Untersuchungen einschließlich Spaltlampenuntersuchung, indirekter Ophthalmoskopie und optischer Kohärenztomographie durchgeführt. Blutproben wurden von allen Studienteilnehmern abgenommen und die folgenden SNPs genotypisiert: rs27071746 (HMOX1), rs243865 (MMP2), rs4789936 (TIMP2), rs1501299 (Adiponektin), rs2241766 (Adiponektin), rs854560 (PON1), rs662 (PON1), rs12218 (SAA), rs10455872 (LPA), rs3798220 (LPA), rs8176719 (AB0) und rs8176746 (AB0).

Ergebnisse

In die Studie wurden 485 RVV-Patient*innen und 295 Kontrollpersonen eingeschlossen. Ausgangsvariablen wie Alter, ausgewählte Komorbiditäten und Medikation waren zwischen den Studiengruppen gut ausbalanciert. Allerdings hatten RVV Patient*innen häufiger einen Schlaganfall und venöse Thromboembolien und nahmen seltener lipidsenkende Medikamente ein.

Der HMOX1 SNP rs2071746 war in beiden Studiengruppen ähnlich verteilt (p=0,443). Der MMP2 SNP rs243865 und der TIMP2 SNP rs4789936 hatten ebenfalls eine ähnliche Verteilung zwischen RVV-Patient*innen und Kontrollpersonen (p=0,691 bzw. p=0,594). Allerdings war

bei Patient*innen unter 56 Jahren das C-Allel im MMP2 SNP signifikant mit einem erhöhten Risiko für RVV assoziiert (OR 16; KI 95% 2-100; p=0,012). Der Adiponektin Polymorphismus rs1501299 zeigte eine signifikant unterschiedliche Verteilung (p=0,023). Hier war das T-Allel mit einem verringerten Risiko für eine RVV assoziiert (OR 0,74; KI 95% 0,55-0,99; p=0,041). Die Genotypenverteilung des zweiten Adiponektin Polymorphismus rs2241766 zeigte keinen signifikanten Unterschied (p=0,732). Die beiden PON1-Polymorphismen rs854560 und rs662 waren ähnlich zwischen den beiden Gruppen verteilt (p=0,451, bzw. p=0,466). Im SAA SNP rs12218 war das T-Allel nach multivariabler Anpassung signifikant mit einem geringeren Risiko für einen RVV assoziiert (OR 0,60; KI 95% 0,39-0,92, p=0,020). Der LPA-Polymorphismus rs3798220 war bei RVV-Patient*innen und Kontrollpersonen ähnlich verteilt (p=0,25). Die Blutgruppenverteilung war zwischen den Gruppen ähnlich. Im Detail hatten 31% der RVV-Patient*innen und 32% der Kontrollpersonen die Blutgruppe 0 (p=0,527).

Diskussion

Unsere Studie zeigt, dass das T-Allel bei dem rs1501299 SNP (+276 G/T) im Adiponektin Gen protektiv gegen RVV scheint. Das T-Allel bei dem rs12218 SNP im SAA1-Gen war nach multivariabler Anpassung ebenfalls protektiv. Bei Patient*innen unter 56 Jahren war das C-Allel beim rs243865-Polymorphismus in der Promotorregion des MMP2-Gens signifikant mit einem erhöhten RVV Risiko assoziiert.

2. Introduction

2.1 Retinal Vein Occlusion

2.1.1 Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disorder, second only to diabetic retinopathy. The occlusion can either occur at the central retinal vein (CRVO) or at a branch of the central retinal vein (BRVO). The prevalence of RVO is about 0.4% (CRVO 0.08% and BRVO 0.32%) in the German population (1).

In around 20 percent of eyes, the veins draining the superior and inferior halves of the retina merge posterior to the lamina cribrosa, so that in case of a retinal vein occlusion at this location only one branch is affected leading to a hemi-retinal vein occlusion (HRVO) instead of a CRVO. The pathophysiology of HRVO is similar to CRVO, but it is usually managed similar to BRVO (2).

In RVO, visual acuity is decreased due to macular edema and retinal ischemia. Macular edema is the result of increased hydrostatic intravascular pressure behind the occlusion, hypoxia, endothelial dysfunction and the breakdown of the blood-retinal barrier (1).

2.1.2 Pathomechanism

CRVO results from an obstruction of blood flow in the central retinal vein at the optic nerve head or behind the lamina cribrosa. It remains unclear whether this obstruction is caused by a thrombus, as suggested in postmortem studies, or the compression of the central vein by the central artery sharing the adventitial sheath within the lamina cribrosa. Compression of the venous lumen at arteriovenous crossings is assumed to cause BRVO. Here the retinal artery and vein share an adventitial sheath. Therefore the rigidity of retinal arteries seems to play a role in RVO and explains that the main risk factors for RVO such as age and atherosclerosis coincide with risk factors for cardiovascular disease.

The turbulent blood flow at the compression site may lead to chronic endothelial damage. This endothelial damage may lead to hemorrhage and leakage resulting in macular edema.

Further, the increase in venous pressure may lead to secondary arterial constriction with retinal ischemia. Retinal ischemia induces angiogenesis by increasing levels of hypoxia-inducible

factor-1α and heme oxygenase-1 (HO-1). These factors bind to the hypoxia response elements of the target genes triggering the expression of vascular endothelium growth factor (VEGF) and various matrix metalloproteinases (MMPs) especially MMP-9. This upregulation may lead to hemorrhage and macular edema. (3)

2.1.3 Risk factors

2.1.3.1 Demographic risk factor

The incidence of RVO increases with advanced age. RVO is equally distributed between men and women. Asians and Hispanics have an increased risk of RVO compared to white individuals (4).

2.1.3.2 Ocular Risk Factors

The main ocular risk factor for RVO is glaucoma. A meta-analysis on the impact of glaucoma on RVO found a significant association with substantial differences in the RVO subtypes. An odds ratio of 6.21 was reported for CRVO and of 4.6 for HRVO suggesting glaucoma as a significant risk factor. In contrary, in BRVO the reported odds ratio was 2.38 and much lower than in CRVO and HRVO (5).
The other ocular risk factor discussed is ocular perfusion pressure. In the Singapore Malay Eye Study (6) ocular perfusion pressure was significantly associated with RVO, however, this association did not remain significant after multivariate adjustment. The Beaver Dam Eye study (11) also found this assocation. This association may be partly explained by an increased systolic blood pressure.

2.1.3.3 Cardiovascular risk factors

Systemic arterial hypertension is one of the classic risk factors for RVO. The association between systemic arterial hypertension and RVO risk was consistently found in studies. In a meta-analysis, the pooled odds ratio (OR) was 3.8 (95%CI 1.9-7.4) for CRVO and 3.0 (95%CI 2.0-4.4) for BRVO (7).
Diabetes mellitus is a risk factor associated with CRVO, but not consistently for BRVO. Again, a meta-analysis found a pooled OR of 2.0 for CRVO (95%CI 1.2-3.4) (7).

Hyperlipidemia is another cardiovascular risk factor, which is repeatedly reported in RVO. The aforementioned meta-analysis found a pooled OR of 2.5 (95%CI 1.7-3.7). However, the role of hyperlipidemia is difficult to conceive as the definition of hyperlipidemia is inconsistent across studies (7). Nevertheless, high-density lipoprotein (HDL) blood levels were found to be negatively correlated to RVO risk (8), while high low-density lipoprotein (LDL) levels and high lipoprotein(a) (Lp(a)) blood levels were associated with an increased RVO risk (9).
Current smoking has also been associated with RVO risk. Studies found an increased risk for RVO with an OR of 1.11 to 4.43 (10, 11).
In case series, RVO has been reported as a complication of inflammatory diseases such as Behcet disease, patients infected with human immunodeficiency virus, Takayasu arteritis, Churg-Strauss syndrome, sarcoidosis, ocular tuberculosis and non-Hodgkin lymphoma (12).
There are several case series of RVO in dehydrated patients (13-15). Severe dehydration increases the blood haematocrit leading to a hypercoagulable state.

2.1.3.4 Medications

There are case reports of women taking oral contraceptives developing RVO (16) and postmenopausal women on testosterone treatment (17). There was a case series of young male RVO patients associated with anabolic steroid abuse (18). However, an association or even causality cannot be assumed from case reports and series.

2.1.3.5 Obstructive sleep apnea

Glacet-Bernard et al (19) were the first to report a high prevalence of obstructive sleep apnea in their RVO patient cohort. This association was subsequently supported by two case-control studies, which demonstrated that obstructive sleep apnea is significantly linked to RVO and suggest it may represent an independent risk factor (20, 21). More recently, a large population-based study confirmed these findings, showing a nearly two-fold (1.94) increased risk of RVO in patients with obstructive sleep apnea, even after adjusting for other known risk factors (22).

2.1.3.6 Thrombophilic risk factors

Thrombophilic risk factors have often been discussed in RVO. The risk factors explored include

hyperhomocysteinemia, Factor V Leiden, methylenetetrahydrofolate reductase C677T polymorphism, prothrombin G20210A polymorphism, protein C and S deficiency, lupic anticoagulant, antiphospholipid antibody, anticardiolipin antibodies and plasminogen activator inhibitor-1 4G/5G polymorphism (23). To date, two of these factors have been associated with RVO. These are cardiolipin antibodies with an OR of 4.59 (95% CI 2.75-7.66) (24). The second is hyperhomocysteinemia, which was associated with CRVO (25) and BRVO risk (26). A meta-analysis by McGimpsey (27) found an association between hyperhomoyteinemia and RVO. It has been recommended to explore these thrombophilic risk factors in atypical RVO patients such as young patients or patients without any cardiovascular risk factors (23). In general, however, thrombophilic risk factors seem to play a minor role in the development of RVO (28, 29).

2.1.4 Symptoms and Complications

2.1.4.1 Symptoms

The clinical presentation of RVO depends largely on the site and extent of the occlusion. Central RVO typically causes a sudden, painless decrease in vision, which may range from mild blurring to severe visual loss. Branch RVO can present more subtly with localized visual field defects or distortion and metamorphopsia, and patients may not notice symptoms if the macula is spared.

2.1.4.2 Cystoid Macular Edema

The main complication of RVO leading to loss of vision is cystoid macular edema (CME; see Figure 1). The severity of vision loss depends on the involvement of the macula. More than 90% of RVO patients develop cystoid macular edema.

The exact mechanism of macular edema is not fully understood. Most probably, it is caused by several factors. The key role to its development is leakage from retinal vessels as seen in fluorescein angiography. As postulated by Starling law, fluid will leak out from vessels when hydrostatic pressure increases due to occlusion. However, leakage on fluorescein angiography does not necessarily lead to CME. This implies that fluid-removing mechanisms also play a role. Fluid is removed from the retina by the pumping ability of the RPE and Müller glial cells.

The external limiting membrane and the outer plexiform layer may also restrict the removal of CME from the midretina.

Although CME may resolve due treatment, prolonged hypoxia may result in irreversible vision loss. Vision loss due to CME is a result of photoreceptor impairment, damage to the neurons in the inner retina and neuro-retinal swelling. Photoreceptor damage in CME can be visualized on optical coherence tomography (OCT). Photoreceptors correspond to the outer nuclear layer (ONL), which reflects the cell bodies, the external limiting membrane (ELM), which reflects the adherens formed between Müller glial cells and the photoreceptor inner segments, the ellipsoid zone (EZ), which reflects the mitochondria-rich portion of the photoreceptor inner segments, and the interdigitation zone, which reflects the interface between photoreceptor outer segments and the apical processes of the RPE. The mechanism of photoreceptor loss in RVO is probably caused by subretinal blood and exudates as a consequence of leaking retinal vessels. Impairment of photoreceptors may be reversible at an early stage of the disease. Neuro-retinal swelling may lead to reduced light intensity transmission to the photoreceptors and impaired transduction from the photoreceptors to the bipolar cells (30).

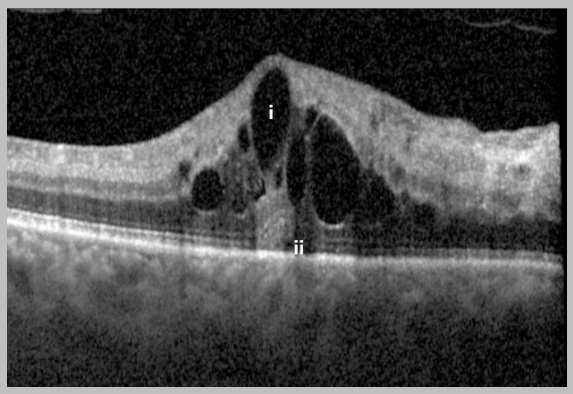

Figure 1. OCT of CME secondary to RVO. Macula of a RVO patient, who has both (i) cystoid macular edema and (ii) subretinal fluid.

2.1.4.3 Ischemia

Ischemia is another factor potentially decreasing visual acuity. The presence and extent of retinal ischemia in RVO is correlated to visual prognosis (30). Ischemic RVO carries a much

greater likelihood of ocular neovascularization and neovascular glaucoma compared with non-ischemic disease. Clinically, it is defined by severe vision loss with a relative afferent pupillary defect or by anterior/posterior segment neovascularization within the first year. Retinal ischemia can be visualized by fluorescein angiography showing non-perfused areas. Angiographically, a baseline ischemic index ≥35% has been shown to be a reliable criterion for ischemia (31). Collateralization (retina to retina anastomoses) can bypass the obstruction improving ischemia. Ischemic RVO may lead to the loss of inner retinal neurons such as bipolar and ganglion cells (30).

The risk of neovascularization in CRVO is strongly determined by both the extent and location of retinal non-perfusion. Posterior pole ischemia carries a significantly higher risk for neovascularization compared with isolated peripheral non-perfusion. In a study using ultra-widefield angiography, 84.6% of eyes with more than 10 disc areas of posterior pole non-perfusion developed neovascularization. Furthermore, the incidence of neovascularization rose progressively with increasing total non-perfusion: from 0% in eyes with <10 DA, to 14.3% in those with 10–30 DA, 20% with 30–75 DA, and as high as 80% in eyes with 75–150 DA (32).

Optical coherence tomography angiography (OCT-A) has emerged as a powerful noninvasive tool for evaluating the retinal microvasculature in RVO and, unlike fluorescein angiography, allows separate assessment of superficial and deep vascular networks (33). In RVO, OCT-A demonstrates foveal avascular zone enlargement, capillary non-perfusion, microvascular abnormalities, and vascular congestion in the superficial and deep plexus (34). Ultra-widefield OCT-A can be used to determine areas of capillary non-perfusion even in the periphery and thus can be used to differentiate ischemic from non-ischemic RVO (35).

Further, OCT-A can show collaterals (see Figure 2). Interestingly, these collaterals are located within the deep vascular complex, with none confined exclusively to the superficial vascular plexus outside the perifoveal vascular ring. This suggests that the retinal venous system is predominantly organized in series, with drainage channeled through the deep vascular complex. This may explain why macular edema in RVO primarily involves the deep vascular complex (36).

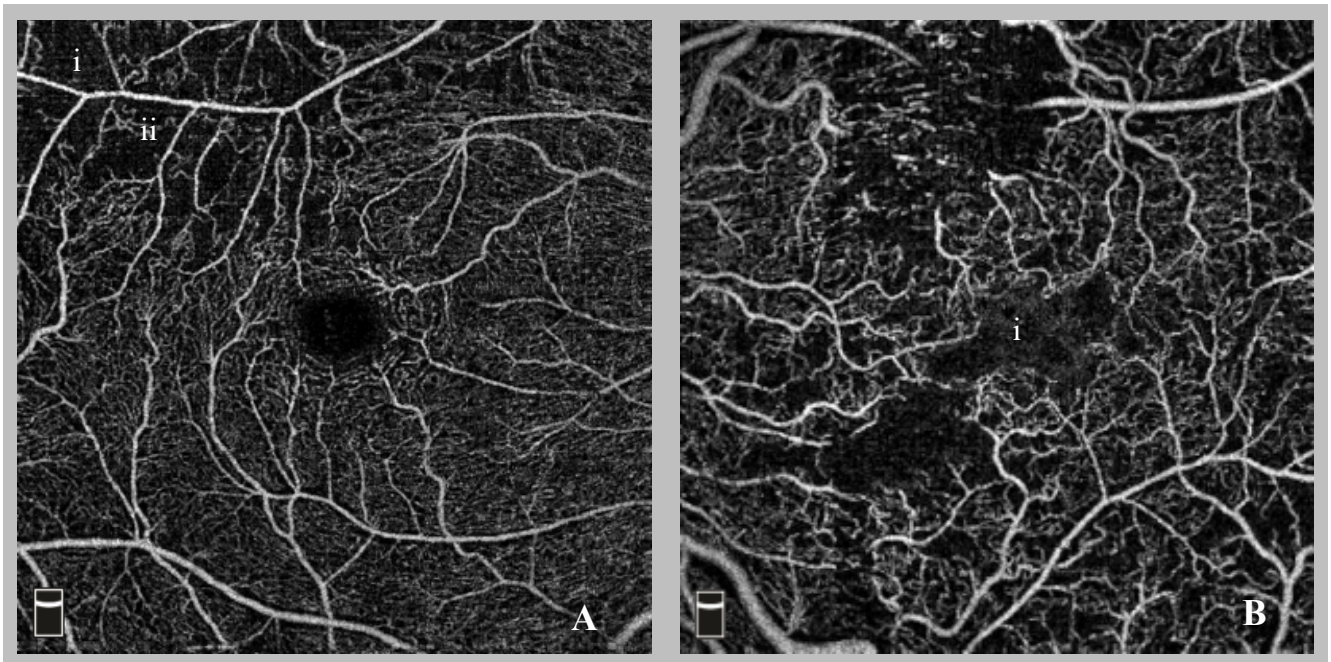

Figure 2. OCT-A of BRVO (A) and CRVO (B). OCT-A showing (i) retinal non-perfusion and (ii) collaterals.

Eyes with ischemia are at risk for ocular neovascularization (see Figure 3). Ocular neovascularization can be divided into neovascularization of the iris or angle (NVI), neovascularization of the disc (NVD) and neovascularization elsewhere (NVE). Ocular neovascularization is associated with large area of non-perfusion; however, no consensus exists on the extent of non-perfusion and the risk of neovascularization (2). In the SCORE study, risk of NVI was 8.5% in CRVO and 2.4% in BRVO within 3 years; respectively risk of NVE/NVD was 8.8% in CRVO and 7.6% in BRVO (37).

Iris neovascularization may compromise aqueous outflow leading to neovascular glaucoma. Neovascular glaucoma if treated sufficiently may have no impact on vision loss, but if left untreated may lead to severe permanent vision loss. NVD and NVE may cause vitreous hemorrhage leading to temporary severe vision loss and possibly requiring vitrectomy. Further retinal neovascularization may lead to vitreous traction, retinal tears and subsequently retinal detachment. Retinal detachment requires major ocular surgery. Untreated retinal detachment leads to permanent vision loss (4).

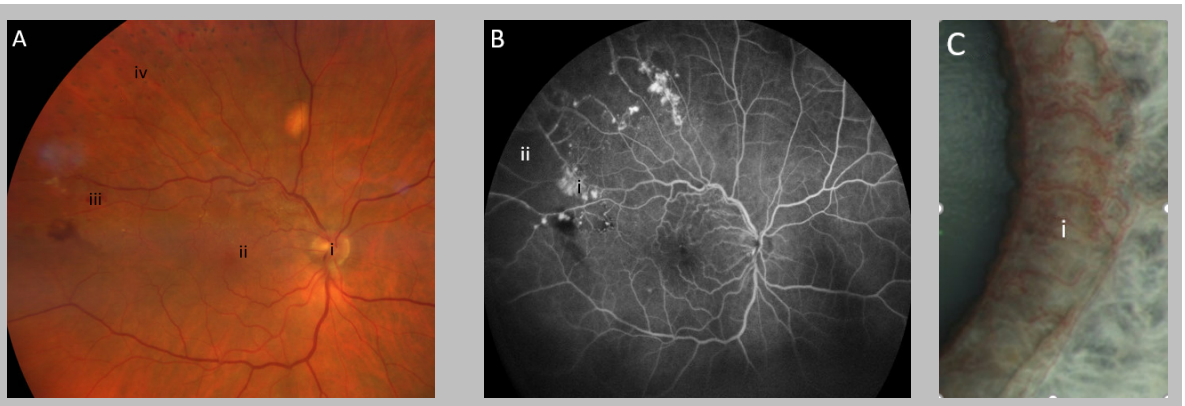

Figure 3. Images of neovascularization. Fundus image (A) of BRVO patient with markers on the optic disc (i) and macula (ii) showing NVE (iii) and sectorial lasercoagulation burns (iv). Fluorescein angiography (B) of the same BRVO patient showing NVE (i) and ischemia (ii). Slit lamp image (C) of CRVO patient with NVI (i).

2.1.5 Diagnostics

2.1.5.1 Slit lamp examination

The slit lamp examination uses a high-intensity light source with a microscope to visualize the anterior segment of the eye and through a special lens the retina.

The anterior segment of the eye needs to be examined in RVO patients to assess NVI. In case of NVI, the angle can become obstructed leading to an increase in intraocular pressure (IOP).

On fundus examination, RVO show venous dilation and tortuosity, and superficial usually flame-shaped hemorrhages. Depending on the degree of ischemia, cotton-wool spots can be found. Further macular edema may be found if present and additionally optic disc edema is often seen. With time, collaterals may develop. These signs can be found on the complete retina in CRVO, on the upper or lower retina in HRVO and upstream of the occlusion site in BRVO (38).

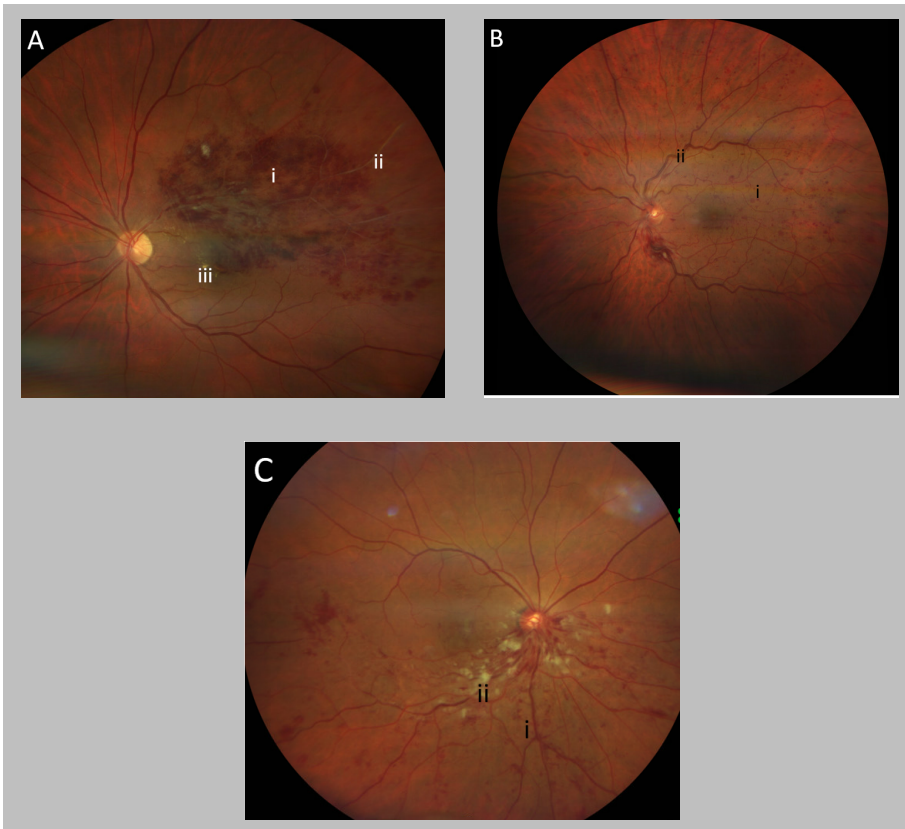

Figure 4. Fundus images of RVO. (A) Patient with BRVO showing (i) hemorrhages, (ii) ghost vessels and (iii) hard exudates. (B) Patient with CRVO showing (i) hemorrhages on the whole fundus and (ii) vessel tortuosity. (C) Patient with HRVO showing (i) hemorrhages and (ii) cotton wool spots.

2.1.5.2 Optical coherence tomography (OCT)

OCT is a fast, non-invasive and highly reliable method allowing microstructural imaging of the retina. OCT imaging can be used to determine several variables essential for diagnosis, assessment of disease activity and prognosis.

In RVO, OCT is used to define central retinal thickness (CRT). CRT is used as a major endpoint in almost all clinical trials. Its increase correlates with functional loss. Further, OCT imaging is used to evaluate the presence of intraretinal and subretinal fluid, which is used to assess disease activity and treatment response (39).

In addition to CRT and macular edema, the OCT can show other prognostic biomarkes, which may help with counseling. The presence of a preserved foveal depression in retinal vein occlusion is discussed as a potential protective factor with better visual outcome and fewer anti-VEGF injection (40). Loss of integrity of the outer retina layers, in particular the ellipsoid zone (EZ) and the external limiting membrane (ELM), and disorganization of the inner retinal layer (DRIL) have been shown to be associated with permanent functional loss (see Figure 5). Hyperreflective foci are small, dot-like, hyperreflective lesions within the retinal layers. It is hypothesized that they correspond to extravasted lipoprotein, photoreceptor and/or RPE debris, activated microglia and/or macrophages. The presence of hyperreflective foci is associated with poor visual outcome and poor response to anti-VEGF treatment (2). Another OCT finding commonly seen in RVO is paracentral acute middle maculopathy. It is characterized by hyperreflective band at the level of the inner nuclear layer on OCT and acute onset of negative scotoma. It is proposed to be caused by retinal capillary ischemia of the intermediate plexus (41). Other signs of retinal ischemia on OCT is the prominent middle liminiting mebrane which represents a hyperreflective line seen at the level of the outer plexiform layer and hyperreflectivity of the inner retinal layers which indicates a more extensive ischemia involving the deep and the superficial capillary plexus (39).

Further, OCT can help visualize and be used to follow-up the presence of vitreoretinal interface abnormalities (42). Vitreoretinal interface abnormalities may lead to further poor visual outcome and may require intervention. Chatziralli et al. (43) found in 93 RVO patients with macular edema that 16% had vitreomacular adhesions, 3% vitreomacular tractions and 18% epiretinal membranes.

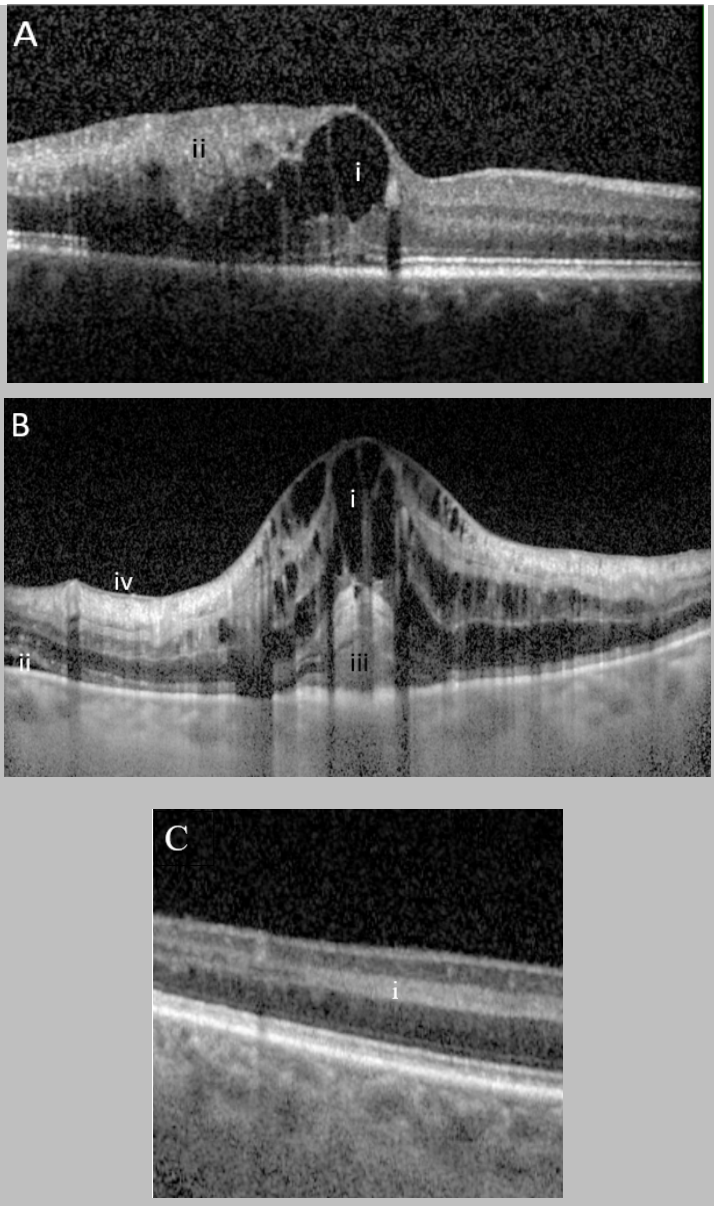

Figure 5. OCT images of RVO. (A) Patient with BRVO showing (i) intraretinal cystic edema and (ii) DRIL. (B) Patient with CRVO showing (i) intraretinal cystic edema, (ii) subretinal fluid, (iii) disruption of EZ and ELM and (iv) epiretinal membrane. (C) Patient with CRVO showing (i) paracentral acute middle maculopathy.

2.1.5.3 Optical coherence tomography angiography (OCT-A)

OCT-A allows a detailed analysis of retinal vessels in a quick and non-invasive way by using motion contrast from erythrocytes within blood vessels. It allows the visualization of the superficial and deep quantifies retinal vessel density in the retinal plexus and allows measurement of the foveal avascular zone. In comparison to fluorescein angiography (FA), OCT-A is non-invasive, allows a more detailed visualization of microvascular abnormalities and the visualization of the superficial and the deep capillary plexus in a layer-by-layer fashion (44).

Limitations of OCT-A are inability to determine the presence of leakage, segmentation errors, image artifacts caused by patient motion and inability to visualize low blood flow rates such as in microaneursyms.

In RVO, vascular perfusion is decreased in deep and superficial capillary plexus. A decrease in the vascular perfusion has also been found in the fellow eye in unilateral RVO supporting the notion of RVO as a systemic disease than a strictly ocular problem. As in fundus examination, venous dilation, vascular tortuosity, disruption of the perifoveal capillary plexus and microaneursyms can be detected in OCT-A. With time, collaterals can be found. At the level of the optic disc, optociliary shunt vessels between the retinal veins and the choroidal circulation can develop in CRVO patients. These vessels form as a compensatory mechanism to facilitate venous outflow and especially large optociliary shunt vessels may be associated with a better visual acuity (45).

Complications of RVO such as macular CME and neovascularization can be visualized by OCT-A. OCT-A allows quantification of vascular changes such as vascular density and foveal avascular zone. In RVO patients, vascular density has been shown to be decreased and foveal avascular zone to be enlarged (3).

2.1.5.3 Fluorescein Angiography

Fluorescein angiography (FA) is an imaging technique that uses fluorescent dye to visualize retinal vessels and leakage from vessels. About ten seconds after injection of fluorescein into the antecubital vein, the choroid is filled. The retinal circulation follows 1-3 seconds later. The retinal filling can be divided into an early arteriovenous phase showing the filling of the retinal

arteries, arterioles and capillaries. Then there is the late arteriovenous phase showing the filling of the veins in a laminar pattern. This is then followed by the recirculation phase, which occurs after three to five minutes. In the late phase (after around 10 minutes), the fluorescein is largely cleared from retinal vasculature, however persists in the choroid and areas of leakage.

FA permits qualitative evaluation of abnormal vascular permeability and areas of non-perfusion. A broken perifoveal capillary arcade and much capillary leakage are associated with poor prognosis. Further FA can identify ocular inflammatory diseases possibly overlooked in fundus examination. Likewise, ocular neovascularization, which in subtle cases may not be easily recognized by fundus examination, can be easily identified in FA (46).

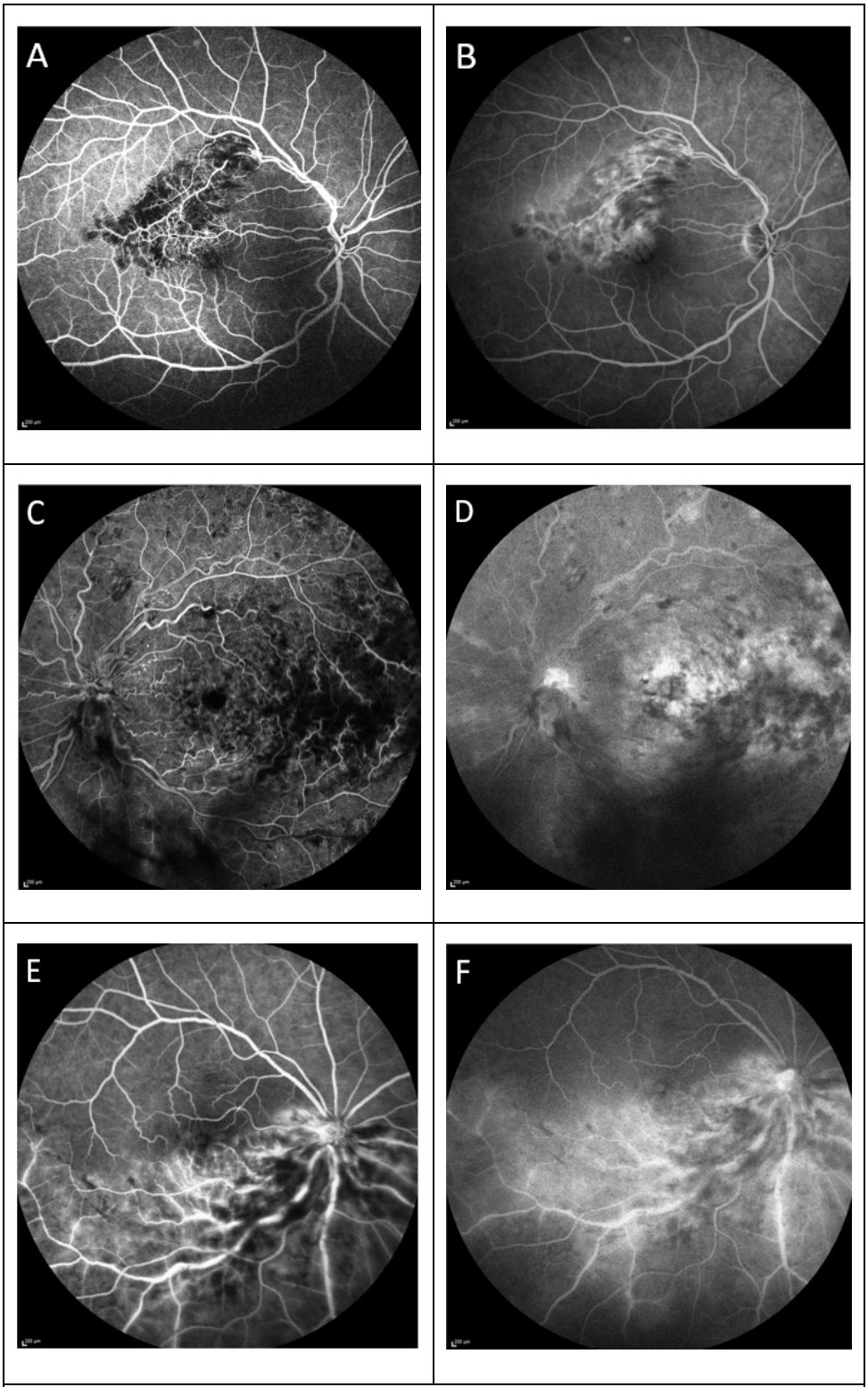

Figure 6. Fluorescein angiography of RVO. (A) Early phase and (B) late phase FLA in patient with BRVO. (C) Early phase and (D) late phase FLA in patient with CRVO. (E) Early phase and (F) late phase FLA in patient with HRVO.

2.1.6 Treatment

2.1.6.1 Treatment

Treatment of RVO is directed at complications rather than re-establishing normal venous circulation. Attempts have been made to relieve the obstruction by thrombolytic administration, to create anastomoses through surgery and laser, by inducing collaterals through radial optic neurotomoy. However, these treatments have not proven beneficial (4).

2.1.6.2 Cystoid Macular Edema

2.1.6.2.1 Laser Treatment

The first recommended treatment for CME secondary to BRVO was macular grid laser photocoagulation with argon laser (47). As more effective treatment options came along, laser treatment was soon dismissed as treatment option for CME caused by RVO. More recently, it has been explored whether peripheral laser photocoagulation to the on FA non-perfused retina may decrease CME and/or reduce the treatment burden of intravitreal VEGF inhibitors. However, no study has so far proven any benefit to this claim (3).

2.1.6.2.1 Intravitreal Steroids

Inflammation plays a vital role in the development of CME in RVO. The SCORE study (48) was the first therapeutic break-through. The study randomized 1:1:1 intravitreal triamcinolone acetonide (TA) 1mg and 4mg to standard treatment (grid laser in BRVO and observation in CRVO). In BRVO, there was no difference in the percentage of patients gaining 15 or more letters (primary endpoint) between intravitreal TA and grid laser (49). While in CRVO, the group receiving TA had a significant visual improvement compared to observation (48). Nowadays, intravitreal TA is used infrequently in practice due to better alternatives.

The GENEVA trial (50) explored 0.7mg and 0.35mg implantable dexamethasone to sham injection (1:1:1). Both arms showed a significant increase in visual acuity after 3 months, but not after 6 months, which was the primary endpoint. Dexamethasone implants are still used less commonly than VEGF inhibitors due to increased risk of side effects such as ocular hypertension and cataract formation.

2.1.6.2.1 Intravitreal VEGF Inhibitors

Intravitreal injection of VEGF inhibitors is the primary treatment for CME secondary to RVO. A meta-analysis confirmed the notion that VEGF inhibitors should be favored over steroids. It found that VEGF inhibitors showed better functional and anatomic functions with less side effects (51).

2.1.6.2.1.1 Bevacizumab

Bevacizumab is a recombinant monoclonal antibody inhibiting VEGF-A. Due to its low costs, it is widely used despite it being off-label. Its standard dose for intravitreal application is 1.25mg in 0.05ml.
The MARVEL study (52) could show that bevacizumab was not inferior to ranibizumab in the treatment of macular edema secondary to BRVO. The SCORE2 trial (53) showed similarly that visual results after treatment with bevacizumab were not inferior to aflibercept 2mg in macular edema due to central retinal vein occlusion.

2.1.6.2.1.2 Ranibizumab

Ranibizumab is a recombinant, affinity-matured monoclonal antibody fragment neutralizing VEGF-A. Its standard dose for intravitreal application is 0.5mg in 0.05ml.

The BRAVO study (54) randomized patients to ranibizumab 0.3mg, 0.5mg and sham injection in patients with BRVO. They found significant improvement in visual acuity after two years with very little side effects.

The CRUISE trial (55) investigated the use of ranibizumab for CRVO. Patients randomized to ranibizumab showed significant visual improvement for six months. After six months, patients randomized to sham injection could cross over to the treatment arm. These patients never reached the same visual improvement as the patients primarily randomized to ranibizumab suggesting that early anti VEGF treatment is paramount for achieving better visual acuity results.

The follow-up studies HORIZON (56) and RETAIN trials (57) for the BRAVO and CRUISE trial showed that visual and anatomic improvement persisted for two years, respectively four years.

2.1.6.2.1.3 Aflibercept

Aflibercept is a receptor fusion protein that binds to VEGF-A, VEGF-B and placental growth factor. Its standard dose for intravitreal application is 2mg in 0.05ml.

Two parallel randomized, double-masked, phase II trials (COPERNICUS and GALILEO) compared aflibercept to sham treatment for macular edema secondary to CRVO (58) and showed a significant improvement in visual acuity.

The VIBRANT study (59) was the trial exploring aflibercept in BRVO. They compared aflibercept to grid laser and found a significant improvement in visual acuity in the group receiving aflibercept compared to the laser group.

Aflibercept has also become available in a higher dose (8mg) and is currently being investigated for the use in macular edema secondary to RVO in the Phase 3 QUASAR trial (3).

2.1.6.2.1.4 Faricimab

Faricimab is a relatively new drug offering dual inhibition of VEGF-A and angiopoietin-2. Its standard dose for intravitreal application is 6mg in 0.05ml.

The BALATON (BRVO) and COMINO (HRVO and CRVO) trials have shown that faricimab is not inferior to aflibercept 2mg with regard to visual acuity improvement and reduction in macular edema as measured by OCT. Interestingly, a greater proportion of patients treated with faricimab achieved absence of macular leakage as assessed by FA (60)

2.1.6.3 Ocular neovascularization

Laser photocoagulation is the first-line treatment for any neovascularization due to RVO. Panretinal photocoagulation has been shown to lead to resolution of neovascularization due to RVO. There is no evidence for prophylactic laser photocoagulation (before an neovascularization due to RVO develops). However, in cases of extensive retinal ischemia and potentially poor compliance, prophylactic laser photocoagulation can be considered.

Neovascular glaucoma shows a very poor visual prognosis. Intense lowering of IOP is required. Further, laser photocoagulation can be difficult due to corneal cloudiness associated with high

IOP. In these cases, intravitreal VEGF inhibitors have been shown to cause temporarily aid in the resolution of NVI until laser photocoagulation can be applied (4).

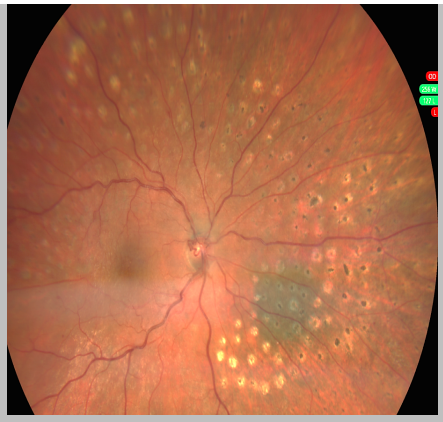

Figure 7. Laser photocoagulation of the peripheral retina in CRVO patients with neovascularization.

2.1.6.4 Medical Work-Up

Patients with RVO are at an increased risk for cardiovascular events and overall mortality (61). Further RVO patients have higher prevalence of several cardiovascular risk factors such as systemic hypertension and diabetes mellitus. This has quite some implications for prevention of cardiovascular disease.

It is recommended that RVO patients should receive a medical work-up at least at initial diagnosis. This work-up should minimally include medical history, blood pressure measurement and basic laboratory tests including blood sugar, blood count, erythrocyte sedimentation rate, and c-reactive protein. Carotid sonography, electrocardiogram, 24-hour blood pressure measurement and in selected cases sleep apnea screening should be performed. Further tests should be performed based on the history and results of initial investigation. In some RVO patients, especially young RVO patients, thrombophilia screening should be additionally performed (2).

2.2 Genetic Polymorphisms

2.2.1 Heme oxygenase-1 polymorphisms

2.2.1.1 Heme oxygenase-1

Heme consists of four porphyrin rings and a central iron ion. It plays a central role to many biological functions. It is most commonly recognized as a component of haemoglobin, myoglobin, cytochrome and endothelial nitric oxide synthase. Unbound heme is highly cytotoxic leading to the production of reactive oxygen species (62).

HO catabolizes heme into biliverdin, carbon monoxide and free iron. Biliverdin is then further catabolized into bilirubin by the biliverdin reductase. So far, two isoforms of HO have been proposed in humans. HO-1 is induced by various pathophysiological conditions such as hypoxia, oxidative stress and upregulation of cytokines. Therefore, it is hypothesized as a potential therapeutic target. HO-2 is a constitutive isoform (63).

Although the exact pathomechanism of its protective effects is still poorly understood, HO-1 is proposed to act anti-inflammatory due to the degradation of cellular pro-oxidant heme and the consequent formation of biliverdin and subsequently bilirubin and of carbon monoxide. Bilverdin, bilirubin and carbon monoxide exert anti-inflammatory and anti-apoptotic effects in several tissue and have been shown to be cardioprotective (64).

Despite its beneficial cytoprotective effects, HO-1 induction has been associated with the development and progression of cancer and neurodegenerative diseases. It seems that HO-1 may lead to these detrimental conditions due to an attempt to protect the cells from stress (65).

2.2.1.2 Heme oxygenase-1 polymorphism

The heme oxygenasis 1- polymorphism (HMOX1) is located on the chromosome 22 at 22q12. Two polymorphisms have so far attracted most attention.

The first is a guanine [G] and thymine [T] dinucleotide repeat polymorphism. The repeat length is divided into short (<25) and long depending on the amounts of repeats. This division is however not consistent in all studies (66). The shorter allele seems to facilitate HMOX-1 gene expression. In a cell model, cells with the shorter more active HMOX-1 allele survived better under oxidative stress and produced less pro-inflammatory mediators (67). This repeat polymorphism has been associated with cardiovascular disease. A recent meta-analysis

concluded that carriers of the higher (GT) number repeat allele have a higher risk of coronary artery disease (68).

Likewise, patients with higher number tandem repeat polymorphisms were more likely to suffer from cardiovascular diseases such as stroke, myocardial infarction and vascular death (66, 69).

The other polymorphism is the SNP rs2071746 located at 22q12.3 (chr22:35613296), where a thymin is changed to an adenin (68). It seems that the adenine [A] allele lead to higher HMOX-1 activity than the T allele (70).

In the Hapmap population the genotype frequency was AA 33.3%, AT 35.6% and TT 31.1%. Persons with the AA genotype had a decreased risk of coronary artery disease (68). One study investigated outcome of stroke patients, and found that patients with at least one A allele had a better outcome than patients with TT alleles (71).

There are two studies investigating HMOX-1 polymorphisms in eye diseases. Both investigated patients with age-related macular degeneration. Synowiec et al (72) found an association between the SNPs rs2071747 (HMOX-1) and rs2270363 (HMOX-2) for the occurrence and progression of AMD. Wysokinski et al (73) found no association between the SNP rs1051308 (HMOX-2) and the presence of age-related macular degeneration.

2.2.2 Matrix Metalloproteinase polymorphism

2.2.2.1 Matrix Metalloproteinase

Matrix metalloproteinases (MMP) are a family of zinc-dependent endopeptidase degrading different kinds of extracellular matrix proteins (74). The MMPs are classified according to substrate specificity into collagenases, gelatinases, stromelysins, matrilysins, membrane type and others. The gelatinases (MMP-2 and MMP-9) are of particular interest as they activate many pro-inflammatory factors. The gelatinases digest collagen type IV, a major component of the basal lamina, and tight junction proteins facilitating the migration of leukocytes through the endothelium.

MMPs are synthesized in an inactive form called zymogens containing a conserved cysteine residue, which interacts with the zinc in the active site preventing its activation. Their activation requires cleavage of this cysteine residue. The gelatinases have three common domains which are the pro-peptide, the catalytic domain with three fibronectin type II-like domains, which adhere specifically to type IV and denatured collagen, and the haemopexin-like C-terminal domain. The haemopexin-like C-terminal domain interacts with endogenous tissue inhibitors of metalloproteinases (TIMPs), which inhibit MMPs (75).

Dysregulated MMP activity seems to interrupt the integrity of the blood-brain barrier and to be pro-inflammatory. A dysregulated MMP activity has been found after stroke and is hypothesized to cause cell death, neurotoxicity, edema and haemorrhage. Although inhibition of MMP activity has been found to be beneficial to reduce edema, infarct size and haemorrhage transformation, there is emerging evidence that MMP activity may also have some beneficial activity. This is mainly contributed to its effect on angiogenesis and neurovascular remodelling suggesting a role in functional recovery after stroke (76). Nonetheless, serum MMPs seem useful biomarkers for cardiovascular events. For example high levels of MMP-2 have been associated with diastolic dysfunction, left atrial dysfunction and a higher risk of incident heart failure (77) and high levels of MMP-9 have been associated with worse functional outcome in stroke patients (78).

TIMP-2 is an endogenous inhibitor of MMP-2. If TIMP-2 is low, it can form a complex and activate the pro-MMP-2 promoting the maturity of MMP-2. If TIMP-2 is high, it can combine with MMP-2 inhibiting MMP-2 activity. The balance between MMP-2 and TIMP-2 is of critical importance in many vascular diseases (79).

In patients with RVO, higher intravitreal levels of MMP-9 have been found suggesting an involvement in the pathogenesis in RVO (80). Likewise aqueous levels of MMP-2 and MMP-9 were found increased in RVO patients (81).

2.2.2.2 Matrix metalloproteinase polymorphism

2.2.2.2.1 MMP2

The MMP2 gene is located chromosome 16q12.2. Mutations of the MMP2 gene have been found to cause several rare congenital connective tissue diseases such as Winchester syndrome and multicentric osteolysis, nodulosis and arthropathy. Many MMP2 polymorphisms have been described. In this study we will focus on the most promising SNP rs243865, which is located at 16q12.2 (chr16:55602757). This SNP is located in the promoter region of the MMP2 gene -1306 bp upstream from the transcription start site and is hence often referred to as -1306 C>T. This polymorphism (Cytosine [C] vs T allele) is in the promoter region of MMP2. The T allele seems to disrupt the promoter leading to lower MMP2 expression and activity. Thus, the CC genotype leads to a higher MMP2 activity. The CC genotype has been associated with stroke (82) and small vessel disease (83). However, a study by Nie et al could not confirm these findings (84).

Ortak et al (85) found an association with the polymorphism rs243865 in patients with RVO. The CC genotype significantly decreased the risk of RVO compared to the CT and the TT genotype. This finding remained significant even after adjusting for risk factors such as hypertension, diabetes and increased lipid levels.

This polymorphism has also been investigated in other ophthalmologic diseases such as age-related macular degeneration. However, a recent meta-analysis could not confirm this association (86). This polymorphism was not associated with glaucoma (87).

2.2.2.2.3 TIMP2

The TIMP2 gene is located on chromosome 17q25.3. The polymorphism rs4789936 at chr17:76897974 was found to be associated with lower risk of large artery atherosclerotic stroke. The T allele seems protective (88). It is classified as a synonymous variant meaning it does no alter the amino acid sequence of the TIMP-2 protein, but may result in dysregulated transcriptionof the TIMP2 gene (89).

Ortak et al (85) investigated the polymorphism rs8179090 in the TIMP2 gene. They found no association.

2.2.3 Adiponectin polymorphism

2.2.3.1 Adiponectin

Adipose tissue is not merely an energy storage, but also secretes numerous hormones. The secretion of hormones has been shown to play a critical role in cardiovascular disease. They can be pro- or anti-inflammatory. In general, the "secretome" of the visceral adipose tissue is pro-inflammatory, while the gluteal adipose tissue is anti-inflammatory (90).

One of these hormones is adiponectin, which unlike most hormones produced by adipose tissue, which contribute to obesity-related conditions, has anti-inflammatory and insulin-sensitizing properties (91). Adiponectin circulates in various forms in the bloodstream. The high-molecular weight form is considered the most active form and correlates with metabolic health (92).

Adiponectin enhances insulin sensitivity by promoting glucose uptake in muscle and liver tissue and increasing fatty acid oxidation. This helps regulate blood sugar levels and improves lipid profiles.

Adiponectin exerts anti-inflammatory properties by reducing lymphocyte recruitment, down-regulation of c-reactive protein (CRP) and inhibiting TNF-α- and NF-κB-mediated pro-inflammatory signaling. Further it reduces the expression of adhesion molecules in endothelial cells and monocytes (91).

Its levels are reduced in obese patients and in patients with insulin resistance. Conversely, weight loss and physical activity may increase adiponectin levels (91).

Reduced adiponectin levels are suggested as a risk factor for cardiovascular disease, in particular ischemic stroke (93, 94). However, in advanced cardiovascular disease such as heart failure adiponectin levels are markedly increased (95). Further, increased adiponectin levels have been associated with an increased mortality (96). This paradox may reflect the underlying disease state and systemic inflammation (91).

2.2.3.2 Adiponectin polymorphism

Although adiponectin levels have been found to increase with weight loss and physical activity, genetic factors also influence its levels and its activity. The adiponectin gene has been mapped to chromosome 3q27 spanning 17kb. Many SNPs have been described (91). However, two SNPs - rs1501299 and rs2241766 – have been consistently reported.

The polymorphism rs1501299 is located at 3q27.3 (chr3:186749046) in intron 2 of the *ADIPOQ* gene. Its influence on adiponectin expression is unclear. Although it is hypothesized that it may modulate gene expression level, this association may also simply reflect a linkage disequilibrium between this SNP and a functional SNP (97). The T allele was found to be associated with an increased risk of BRVO, but not CRVO by Demir et al (98). Christodoulou et al (99) confirmed an association of this polymorphism to RVO in patients ≥ 75 years.

The polymorphism rs2241766 is one of the most common variants of exon 2 and is located at 3q27.3 (chr3:186749619). It has been associated with serum levels of adiponectin (100). So far, no studies have investigated its association with RVO.

2.2.4 Paraoxonase-1 polymorphism

2.2.4.1 Paraoxonase-1

Paraoxonase-1 (PON-1) is a calcium-dependent enzyme responsible for the detoxification of harmful substances and associated with HDL responsible for atheroprotection. It is a member of the paraoxonase family, but is by far the most-studied due to its implication in various diseases.

PON-1 is predominantly found in the liver and secreted into the bloodstream, where it binds to HDL. PON-1 enhances the antioxidative activity of HDL by hydrolyzing oxidized LDL-cholesterol and cleaving phospholipid peroxidation adducts and subsequently leading to its atheroprotective effects (101). This could be shown in a mouse model, where transgenic mice overproducing PON-1 had significantly less atherosclerosis than their wild-type counterparts (102). Further PON-1 by itself may have some antioxidative properties by hydrolyzing homocysteine thiolactone, which might protect against N-homocysteinylation, a process by which homocysteine is incorporated into other proteins and proposed to lead to cell damage (101).

It is suggested that low levels of PON-1 activity are linked to increased cardiovascular risk. This association is primarily hypothesized to be due to its contribution to the anti-oxidative capacity of HDL. Kunutsor et al (103) could show a significant inverse correlation regarding cardiovascular vascular disease and PON-1 activity, which was however dependent on HDL levels (103). PON-1 activity was found to be significantly lower in patient with coronary heart disease in a study by Sharma (104). However, this could not be confirmed by a subsequent study by Azarsiz (105).

2.2.4.2 Paraoxonase1 polymorphism

The human PON1 gene is on chromosome 7 located next to PON2 and PON3. Two common polymorphisms have been reported to affect PON-1 activity and concentration. One is rs854560 located at 7q21.3 (chr7:94937442) and is also known as L55M. The variant rs854560(T) encodes a methionine leading to elevated PON-1 levels. The variant rs854560(A) encodes leucine with less activity. The second is the polymorphism rs662, known as Q192R. It is located at 7q21.3 (Chr7:94938804). The rs662(A), encoding glutamine, has higher enzymatic activity leading to lower heart disease risk. The rs662(G) variant encodes an arginine (101).

The rs662 polymorphism was proposed to be a longevity gene with carriers of the RR and QR genotypes having a higher probability of reaching high ages (106). However subsequent meta-analysis (107, 108) disproved this hypothesis both for the rs662 and for the rs854560 polymorphism.

The rs662 polymorphism was also associated with coronary heart disease, but only in smokers (109). The rs662 polymorphism was associated with ischemic stroke (110).

2.2.5 Serum Amyloid A polymorphism

2.2.5.1 Serum Amyloid A

Serum Amyloid A (SAA) is an acute-phase protein primarily produced by the liver. It plays a crucial role in the acute-phase response subsequent to inflammation, infection and/or trauma intended to re-establish homeostasis. Its levels can rise significantly and thus it can be used as a marker for various inflammatory conditions (111).

SAA are present in quite low levels in healthy individuals (around 20-50 mcg/ml). Their levels can rise 1000-fold within 24 hours during acute-phase response and fall rapidly after homeostasis is reached (111).

In blood SAA is partitioned into HDL, possibly changing its characteristics, inducing recruitment of immune cells to sites of inflammation. SAA also binds bacteria, which is consistent with the notion that SAA is part of the primordial host defense and innate recognition system. Aside from this, it has been implicated in various processes including wound healing and tissue remodeling. However, its role and function in host defense and inflammation is still unknown. Their small size makes enzymatic activity unlikely.

SAA proteins are small and have a poor aqueous solubility. This poor aqueous solubility would also explain its tendency to associate with HDL.

Besides its role in acute infection, elevated SAA levels have also been found in chronic diseases such as rheumatoid arthritis and atherosclerosis (111).

2.2.5.2 Serum Amyloid A polymorphism

The SAA sequence is highly conserved region in mammals. Only SAA1 and SAA2 genes encode acute-phase SAA. All of the genes inducing acute-phase SAA synthesis are clustered within a 160kb region of chromosome 11p15.1.

Two chromosomal regions affecting SAA blood levels were identified in a genome-wide association study. The first region on chromosome 11p15.5-p13 contains the SAA gene family. The second region on chromosome 1p31 contains the leptin receptor implicating leptin with SAA biology (111).

The SNP rs12218 on chromosome 11p15.1 (chr11:18231142) has been found to affect activity with the T allele showing greater activity. This SNP has been associated not only with serum SAA levels, but also lipid levels (i.e. triglycerides, total cholesterol and low-density lipoprotein) (112). This polymorphism has not been investigated in RVO, so far. However associations have

been found with myocardial infarction (113), stroke (114, 115) and coronary artery disease (116).

2.2.6 Lipoprotein(a) polymorphism

2.2.6.1 Lipoprotein(a)

Lp(a) is a genetically determined lipoprotein that plays a significant role in cardiovascular health and atherosclerosis. Atherosclerosis is a chronic inflammatory lipid-fuelled disease characterized by progressive accumulation of lipids such as oxidized LDL, necrotic cell debris and extracellular matrix proteins in the vessel walls. This accumulation leads to total or partial occlusion of the vessel walls or to occlusion by a ruptured atherosclerotic plaque. Lp(a) is in its physical and chemical characteristics similar to LDL and thus considered a likely candidate and strong predictor of atherosclerosis. Its exact function is still unknown. At the moment its function is hypothesized similar to LDL. Like LDL, Lp(a) can enter the intima of arteries and aortic valve leaflets, and can be taken up by macrophages to produce foam cells (117).

The liver is the only site of Lp(a) synthesis. Its production is mainly genetically determined and only minimally impacted by diet and environmental factors. The site of Lp(a) clearance is still debated between the liver and kidneys (118).

Lp(a) compromises two components – an apoliprotein B-100 and apolipoprotein(a). The hydrophilic apo-B100 is located around a lipid core of cholesteryl esters, phospholipids and unesterified cholesterol. Apo(a) is extremely variable in size within and between individuals. This is due to the presence of two genetically determined apo(a) isoform sizes (118).

Lp(a) levels are primarily genetically determined. Unlike other serum lipids, lifestyle changes such as diet and exercise has little to no effect of Lp(a) levels. This genetic determination means that Lp(a) levels are relatively stable throughout an individual's life. It seems to be inherited in an autosomal dominant manner (118).

Lp(a) levels range from <0.1 to more than 200mg/dl and are skewed towards lower values. The relatively few patients with high Lp(a) levels display high cardiovascular risk (119). Elevated Lp(a) levels are known causal risk factors for cardiovascular disease such as myocardial infarction, atherosclerotic stenosis and aortic valve stenosis (120).

Lp(a) serum levels have been found thoroughly investigated in RVO patients. Of the five studies investigating Lp(a) levels in RVO patients, four found significantly higher Lp(a) levels in RVO patients than in controls (9, 121-123). One study by Wang et al (11) could not confirm this and found no significant differences.

2.2.6.2 LPA polymorphism

The LPA gene has evolved through replication and modification of the plasminogen gene. The LPA gene is found on chromosome 6q, which also harbours the plasminogen gene. The LPA gene includes kringles. The kringle domains are triple loop structures stabilized by three internal disulfide bonds. This structure is present in many coagulation factors (including plasminogen and prothrombin) (117). The kringle repeats (especially the K4 domain) vary in numbers leading to the highly polymorphic size of Lp(a) (119).

The LPA gene is the major influencing factor for Lp(a) plasma levels. A genome wide association study found that two SNPs (e.g. rs10455872 and rs3798220) account for 36% of Lp(a) levels (124). The rs10455872 polymorphism is located within the LPA gene at 6q25.3 (chr6:160589086) (125). The rs3798220 polymorphism is also located within the LPA gene at 6q25.3 (chr6:160989154) (126). Further a study by Clarke et al (127) found that besides Lp(a) levels these two SNPs were also associated with Lp(a) protein size and kringle repeats. These two SNPs have been associated with myocardial infarction (rs 10466872 OR 1.7 and rs3798220 OR 1.92) (128), heart failure (rs 10466872 OR 1.16 and rs3798220 OR 2.06) (129), and ischemic stroke (rs 10455872 OR 1.23 and rs3798220 OR 1.32) (130). Another study by Langsted et al (131) could not find an association between the rs10455872 genotype and cardiovascular mortality. At the moment, there is no known explanation for the association between the two above mentioned SNPs and Lp(a) serum levels. This however, does not invalidate their use as a risk factor (129).

There are no studies so far on RVO and the LPA gene.

2.2.7 ABO polymorphism

2.2.7.1 ABO Blood group

Karl Landsteiner discovered the first human blood group the ABO blood group system in 1901. It is still the most recognized method for classifying blood. It describes the presence of A and B antigens on erythrocytes. It categorizes patient into Type A (A antigens on erythrocyte, anti-B antibodies), Type B (B antigens on erythrocytes, anti-A antibodies), Type AB (A and B antigens on erythrocytes) and Type O (neither A nor B antigens on erythrocytes, anti-A and anti-B antibodies). It is primarily known as a system important for blood transfusion as a mismatch with the presence of antibodies in the plasma may cause potentially fatal adverse reaction (132, 133).

Multiple studies have found that individuals with non-O blood group are at an increased risk for venous thromboembolism and thromboembolic events such as stroke and myocardial infarction (134).

One of the possible explanations for the pathomechanism by which ABO phenotypes influences the risk of thromboembolism is the correlation between ABO blood group and level of von Willebrand's factor. Plasma levels of von Willebrand's factor have been reported to be approximately 30% higher in non-O individuals, which might predispose them to pathologic clot formation. The A and B antigens have also been found on von Willebrand's factor. One suggestion is that these antigens may affect the secretion of von Willebrand's factor into the plasma or its clearance (133).

To our knowledge, there are only two studies reporting on ABO blood group and RVO. White et al (135) reported no association, while Borella et al (136) found that non-O blood groups had an increased risk for RVO.

2.2.7.2 ABO blood group genetics

The ABO blood group system is a well-known genetic risk factor for thrombotic vascular diseases with the Non-O blood type being an independent risk factor. It has been associated with stroke (137, 138), coronary artery disease (139, 140), myocardial infarction (141) and venous thromboembolism (142, 143) in several studies.

To determine blood group, we determined two SNPs - rs8176719 and rs8176746. The rs8176719 polymorphism is located within the ABO gene on chromosome 9 (chr9:133257521). The rs8176746 polymorphism is also located within the ABO gene on chromosome 9

(chr9:133255935). Individuals with type A had a G allele at rs8176719 and a T allele at rs8176746. Individuals with type B had a C or G allele at rs8176719 and an A allele at rs8176746. Individuals with type AB had a T and A allele at rs8176746. Individuals with type O had a C and C allele at rs8176719 and a T allele at rs8176746.

Although these two SNPs are commonly used, there is a small chance of error. If there is a G at the rs8176719 site it encodes blood group type A, type B or type AB (see above). However theoretically, a person with G genotype can still be type O due to brought about mutations in another SNP.

2.3 Study Purpose

Although numerous risk factors for RVO have been identified, the exact pathophysiological mechanism underlying this condition remains incompletely understood. Notably, a subset of patients with RVO present in the absence of any established systemic or ocular risk factors, suggesting that additional, as yet unrecognized, contributors may be involved in disease development.

In this study, we hypothesize that specific SNPs may influence the susceptibility to RVO by contributing to its underlying pathogenesis. Our investigation focuses on a selection of general SNPs, some of which have previously been examined in the context of RVO, while other have not been studied in this patient population.

The aim of this work is to determine whether the aforementioned SNPs are associated with RVO risk, thereby providing evidence that genetic factors may play a contributory role in the disease.

3. Methods

3.1 Study Design

This study was designed as a case-control study. The Medical University Graz was the only study center.

3.2 Patients

3.2.1 Recruitment of Study Population

Patients with RVO were recruited at initial diagnosis at the outpatient clinic for medical retina at the Department of Ophthalmology, Medical University Graz. Control patients were recruited at the day unit for cataract surgery or at preliminary examination for cataract surgery at the Department of Ophthalmology, Medical University Graz.
We explained the purpose, the extent and possible side effects of the study participation to each study subject. Subjects were then asked to sign a consent form.

3.2.2 Sample Size Calculation

Assuming a 25% prevalence of the SNP in controls, a matched-case-control study design with a correlation of 0.5 between cases and controls, a 1:2 matching of cases and controls, a power of 90%, an alpha of 0.05, and an odds ratio for the SNP of 2, we required 287 cases and 574 controls.

3.2.3 Inclusion Criteria

Inclusion criteria for RVO patients were the presence of RVO confirmed by fundus examination, optical coherence tomography and if required fluorescein angiography. Control patients required fundus examination and optical coherence tomography images without the presence of retinal diseases such as RVO, age-related macular degeneration, epiretinal gliosis and any signs of inflammatory diseases.

3.2.4 Exclusion Criteria

Exclusion criteria were age under 18, incapacity to consent or withdrawal of consent, and any ocular pathology which interferes with the study relevant measurements.

3.2.4 Pre-Study Screening

The following examinations were performed to screen patients for inclusion.

- Recording of the medical history and concomitant medication
- Best-corrected visual acuity
- Slit lamp biomicroscopy
- Indirect ophthalmoscopy
- Spectralis® OCT device (Spectralis, Heidelberg Engineering, Heidelberg, Germany)

3.3 Visit procedures, measurements and assessments

3.3.1 Visit procedures

Patients were screened at the Department of Ophthalmology, Medical University Graz. After obtaining written informed consent, patients were included to the study. In most cases, patients were included on the same day as screening. Medical history was taken and thereafter blood was collected.

3.3.2 Medical history

Patients were asked about their body weight, height, their medical history including arterial hypertension, diabetes mellitus, smoking history, stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism, and their current medication especially the use of anticoagulants, antiplatelet drugs and lipid-lowering drugs.

3.3.3 Blood Sample Collection

Patients were asked for blood samples at the initial study visit. Blood samples were drawn from the antecubital vein. Of each subject two EDTA Tubes (VACUETTE®, GreinerBioOne, Kremsmünster, Austria, 5 ml K3E K3EDTA), one lithium heparin tube (VACUETTE®, GreinerBioOne, Kremsmünster, Austria, Tube 8 ml LH Lithium Heparin) and two serum tubes (VACUETTE®, GreinerBioOne, Kremsmünster, Austria, Tube 6 ml Z Serum Separator Clot Activator) were collected.

The EDTA tubes were sent to the Clinical Institute for Medical and Chemical Laboratory Diagnostics (KIMCL), Medical University Graz, for further analysis. The lithium heparin tube was sent for analysis of full blood exam, serum concentrations of cholesterol and triglycerides, GOT, GPT, C- reactive protein (CRP) and Lipoprotein A (Lp(a)) were determined by standard methods at the Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz. The two serum tubes were centrifuged at 1.00G at 4°C for 15 minutes. The tubes were aliquoted, stored at -80°C.

3.4 Variables

3.4.1 Demographic Variables

i. Sex
ii. Age
iii. Body Mass Index

3.4.2 Genetic polymorphism

i. rs27071746 (HMOX1)
ii. rs243865 (MMP2)
iii. rs4789936 (TIMP2)
iv. rs1501299 (Adiponectin)
v. rs2241766 (Adiponectin)
vi. rs854560 (PON1)
vii. rs662 (PON1)

viii. rs12218 (SAA)
ix. rs10455872 (LPA)
x. rs3798220 (LPA)
xi. rs8176719 (AB0)
xii. rs8176746 (AB0)

3.4.3 Ophthalmologic Variables (RVO eyes only)

i. Affected eye (right, left or bilateral)
ii. Type of RVO (BRVO, HRVO or CRVO)

3.4.4 Systemic Risk Factors

i. Systemic arterial hypertension
ii. Diabetes mellitus
iii. Smoking
iv. Stroke
v. Myocardial infarction
vi. Anticoagulants
vii. Antiplatelet drugs
viii. Lipid-lowering drugs
ix. Deep vein thrombosis
x. Pulmonary embolism

3.5 Genotyping

Genomic DNA was extracted from anticoagulated whole blood samples using the MagNA Pure the MagNA Pure instrument (Roche, Vienna, Austria). Genotyping was carried out using the 5'-exonuclease (TaqMan™) technology, a reliable and widely used method for SNP detection. To ensure the accuracy and consistency of the genotyping process, we performed a quality control step by repeating the analysis on 48 randomly selected samples. The results from both

rounds of analysis were identical, with no discrepancies observed, confirming the reliability of the genotyping procedure.

3.6 Statistics

Statistical analyses were performed by Florian Posch (MSc in Statistics, London School of Hygiene & Tropical Medicine) using Stata 15.1 (Stata Corp., Houston, TX, USA). Continuous variables were expressed as medians with the corresponding interquartile range (25^{th}-75^{th} percentile), while count data were presented as absolute frequencies with corresponding column percentages. The distribution of continuous and categorical variables across different groups (e.g. patients vs. controls) were assessed using appropriate statistical tests including ranksum-tests, Kruskal-Wallis tests, χ^2-tests, Fisher's exact tests, and a non-parametric test for trend among ordered groups.

The association between SNPs and patient/control status was examined using three co-primary univariable logistic regression models: the "dominant" model, the "recessive" model, and the "co-dominant" model. Multivariable adjustments were performed by including age and sex as covariates instead of age- and sex-matching of controls, as well as variables that showed statistically significant differences between SNP groups, and/ or between patients and controls. In addition to the main analyses, we performed two subgroup evaluations to further explore potential genotype–phenotype relationships. First, we investigated whether the associations between polymorphisms and RVO were more pronounced in younger patients (≤55 years), under the rationale that genetic factors may play a larger role in individuals with fewer conventional vascular risk factors. Second, we analyzed whether specific genotypes were associated with bilateral RVO, as this clinical presentation may represent a more severe phenotype with stronger systemic or genetic contributions.

3.7 AI Use Statement

AI tool ChatGPT 3.5 (OpenAI, 05/06/2025; https://chatgpt.com) was used only for grammar correction and language polishing. No AI tools were used for generating ideas, analysis or conclusions.

4. Results

4.1 Demographics

This study cohort included 781 subjects. Baseline covariables such as age, selected comorbidities and medications were mostly well-balanced between RVO patients (n=485, 62%) and control subjects (n=295, 38%). However, patients had a significantly higher prevalence of a history of stroke and venous thromboembolism (VTE) than controls. In contrast, control subjects had a higher prevalence of taking lipid-lowering agents (see Table 1).

Variable	**n (%miss.)**	**Controls (n=296)**	**Patients (n=485)**	**p***
Demographic variables				
Age (years)	781 (0%)	74 [66-80]	72 [64-79]	0.43
Female sex	781 (0%)	163 (55%)	237 (49%)	0.08
BMI (kg/m²)	642 (18%)	27 [24-30]	27 [24-29]	0.81
Current smoker	656 (16%)	43 (16%)	48 (12%)	0.13
RVO variables				
Laterality of RVO		/	/	N/A
---Both eyes	/	N/A	15 (3%)	/
---Left eye	/	N/A	243 (50%)	/
---Right eye	/	N/A	227 (47%)	/
Type of RVO		/	/	N/A
---Branch	/	N/A	303 (63%)	/
---Hemiretinal	/	N/A	16 (3%)	/
---Central	/	N/A	166 (34%)	/
Comorbidity variables				
Arterial hypertension	719 (8%)	220 (75%)	304 (72%)	0.29
Diabetes mellitus	694 (11%)	47 (16%)	73 (18%)	0.45
Stroke	691 (12%)	15 (5%)	40 (10%)	**0.018**
Myocardial infarction	688 (12%)	18 (6%)	24 (6%)	0.98
VTE	669 (14%)	11 (4%)	43 (11%)	**<0.001**
Selected co-medications**				
Anticoagulants	671 (14%)	55 (19%)	52 (14%)	0.08
Platelet inhibitors	674 (14%)	69 (23%)	106 (28%)	0.20
Lipid-lowering agents	670 (14%)	80 (27%)	76 (20%)	**0.031**

Table 1. Baseline characteristics of the study population (n=781). Distribution overall and by patient/control status. Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. n (%miss.) reports the number of patients

with fully observed data for the respective variable (% missing). *p-values are from ranksum-tests, χ^2-tests, and Fisher's exact tests, as appropriate. **Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); **Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; **Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. ***no formal testing was performed for the comparison of lipoprotein(a) levels between patients and controls because lipoprotein(a) levels were only measured in 4 (<1%) out of 295 controls. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, N/A – not applicable, VTE – Venous thromboembolism.

4.2 Heme oxygenase-1 gene (HMOX1)

All study participants were genotyped for the rs2071746 polymorphism. In one RVO patient and in one control patient genotyping failed. The 779 study participants showed a distribution of 30%, 51% and 19% for the AA, AT and TT genotypes, respectively, which follows the Hardy Weinberg equilibrium (p=0.09). The HMOX1 rs2071746 genotype distribution revealed no significant differences between RVO patients and controls (see **Table 2**).
The odds ratio (OR) for having a RVO in patients with at least one T (risk) allele was 1.1 (CI 95% 0.8-1.5, p=0.56) using the dominant model and 0.85 (CI 95% 0.59-1.22, p=0.37) in patients with TT using the recessive model. The different regression models (dominant, recessive, and co-dominant) consistently showed non-significant associations, even after adjusting for age, sex, and comorbidities (see **Table 3**).
When baseline characteristics were stratified by genotype, two clinically relevant associations emerged. First, the prevalence of diabetes mellitus was significantly higher among carriers of the TT genotype (25%) compared to AA (11%) and AT (18%) (p=0.005). Second, lipid-lowering agent use was significantly less common among TT carriers (15%) than in AA (24%) or AT (26%) carriers (p=0.046, see **Table 4**).
In a subgroup analysis investigating young patient (55 years and younger), we found no sifgnificant association with HMOX1 genotypes regardless of the regression model used (p=0.54). Likewise in a subgroup analysis investigation patients with bilateral RVO, we foud no significant association (p=0.20).

Variable	NMP (‰)	Overall (n=781)	Controls (n=296)	Patients (n=485)	p*
***HMOX1*rs2071746**	2 (2.6‰)	/	1 (3‰)	1 (2‰)	0.44
---AA	/	236 (30%)	93 (32%)	143 (29%)	/
---AT	/	397 (51%)	142 (48%)	255 (53%)	/
---TT	/	146 (19%)	60 (20%)	86 (18%)	/

Table 2. Distribution of *HMOX1*rs2071746. Distribution overall and by patient/control status. Data are absolute frequencies (column %) for count data. NMP (‰) reports the number of missing patients. *p-values are from ranksum-tests.

Model type	Groups	Univariable Odds ratio (95%CI, p)	Multivariable Odds ratio #1* (95%CI, p)	Multivariable Odds ratio #2** (95%CI, p)
„Dominant“	AA	Ref.	Ref.	Ref.
	AT+TT	1.10 (0.80-1.50, p=0.56)	1.11 (0.81-1.52, p=0.52)	1.24 (0.87-1.76, p=0.23)
„Recessive“	AA+AT	Ref.	Ref.	Ref.
	TT	0.85 (0.59-1.22, p=0.37)	0.84 (0.58-1.22, p=0.36)	0.81 (0.54-1.22, p=0.31)
„Co-Dominant“	AA	Ref.	Ref.	Ref.
	AT	1.17 (0.84-1.63, p=0.36)	1.18 (0.85-1.65, p=0.33)	1.35 (0.93-1.95, p=0.11)
	TT	0.93 (0.61-1.42, p=0.74)	0.94 (0.61-1.43, p=0.76)	0.98 (0.61-1.57, p=0.92)

Table 3. Uni- and multivariable logistic regression models of patient/control status. *#1 means that the association between *HMOX1*rs2071746 genotype and patient/control status is adjusted for age and sex. **#2 means that the association between *HMOX1*rs2071746 genotype and patient/control status is adjusted for age, sex, stroke, VTE, and diabetes. Abbreviations: 95%CI – 95% confidence interval, p – Wald test p-value, Ref. – Reference category, AA – *HMOX1*rs2071746 genotype with two adenine alleles, AT – genotype with one adenine and one thymine allele, TT – genotype with two thymine alleles.

Variable	AA (n=236)	AT (n=397)	TT (n=146)	p*
Demographic variables				
Age (years)	73 [64-80]	74 [66-80]	72 [63-78]	0.25
Female sex	117 (50%)	207 (52%)	75 (51%)	0.82
BMI (kg/m²)	27 [24-29]	26 [24-29]	27 [25-31]	0.3
Current smoker	23 (12%)	51 (15%)	17 (14%)	0.44
RVO variables**				
Laterality of RVO	/	/	/	/
---Both eyes	5 (4%)	8 (3%)	2 (2%)	/
---Left eye	61 (43%)	136 (53%)	46 (53%)	/
---Right eye	77 (54%)	111 (44%)	38 (44%)	/
Extent of RVO	/	/	/	0.67
---Branch RVO	89 (62%)	155 (61%)	59 (69%)	/
---Hemiretinal RVO	5 (4%)	10 (4%)	1 (1%)	/
---Central RVO	49 (34%)	90 (35%)	26 (30)	/
Comorbidity variables				
Arterial hypertension	147 (69%)	276 (75%)	100 (75%)	0.25
Diabetes mellitus	23 (11%)	66 (18%)	31 (25%)	**0.005**
Stroke	16 (8%)	32 (9%)	7 (5%)	0.46
Myocardial infarction	14 (7%)	23 (6%)	5 (4%)	0.50
VTE	13 (7%)	30 (9%)	11 (9%)	0.67
Selected co-medications***				
Anticoagulants	30 (15%)	57 (17%)	19 (15%)	0.82
Platelet inhibitors	49 (25%)	96 (28%)	30 (23%)	0.51
Lipid-lowering agents	47 (24%)	89 (26%)	20 (15%)	**0.046**

Table 4. Distribution of baseline characteristics by *HMOX1* rs2071746 genotypes (n=779). Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher's exact tests, as appropriate. **RVO variables are only reported for the n=484 patients) but of course not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists

(phenprocoumon, acenocoumarol); ***Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; ***Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: AA – *HMOX1*rs2071746 genotype with two adenine alleles, AT – genotype with one adenine and one thymine allele, TT – genotype with two thymine alleles, BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

4.3 Matrix Metalloproteinase

4.3.1 Matrix Metalloproteinase 2 (MMP2)

All study participants were genotyped for the rs243865 polymorphism. In our study cohort of 781 patients, 61% showed a CC genotype, 33% CT genotype and 6% TT genotype. These genotypes were homogeneously distributed between RVO patients and control patients (p=0.69, **Table 5**).

The logistic regression models further reinforced this interpretation. Across dominant, recessive, and co-dominant models, the odds ratios for RVO associated with MMP2 rs243865 genotypes did not reach statistical significance in either univariable or adjusted analyses (see **Table 6**).

Looking at all study participants, patients with a C allele, which was associated with cardiovascular disease in the past, were not more likely to have a RVO (OR 1.02; CI 95% 0.56-1.86; p=0.95) even after multivariable adjustment (OR 1.08; CI 95% 0.55-2.12; p=0.83)

However, subgroup analysis revealed that in patients aged 55 years and younger the C allele was significantly associated with an increased risk for RVO (OR 16; CI 95% 2-100; p=0.012) using a recessive model. The second subgroup analysis on patients with bilateral RVO showed no significant association (p=0.57).

The baseline characteristics were similar in the genotype groups (**Table 7**).

4.3.2 Tissue inhibitor of metalloproteinase 2

Genotyping for rs4789936 failed in one of 781 study participants. Of the 780 subjects, 24% had a GG genotype, 51% GT and 25% TT. The TIMP2 rs4789936 variant showed balanced distribution across genotypes without significant differences between groups (p=0.59, see **Table 5**).

In the logistic regression model, the odds ratio for RVO did not reach any significant association with the TIMP2 rs4789936 genotype distribution across the dominant, recessive and co-dominant models. There was no signal that the T allele at rs4789936 was protective in RVO (OR 1.19; CI 95% 0.85-1.66; p=0.31, see **Table 6**).

In subgroup analysis, the association remained insignificant in patients aged 55 years and younger in the dominant (p=0.34) and the recessive model (p=0.09). Likewise the second subgroup analysis did not reveal a significant association between patients with bilateral RVO and the TIMP2 rs4789936 SNP (p=0.18).

The genotype groups did not differ in baseline characteristics (see **Table 8**).

Variable	**NMP (‰)**	**Overall (n=781)**	**Controls (n=296)**	**Patients (n=485)**	**p***
MMP2 rs243865	0 (0‰)	/	/	/	0.69
---CC	/	473 (61%)	174 (59%)	299 (62%)	/
---CT	/	260 (33%)	104 (35%)	156 (32%)	/
---TT	/	48 (6%)	18 (6%)	30 (6%)	/
TIMP2 rs4789936	1 (1‰)	/	1 (3‰)	/	0.59
---GG	/	188 (24%)	77 (26%)	111 (23%)	/
---GT	/	395 (51%)	145 (49%)	250 (51%)	/
---TT	/	197 (25%)	73 (25%)	124 (26%)	/

Table 5. Distribution of rs243865 and rs4789936 polymorphisms. Distribution overall and by patient/control status. Data are absolute frequencies (column %) for count data. NMP (‰) reports the number of missing patients. *p-values are from ranksum-tests.

Polymorphism	Model type	Groups	Univariable Odds ratio (95%CI, p)	Multivariable Odds ratio (95%CI, p)
MMP2 rs243865	**„Dominant“**	CC (n=473)	Ref.	Ref.
		CT+TT (n=308)	0.89 (0.66-1.19, p=0.43)	0.91 (0.66-1.27, p=0.58)
	„Recessive“	CC+CT (n=733)	Ref.	Ref.
		TT (n=48)	1.02 (0.56-1.86, p=0.95)	1.08 (0.55-2.12, p=0.83)
	„Co-Dominant“	CC (n=473)	Ref.	Ref.
		CT (n=260)	0.87 (0.64-1.19, p=0.39)	0.89 (0.63-1.26, p=0.51)
		TT (n=48)	0.97 (0.53-1.79, p=0.92)	1.03 (0.52-2.05, p=0.93)

Table 6. Uni- and multivariable logistic regression models of patient/control status. Reported data are uni- and multivariable odds ratios from logistic regression models with patient/control status as the dependent variable. Genotype alleles were examined as “dominant”, “recessive”, and “co-dominant” specifications. P-values ≤ 0.05 are highlighted in bold font. The multivariable model adjusts the association between polymorphisms and patient/control status for all variables that were differently distributed between patients and controls as well as the respective polymorphism genotype groups excluding laboratory parameters (see Tables 1 and 2 for chosen variables). Abbreviations: 95%CI – 95% confidence interval, p – Wald test p-value, Ref. – Reference category.

Polymorphism	**MMP2 rs243865**			
Genotype	**CC (n=473)**	**CT (n=260)**	**TT (n=48)**	**p***
Demographic variables				
Age (years)	74 [65-80]	73 [66-80]	71 [58-78]	0.27
Female sex	230 (49%)	148 (57%)	22 (46%)	0.07
BMI (kg/m²)	27 [24-29]	26 [24-30]	28 [24-31]	0.76
Current smoker	57 (14%)	29 (13%)	5 (13%)	0.92
RVO variables**				
Laterality of RVO	/	/	/	/
---Both eyes	8 (3%)	6 (4%)	1 (3%)	/
---Left eye	153 (51%)	75 (48%)	15 (50%)	/
---Right eye	138 (46%)	75 (48%)	14 (47%)	/
Extent of RVO	/	/	/	0.43
---Branch RVO	185 (62%)	96 (62%)	22 (73%)	/
---Hemiretinal RVO	10 (3%)	4 (3%)	2 (7%)	/
---Central RVO	104 (35%)	56 (36%)	6 (20%)	/
Comorbidity variables				
Arterial hypertension	323 (74%)	178 (74%)	23 (59%)	0.11
Diabetes mellitus	64 (15%)	49 (21%)	7 (18%)	0.19
Stroke	34 (8%)	19 (8%)	2 (5%)	0.75
Myocardial infarction	27 (7%)	13 (6%)	2 (5%)	0.85
VTE	35 (9%)	18 (8%)	1 (3%)	0.39
Selected co-medications***				
Anticoagulants	73 (18%)	31 (14%)	3 (8%)	0.16
Platelet inhibitors	97 (24%)	64 (29%)	14 (35%)	0.15
Lipid-lowering agents	98 (24%)	53 (24%)	5 (13%)	0.25

Table 7. Distribution of baseline characteristics by rs243865 polymorphism in the MMP2 gene (n=781). Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher's exact tests, as appropriate. P-values ≤0.05 are highlighted in bold font. **RVO variables are only reported for the n=485 patients but of course not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban,

rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

Polymorphism	**TIMP2 rs4789936**			
Genotype	**GG (n=188)**	**GT (n=395)**	**TT (n=197)**	**p***
Demographic variables				
Age (years)	73 [66-80]	73 [65-79]	72 [64-80]	0.66
Female sex	100 (53%)	189 (48%)	110 (56%)	0.15
BMI (kg/m²)	26 [24-29]	27 [24-30]	27 [24-30]	0.90
Current smoker	19 (12%)	48 (14%)	24 (15%)	0.76
RVO variables**				
Laterality of RVO	/	/	/	/
---Both eyes	1 (1%)	9 (4%)	5 (4%)	/
---Left eye	67 (60%)	114 (46%)	62 (50%)	/
---Right eye	43 (39%)	127 (51%)	57 (46%)	/
Extent of RVO	/	/	/	0.80
---Branch RVO	65 (59%)	156 (62%)	82 (66%)	/
---Hemiretinal RVO	4 (4%)	9 (4%)	3 (2%)	/
---Central RVO	42 (38%)	85 (34%)	39 (31%)	/
Comorbidity variables				
Arterial hypertension	121 (71%)	267 (74%)	135 (72%)	0.78
Diabetes mellitus	30 (18%)	64 (18%)	26 (15%)	0.63
Stroke	15 (9%)	29 (8%)	11 (6%)	0.62
Myocardial infarction	11 (7%)	16 (5%)	15 (9%)	0.16
VTE	15 (9%)	28 (8%)	11 (6%)	0.62
Selected co-medications***				
Anticoagulants	29 (82%)	52 (16%)	25 (14%)	0.69
Platelet inhibitors	47 (29%)	93 (28%)	35 (20%)	0.13
Lipid-lowering agents	37 (23%)	81 (24%)	38 (22%)	0.86

Table 8. Distribution of baseline characteristics by rs4789936 polymorphism in the TIMP2 gene (n=780). Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher's exact tests, as appropriate. P-values ≤0.05 are highlighted in bold font. **RVO variables are only reported for the n=485 patients but of course not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban,

rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

4.4 Adiponectin

All study participants were genotyped for the adiponectin polymorphisms rs1501299 and rs2241766. In four RVO patients and one control genotyping failed for the adiponectin polymorphism rs1501299.

The allele frequencies in the adiponectin polymorphism rs1501299 were significantly different between RVO patients and controls (p=0.023; see **Table 9**). Patients were more likely to carry the GG genotype (55% vs. 47% in controls), whereas the TT genotype was less common in patients (7% vs. 12% in controls).

This is supported by the regression models. Patients with at least one T allele (GT+TT) were less likely to have an RVO (OR 0.74, 95% CI 0.55-0.99, p=0.041) using a dominant model. This remained significant after multivariable adjustment (OR 0.72, 95% CI 0.52-0.99, p=0.046). Patients with a TT genotype had an OR of 0.55 (95% CI 0.33-0.90, p=0.018) for having a RVO using a recessive model. This also remained significant after multivariable adjustment (OR 0.46, 95% CI 0.26-0.83, p=0.010). The co-dominant model confirmed these results, showing a significant protective effect for TT individuals (adjusted OR 0.42, 95% CI 0.23–0.77, p=0.005; see **Table 10**).

In subgroup analysis, we did not find an association of rs1501299 adiponectin genotype distribution in patients aged 55 years and younger (p=0.43 in the dominant model and p=0.20 in the recessive model). In the other subgroup analysis, there was no association with bilateral RVO (p=0.62).

There was no association of the rs1501299 SNP (+45T/G) with demographic variables, medical history and co-medications (see **Table 11**). Thus, the observed genetic association appears independent of classical vascular risk factors.

The adiponectin polymorphism rs2241766 did not demonstrate significant differences between patients and controls (p=0.73; see **Table 9**).

In a regression model, the allele distribution remained insignificant independently of which model used (dominant model p=0.45, recessive model p=0.97) and also after multivariable adjustment (dominant model p=0.26, recessive model p=0.42; see **Table 10**).

In subgroup analysis, the adiponectin rs2241766 polymorphism was not associated with RVO in patients aged 55 years and younger using the dominant model (p=0.55) and the recessive model (p=0.82).

However, the second subgroup analysis revealed that patients with bilateral RVO were more likely to have two T alleles (p=0.045).

Regarding analysis of baseline characteristics by adiponectin rs2241766, the GG allele was more common in current smokers (p=0.001), otherwise the allele frequencies was similarly distributed between control and patients regarding demographic variables, medical history and co-medication (see **Table 11**).

Variable	**NMP (‰)**	**Overall (n=781)**	**Controls (n=296)**	**Patients (n=485)**	**p***
adiponectin rs1501299	5 (6‰)	/	1 (3‰)	4 (8‰)	**0.023**
---GG	/	402 (52%)	139 (47%)	263 (55%)	/
---GT	/	306 (39%)	121 (41%)	185 (38%)	/
---TT	/	68 (9%)	35 (12%)	33 (7%)	/
adiponectin rs2241766	0 (0‰)	/	/	/	0.73
---GG	/	13 (2%)	5 (2%)	8 (2%)	/
---GT	/	151 (19%)	53 (18%)	98 (20%)	/
---TT	/	617 (79%)	238 (80%)	379 (78%)	/

Table 9. Distribution of rs1501299 and at rs2241766 polymorphisms. Distribution overall and by patient/control status. Data are absolute frequencies (column %) for count data. NMP (‰) reports the number of missing patients. *p-values are from ranksum-tests.

Polymorphism	Model type	Groups	Univariable Odds ratio (95%CI, p)	Multivariable Odds ratio #1* (95%CI, p)
adiponectin rs1501299	**„Dominant“**	GG	Ref.	Ref.
		GT+TT	0.74 (0.55-0.99, **p=0.041**)	0.72 (0.52-0.99, **p=0.046**)
	„Recessive“	GG+GT	Ref.	Ref.
		TT	0.55 (0.33-0.90, **p=0.018**)	0.46 (0.26-0.83, **p=0.010**)
	„Co-Dominant“	GG	Ref.	Ref.
		GT	0.81 (0.59-1.10, **p=0.175**)	0.81 (0.57-1.14, p=0.22)
		TT	0.50 (0.30-0.84, **p=0.008**)	0.42 (0.23-0.77, **p=0.005**)
adiponectin rs2241766	**“Dominant”**	TT	Ref.	Ref.
		GT+GG	1.15 (0.80-1.64, p=0.45)	1.25 (0.84-1.86, p=0.26)
	“Recessive”	TT+GT	Ref.	Ref.
		GG	0.98 (0.32-3.01, p=0.97)	0.55 (0.13-2.38, p=0.42)
	“Co-Dominant”	TT	Ref.	Ref.
		GT	1.16 (0.80-1.68, p=0.43)	1.32 (0.88-1.98, p=0.18)
		GG	1.00 (0.32-3.11, p=0.99)	0.58 (0.13-2.52, p=0.47)

Table 10. Uni- and multivariable logistic regression models of patient/control status. Reported data are uni- and multivariable odds ratios from logistic regression models with patient/control status as the dependent variable. Genotype alleles were examined as “dominant”, “recessive”, and “co-dominant” specifications. P-values ≤ 0.05 are highlighted in bold font. *#1 is a multivariable model that adjusts the association between polymorphisms and patient/control status for all variables that were differently distributed between patients and controls as well as the respective polymorphism genotype groups excluding laboratory parameters (see Tables 1, 2, and 3 for chosen variables). **#2 is a multivariable model that further adjusts for differently distributed laboratory parameters (see Tables 1, 2, and 3 for chosen variables). Abbreviations: 95% CI – 95% confidence interval, p – Wald test p-value, Ref. – Reference category.

Polymorphism	adiponectin rs1501299					adiponectin rs2241766			
Genotype	**GG (n=402)**	**GT (n=306)**	**TT (n=68)**	**p***		**GG (n=13)**	**GT (n=151)**	**TT (n=617)**	**p***
Demographic variables									
Age (years)	74 [65-80]	72 [64-80]	74 [66-78]	0.67		65 [58-81]	75 [67-80]	73 [64-79]	0.38
Female sex	210 (52%)	151 (49%)	37 (54%)	0.65		3 (23%)	81 (54%)	316 (51%)	0.11
BMI (kg/m²)	27 [24-30]	27 [24-30]	26 [24-29]	0.93		25 [25-26]	26 [24-30]	27 [24-30]	0.55
Current smoker	44 (13%)	35 (14%)	11 (20%)	0.36		5 (56%)	18 (14%)	68 (13%)	**0.001**
RVO variables**									
Laterality of RVO	/	/	/	0.69		/	/	/	**0.014**
---Both eyes	8 (3%)	5 (3%)	2 (6%)	/		0 (0%)	0 (0%)	15 (4%)	/
---Left eye	127 (48%)	97 (52%)	18 (55%)	/		3 (38%)	39 (40%)	201 (53%)	/
---Right eye	128 (49%)	83 (45%)	13 (39%)	/		5 (63%)	59 (60%)	163 (43%)	/
Extent of RVO	/	/	/	0.99		/	/	/	0.75
---Branch RVO	167 (64%)	113 (61%)	21 (64%)	/		6 (75%)	63 (64%)	234 (62%)	/
---Hemiretinal RVO	9 (3%)	6 (3%)	1 (3%)	/		0 (0%)	4 (4%)	12 (3%)	/
---Central RVO	87 (33%)	66 (36%)	11 (33%)	/		2 (25%)	31 (32%)	133 (35%)	/
Comorbidity variables									
Arterial hypertension	274 (73%)	204 (73%)	43 (70%)	0.88		7 (70%)	107 (78%)	410 (72%)	0.30
Diabetes mellitus	65 (18%)	45 (17%)	9 (15%)	0.75		2 (20%)	24 (18%)	94 (17%)	0.88
Stroke	29 (8%)	20 (8%)	5 (8%)	0.96		1 (10%)	13 (9%)	41 (8%)	0.54
Myocardial infarction	21 (6%)	19 (7%)	2 (3%)	0.52		0 (0%)	10 (10%)	32 (6%)	0.77
VTE	31 (9%)	19 (7%)	4 (7%)	0.73		1 (11%)	15 (11%)	38 (7%)	0.32
Selected co-medications***									
Anticoagulants	57 (16%)	40 (15%)	10 (17%)	0.91		1 (10%)	22 (17%)	84 (16%)	0.93
Platelet inhibitors	91 (26%)	66 (25%)	17 (29%)	0.76		3 (33%)	35 (26%)	137 (26%)	0.83
Lipid-lowering agents	76 (22%)	71 (27%)	9 (16%)	0.12		3 (33%)	30 (22%)	123 (23%)	0.69

Table 11. Distribution of baseline characteristics by rs1501299 (n=776) and rs2241766 (n=781) polymorphisms in the adiponectin gene. Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher's exact tests, as appropriate. P-values ≤0.05 are highlighted in bold font. **RVO variables are only reported for

the n=481, respectively n=485 patients but of course not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

4.5 Paraoxonase-1 polymorphism

Study participants were genotyped for the PON1 polymorphism rs854560 (L55M) and rs662 (Q192R). Genotyping failed in two patients for the polymorphism rs854560 and in three patients for rs662 (Q192R).

The analysis of the PON1 rs854560 polymorphism revealed no significant association between genotype distribution (p=0.45). The frequencies of the TT (41% vs 43%), the TA (45% vs 46%) and the AA (14% vs 11%) were very similar between RVO patients and control subjects (see **Table 12**).

Logistic regression analyses across dominant, recessive, and co-dominant inheritance models likewise failed to demonstrate a significant association with RVO. The A allele had an OR of 1.08 (95% CI 0.8-1.44, p=0.62) for having an RVO using a dominant model. In the recessive model, patients with AA had an OR of 1.33 (95% CI 0.85-2.07, p=0.21) for being an RVO patient. This missing association remained after multivariable adjustment (p=0.85, respectively p=0.32; see **Table 13**).

In subgroup analysis, the genotype distribution at PON1 rs854560 in patients aged 55 years and younger was not significantly associated with RVO in the dominant model (p=0.98) and the recessive model (p=0.56). There was also no association with bilateral RVO (p=0.44).

For rs854560, no associations with subtype, or systemic comorbidities were observed. Variables such as hypertension, diabetes, stroke, and medication use were evenly distributed across TT, TA, and AA carriers, with no significant trends (see **Table 14**).

The genotype distribution of the second PON1 associated polymorphism rs662 (Q192R) investigated was similarly distributed between RVO patients (GG 6%, AG 40% and AA 54%) and controls (GG 8%, AG 40% and 52% AA; p=0.47, see **Table 12**).

In logistic regression, subjects with an A allele had an OR of 1.42 (95% CI 0.8-2.53, p=0.23) for having an RVO in the dominant model. Subjects with two A alleles had an OR of 1.1 (95%

CI 0.82-1.47, p=0.53) for being an RVO patient in the recessive model. This lack of association remained after multivariable adjustment (see **Table 13**).

In subgroup analysis, there was no significant association of the rs662 polymorphism and RVO in patients aged 55 years and younger (dominant model p=0.98 and after multivariable adjustment p=0.64, and recessive model p=0.56 and after multivariable adjustment p=0.13). There was no significant association with bilateral RVO (p=0.051).

Rs662 showed significant correlations with myocardial infarction, which was more prevalent in patients with the GG genotype (9%) compared with AG (3%) and AA (8%), reaching statistical significance (p=0.022). The rs662 polymorphism was further associated with differences in lipid-lowering agent use. Use of lipid-lowering agents was significantly more common among GG carriers (38%) compared to AG (20%) and AA (24%), with a p value of 0.033 (see **Table 14**).

Variable	**NMP (‰)**	**Overall (n=781)**	**Controls (n=296)**	**Patients (n=485)**	**p***
PON1 rs854560	2 (2‰)	/	/	2 (4‰)	0.45
---TT	/	323 (41%)	126 (43%)	197 (41%)	/
---TA	/	354 (45%)	137 (46%)	217 (45%)	/
---AA	/	102 (13%)	33 (11%)	69 (14%)	/
PON1 rs662	3 (4‰)	/	/	3 (6‰)	0.47
---GG	/	50 (6%)	23 (8%)	27 (6%)	/
---AG	/	312 (40%)	119 (40%)	193 (40%)	/
---AA	/	416 (53%)	154 (52%)	262 (54%)	/

Table 12. Distribution of rs854560 and rs662 polymorphisms. Distribution overall and by patient/control status. Data are absolute frequencies (column %) for count data. NMP (‰) reports the number of missing patients. *p-values are from ranksum-tests.

Polymorphism	Model type	Groups	Univariable Odds ratio (95%CI, p)	Multivariable Odds ratio * (95%CI, p)
PON1 rs854560	„Dominant“	TT	Ref.	Ref.
		TA+AA	1.08 (0.80-1.44, p=0.62)	1.03 (0.75-1.43, p=0.85)
	„Recessive“	TT+TA	Ref.	Ref.
		AA	1.33 (0.85-2.07, p=0.21)	1.28 (0.78-2.10, p=0.32)
	„Co-Dominant“	TT	Ref.	Ref.
		TA	1.01 (0.74-1.38, p=0.93)	0.98 (0.69-1.38, p=0.89)
		AA	1.34 (0.83-2.14, p=0.23)	1.27 (0.75-2.14, p=0.38)
PON1 rs662	„Dominant“	GG	Ref.	Ref.
		AG+AA	1.42 (0.80-2.53, p=0.23)	1.09 (0.58-2.03, p=0.79)
	„Recessive“	GG+AG	Ref.	Ref.
		AA	1.10 (0.82-1.47, p=0.53)	1.11 (0.80-1.54, p=0.53)
	„Co-Dominant“	GG	Ref.	Ref.
		AG	1.38 (0.76-2.52, p=0.29)	1.03 (0.53-1.98, p=0.93)
		AA	1.45 (0.80-2.62, p=0.22)	1.14 (0.60-2.16, p=0.7)

Table 13. Uni- and multivariable logistic regression models of patient/control status. Reported data are uni- and multivariable odds ratios from logistic regression models with patient/control status as the dependent variable. Genotype alleles were examined as “dominant”, “recessive”, and “co-dominant” specifications. * multivariable model that adjusts the association between PON1 polymorphism and patient/control status for all variables that were differently distributed between patients and controls as well as PON1 polymorphism genotype groups. Abbreviations: 95%CI – 95% confidence interval, p – Wald test p-value, Ref. – Reference category.

Polymorphism	PON1 rs854560					PON1 rs662			
Genotype	**TT (n=323)**	**TA (n=354)**	**AA (n=102)**	**p***		**GG (n=50)**	**AG (n=312)**	**AA (n=416)**	**p***
Demographic variables									
Age (years)	74 [66-80]	74 [65-80]	70 [63-79]	0.31		74 [67-81]	73 [65-80]	73 [64-79]	0.58
Female sex	160 (50%)	194 (55%)	45 (44%)	0.12		21 (42%)	167 (54%)	210 (50%)	0.29
BMI (kg/m²)	27 [24-30]	27 [24-30]	26 [24-28]	0.23		28 [25-32]	27 [24-29]	26 [24-30]	0.14
Current smoker	37 (13%)	38 (13%)	15 (18%)	0.47		7 (15%)	32 (13%)	51 (14%)	0.80
RVO variables**									
Laterality of RVO	/	/	/	/		/	/	/	/
---Both eyes	4 (2%)	8 (4%)	3 (4%)	/		0 (0%)	2 (1%)	13 (5%)	/
---Left eye	110 (56%)	104 (48%)	28 (41%)	/		18 (67%)	103 (54%)	121 (46%)	/
---Right eye	83 (42%)	105 (48%)	38 (55%)	/		9 (33%)	88 (46%)	128 (49%)	/
Extent of RVO	/	/	/	0.50		/	/	/	0.75
---Branch RVO	117 (59%)	142 (65%)	42 (61%)	/		15 (56%)	119 (62%)	167 (64%)	/
---Hemiretinal RVO	7 (4%)	5 (2%)	4 (6%)	/		2 (7%)	6 (3%)	8 (3%)	/
---Central RVO	73 (37%)	70 (32%)	23 (33%)	/		10 (37%)	68 (35%)	87 (33%)	/
Comorbidity variables									
Arterial hypertension	214 (71%)	246 (75%)	63 (69%)	0.35		43 (86%)	202 (71%)	278 (72%)	0.09
Diabetes mellitus	51 (17%)	54 (18%)	14 (16%)	0.92		14 (29%)	42 (15%)	63 (17%)	0.08
Stroke	25 (9%)	25 (8%)	5 (6%)	0.70		6 (13%)	22 (8%)	27 (7%)	0.43
Myocardial infarction	12 (4%)	23 (7%)	7 (8%)	0.18		4 (9%)	8 (3%)	30 (8%)	**0.022**
VTE	19 (7%)	25 (8%)	10 (12%)	0.33		3 (6%)	16 (6%)	34 (9%)	0.29
Selected co-medications***									
Anticoagulants	38 (14%)	51 (17%)	18 (21%)	0.25		9 (21%)	41 (15%)	57 (16%)	0.63
Platelet inhibitors	79 (28%)	76 (25%)	18 (21%)	0.37		12 (27%)	72 (27%)	89 (25%)	0.87
Lipid-lowering agents	71 (25%)	63 (21%)	22 (26%)	0.41		17 (38%)	54 (20%)	84 (24%)	**0.033**

Table 14. Distribution of baseline characteristics by rs854560 (n=779) and rs662 (n=778) polymorphisms in the PON1 gene. Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher's exact tests, as appropriate. P-values ≤0.05 are highlighted in bold font. **RVO variables are only reported for the n=483, respectively n=482 patients but of course not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

4.6 Serum Amyloid A polymorphism

Genotyping failed in 12 (1.5%) control subjects of the 781 participants at the SAA1 polymorphism rs12218.

The analysis of the SAA1 rs12218 polymorphism demonstrated no significant difference in genotype frequencies between patients and controls. The distribution of TT, TC, and CC genotypes was 39%, 41% and 20% in RVO patients and 39%, 45% and 16% in control subjects (p=0.27; see **Table 15**).

In the logistic regression model, the dominant model (CT+TT vs. CC) initially showed a non-significant trend towards a protective against RVO (OR 0.73, 95% CI 0.50–1.08, p=0.12). Notably, after multivariable adjustment, this association became statistically significant (OR 0.60, 95% CI 0.39–0.92, p=0.020). Similarly, the co-dominant model provided further insights. When considered separately, individuals with the CT genotype exhibited a significantly lower risk after adjustment (OR 0.59, 95% CI 0.37–0.93, p = 0.023). TT homozygotes also demonstrated a significant protective effect (OR 0.62, 95% CI 0.39–0.99, p=0.044). In the recessive model, the TT genotype was not associated with RVO (0.96, 95% CI 0.71-1.30, p=0.81) even after multivariable adjustment (p=0.53, see **Table 16**).

In subgroup analysis, the genotype distribution at rs12218 SAA1 polymorphism in patients aged 55 years and younger were not significantly associated with RVO using the dominant model (p=0.43) or the recessive model (p=0.2). Further the subgroup analysis investigating patients with bilateral RVO found no significant association (p=0.92).

When baseline characteristics were analyzed by genotype, we found no statistical significance (see **Table 17**).

Variable	NMP (%)	Overall (n=781)	Controls (n=296)	Patients (n=485)	p*
SAA1 rs12218	12 (2 %)	/	12 (4%)	/	0.27
---TT	/	299 (39%)	112 (39%)	187 (39%)	/
---TC	/	326 (42%)	127 (45%)	199 (41%)	/
---CC	/	144 (19%)	45 (16%)	99 (20%)	/

Table 15. Distribution of rs12218 polymorphisms (n=769). Distribution overall and by patient/control status. Data are absolute frequencies (column %) for count data. NMP (%) reports the number of missing patients. *p-values are from ranksum-tests.

Polymorphism	Model type	Groups	Univariable Odds ratio (95%CI, p)	Multivariable Odds ratio* (95%CI, p)
SAA1 rs12218	„Dominant“	CC	Ref.	Ref.
		CT+TT	0.73 (0.50-1.08, p=0.12)	0.60 (0.39-0.92, **p=0.020**)
	„Recessive“	CC+CT	Ref.	Ref.
		TT	0.96 (0.71-1.30, p=0.81)	0.90 (0.64-1.25, p=0.527)
	„Co-Dominant“	CC	Ref.	Ref.
		CT	0.71 (0.47-1.08, p=0.11)	0.59 (0.37-0.93, **p=0.023**)
		TT	0.76 (0.50-1.16, p=0.20)	0.62 (0.39-0.99, **p=0.044**)

Table 16. Uni- and multivariable logistic regression models of patient/control status. Reported data are uni- and multivariable odds ratios from logistic regression models with patient/control status as the dependent variable. Genotype alleles were examined as “dominant”, “recessive”, and “co-dominant” specifications. P-values ≤ 0.05 are highlighted in bold font. * multivariable model that adjusts the association between polymorphisms and patient/control status for all variables that were differently distributed between patients and controls as well as the respective polymorphism genotype groups excluding laboratory parameters (see Tables 1, 2, and 3 for chosen variables).

Polymorphism	SAA1 1rs12218			
Genotype	**TT (n=299)**	**TC (n=326)**	**CC (n=144)**	**p***
Demographic variables				
Age (years)	73 [65-80]	74 [66-80]	72 [64-79]	0.63
Female sex	137 (46%)	177 (54%)	80 (56%)	0.06
BMI (kg/m²)	27 [24-29]	26 [24-29]	27 [25-31]	0.12
Current smoker	34 (14%)	43 (15%)	13 (11%)	0.56
RVO variables**				
Laterality of RVO	/	/	/	/
---Both eyes	6 (3%)	6 (3%)	3 (3%)	/
---Left eye	92 (49%)	96 (48%)	55 (56%)	/
---Right eye	89 (48%)	97 (49%)	41 (41%)	/
Extent of RVO	/	/	/	0.82
---Branch RVO	116 (62%)	122 (61%)	65 (66%)	/
---Hemiretinal RVO	7 (4%)	5 (3%)	4 (4%)	/
---Central RVO	64 (34%)	72 (36%)	30 (30%)	/
Comorbidity variables				
Arterial hypertension	201 (73%)	221 (73%)	95 (73%)	0.99
Diabetes mellitus	37 (14%)	54 (19%)	27 (21%)	0.14
Stroke	20 (8%)	29 (10%)	5 (4%)	0.12
Myocardial infarction	11 (4%)	20 (7%)	10 (8%)	0.23
VTE	21 (8%)	26 (9%)	6 (5%)	0.34
Selected co-medications***				
Anticoagulants	39 (15%)	46 (16%)	19 (16%)	0.90
Platelet inhibitors	67 (26%)	76 (27%)	30 (25%)	0.87
Lipid-lowering agents	51 (20%)	71 (25%)	31 (26%)	0.41

Table 17. Distribution of baseline characteristics by rs12218 (n=769) polymorphism in the SA1 gene. Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher’s exact tests, as appropriate. P-values ≤0.05 are highlighted in bold font. **RVO variables are only reported for the n=483, respectively n=482 patients but of course not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants

(apixaban, rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

4.7 Lipoprotein A

All study participants were genotyped for the two LPA associated polymorphisms. Genotyping failed in three patients (<1%) for the LPA polymorphism rs3798220 and in two patients (<1%) for the polymorphism rs10455872.

The analysis of rs3798220 demonstrated no statistically significant difference in genotype distribution between patients and controls. The TT, TC, and CC genotypes were observed in 90%, 10%, and <1% of RVO patients, and in 93%, 7%, and 0% of controls, respectively (p=0.25; see **Table 18**).

As only one patient showed a CC genotype, we could only use a dominant model, to investigate a possible association to RVO. In the logistic regression model, carriers of the C allele at rs3798220 had an OR of 1.49 (95% CI 0.86-2.57, p=0.15) for having an RVO. Notably, after multivariable adjustment for vascular comorbities and medication use, this association became statistically significant (OR 1.84, 95% CI 1.02-3.32, p=0.044, see **Table 19**).

In subgroup analysis, there was no significant association between the rs3798220 polymorphism and RVO in subjects aged 55 years and younger (p=0.76). There was also no significant association in subgroup analysis when investigating patients with bilateral RVO (p=0.99).

Further subgroup analysis demonstrated a significant difference in RVO subtype distribution. C-allele carriers at rs3798220 were less frequently found in central RVO (17% vs. 36%) compared with TT homozygotes (p=0.028, see **Table 20**). Other variables did not reveal significant differences.

The analysis of rs10455872 demonstrated no significant difference in genotype frequencies between patients and controls. The distribution of AA, AG, and GG genotypes was 96%, 4%, and 0% in RVO patients, and 95%, 5%, and 0% in control subjects, respectively (p=0.35; see **Table 18**).

None of our study participants showed a GG genotype, therefore we could only use a dominant model. In logistic regression, the dominant model did not reveal any significant association with RVO. The OR of having an RVO for patients with a G allele at rs10455872 was 1.46

(95% CI 0.57-2.27, p=0.72). This remained insignificant even after multivariable adjustment (p=0.34, see **Table 19**).

In subgroup analysis, there was no significant association in subjects aged 55 years and younger (p=0.18) and no significant in patients with bilateral RVO (p=0.66).

When baseline variables were analyzed by rs10455872 genotype, no differences were detected in demographic or cardiovascular risk factors. However, a significant difference was observed in concomitant medication: anticoagulant use was higher in AG carriers (37% vs. 15%, p=0.006), whereas platelet inhibitor use was lower (7% vs. 27%, p=0.024). No differences were observed in lipid-lowering therapy (p=0.82; see **Table 20**).

Variable	NMP (‰)	Overall (n=781)	Controls (n=296)	Patients (n=485)	p*
LPA rs3798220	3 (4‰)	/	/	3 (6‰)	0.25
---TT	/	711 (91%)	276 (93%)	435 (90%)	/
---TC	/	66 (8%)	20 (7%)	46 (10%)	/
---CC	/	1 (<1%)	0 (0%)	1 (<1%)	/
LPA rs10455872	2 (3‰)	/	/	2 (4‰)	0.35
---GG	/	0 (0%)	0 (0%)	0 (0%)	/
---AG	/	32 (4%)	15 (5%)	17 (4%)	/
---AA	/	747 (96%)	281 (95%)	466 (96%)	/

Table 18. Distribution of rs3798220 and rs10455872 polymorphisms (n=781). Distribution overall and by patient/control status. Data are absolute frequencies (column %) for count data. NMP (‰) reports the number of missing patients. *p-values are from ranksum-tests.

Polymorphism	Groups	Univariable Odds ratio (95%CI, p)	Multivariable Odds ratio* (95%CI, p)
LPA	TT	Ref.	Ref.
rs3798220	TC+CC	1.49 (0.86-2.57, p=0.15)	1.84 (1.02-3.32, p=**0.044**)
LPA	AA	Ref.	Ref.
rs10455872	AG+GG	1.46 (0.57-2.27, p=0.72)	1.50 (0.65-3.45, p=0.34)

Table 19. Uni- and multivariable logistic regression models of patient/control status. Reported estimates represent uni- and multivariable odds ratios from logistic regression models with patient/control status as the dependent variable. Due to only n=1 subject having LPA rs10455872 CC type, this genotype was pooled with the TC genotype for regression analyses. *Multivariable OR adjusts for all variables that were differently distributed between patients and controls. Abbreviations: 95%CI – 95% confidence interval, p – Wald test p-value, Ref. – Reference category.

Polymorphism	**LPA rs3798220**					**LPA rs10455872**			
Genotype	**TT (n=711)**	**TC (n=66)**	**CC (n=1)**	**p***		**GG (n=0)**	**AG (n=32)**	**AA (n=747)**	**p***
Demographic variables									
Age (years)	73 [65-80]	71 [63-78]	54 [54-54]	0.18		N/A	77 [64-83]	73 [65-79]	0.37
Female sex	363 (51%)	34 (52%)	1 (100%)	0.99		N/A	13 (41%)	36 (52%)	0.28
BMI (kg/m²)	27 [24-30]	28 [25-32]	26 [26-26]	0.23		N/A	27 [24-30]	27 [24-30]	0.99
Current smoker	81 (14%)	9 (14%)	0 (0%)	0.87		N/A	6 (22%)	84 (13%)	0.25
RVO variables**									
Laterality of RVO	/	/	/	/		/	/	/	/
---Both eyes	13 (3%)	2 (4%)	0 (0%)	/		N/A	0 (0%)	15 (3%)	/
---Left eye	223 (51%)	19 (41%)	0 (0%)	/		N/A	9 (53%)	233 (50%)	/
---Right eye	199 (46%)	25 (54%)	1 (100%)	/		N/A	8 (47%)	218 (47%)	/
Extent of RVO	/	/	/	**0.028**		/	/	/	0.18
---Branch RVO	264 (61%)	35 (76%)	1 (100%)	/		N/A	10 (59%)	291 (62%)	/
---Hemiretinal RVO	13 (3%)	3 (6%)	0 (0%)	/		N/A	2 (12%)	14 (3%)	/
---Central RVO	158 (36%)	8 (17%)	0 (0%)	/		N/A	5 (29%)	161 (35%)	/
Comorbidity variables									
Arterial hypertension	473 (73%)	49 (75%)	0 (0%)	0.31		N/A	22 (76%)	501 (73%)	0.83
Diabetes mellitus	105 (17%)	14 (24%)	0 (0%)	0.34		N/A	8 (28%)	111 (17%)	0.13
Stroke	50 (8%)	5 (8%)	0 (0%)	0.99		N/A	4 (14%)	51 (8%)	0.27
Myocardial infarction	41 (7%)	1 (2%)	0 (0%)	0.22		N/A	1 (3%)	41 (6%)	0.99
VTE	48 (8%)	6 (10%)	0 (0%)	0.51		N/A	4 (14%)	50 (8%)	0.28
Selected co-medications***									
Anticoagulants	96 (16%)	11 (19%)	0 (0%)	0.64		N/A	10 (37%)	97 (15%)	**0.006**
Platelet inhibitors	155 (25%)	18 (31%)	0 (0%)	0.58		N/A	2 (7%)	171 (27%)	**0.024**
Lipid-lowering agents	138 (23%)	18 (30%)	0 (0%)	0.39		N/A	7 (26%)	149 (23%)	0.82

Table 20. Distribution of baseline characteristics by rs3798220 (n=778) polymorphism and rs10455872 (n=779) in the LPA gene. Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher's exact tests, as appropriate. P-values ≤0.05 are highlighted in bold font. **RVO variables are only reported for the n=483, respectively n=482 patients but of course not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

4.8 AB0 Blood group

Genotyping for AB0 blood group failed in one RVO patient. Among patients, 52% had blood group A, 11% group B, 7% group AB, and 31% group 0, compared with 47%, 14%, 6%, and 32% in controls, respectively (p=0.53, see **Table 21**).

In logistic regression models, there was no significant association between blood group 0 and RVO risk. AB0 blood group 0 was associated with 0.9-fold lower odds of being a patient (Odds ratio=0.94, 95% CI: 0.69-1.28, p=0.69), and this lack of association prevailed upon multivariable adjustment (see **Table 22**).

In subgroup analysis, we did not find an association between blood group and RVO in patients aged 55 years and younger (p=0.16) and in patients with bilateral RVO (p=0.88).

Further we did not find a significant association of blood group and baseline demographic variables, major vascular comorbities and concurrent selected medications (see **Table 23**).

Variable	**NMP (‰)**	**Overall (n=781)**	**Controls (n=296)**	**Patients (n=485)**	**p***
AB0 bloodgroup	1 (1‰)	/	1 (3‰)	/	0.53
---A	/	391 (50%)	140 (47%)	251 (52%)	/
---B	/	96 (12%)	42 (14%)	54 (11%)	/
---AB	/	51 (7%)	19 (7%)	32 (7%)	/
---0	/	242 (31%)	94 (32%)	148 (30%)	/

Table 21. Distribution of AB0 blood group. Distribution overall and by patient/control status. Data are absolute frequencies (column %) for count data. NMP (‰) reports the number of missing patients. *p-values are from ranksum-tests.

	Odds ratio (95%CI, p)	
Variable	**Univariable model**	**Multivariable Model #2****
AB0: A, B, AB	Ref.	Ref.
AB0: 0	0.94 (0.69-1.28, p=0.69)	0.79 (0.47-1.33, p=0.38)

Table 22. Uni- and multivariable logistic regression models of patient/control status. *Multivariable OR adjusts for all variables that were differently distributed between patients and controls. Abbreviations: 95%CI – 95% confidence interval, p – Wald test p-value, Ref. – Reference category.

Variable	Subjects with blood groups A, B, or AB (n=538)	Subjects with blood group 0 (n=242)	p*
Demographic variables			
Age (years)	74 [65-80]	73 [64-78]	0.61
Female sex	277 (51%)	123 (51%)	0.86
BMI (kg/m²)	27 [24-30]	27 [24-29]	0.50
Current smoker	63 (14%)	28 (14%)	0.44
RVO variables**			
Laterality of RVO	/	/	/
---Both eyes	7 (2%)	8 (5%)	/
---Left eye	171 (51%)	72 (49%)	/
---Right eye	159 (47%)	68 (46%)	/
Extent of RVO	/	/	0.88
---Branch RVO	213 (63%)	90 (61%)	/
---Hemiretinal RVO	11 (3%)	5 (3%)	/
---Central RVO	113 (34%)	53 (36%)	/
Comorbidity variables			
Arterial hypertension	360 (73%)	164 (72%)	0.66
Diabetes mellitus	81 (17%)	39 (18%)	0.70
Stroke	36 (8%)	19 (9%)	0.64
Myocardial infarction	27 (6%)	15 (7%)	0.55
VTE	39 (8%)	15 (7%)	0.58
Selected co-medications***			
Anticoagulants	74 (16%)	33 (16%)	0.95
Platelet inhibitors	122 (26%)	53 (26%)	0.88
Lipid-lowering agents	111 (24%)	45 (22%)	0.49

Table 23. Distribution of baseline characteristics by ABO blood group (780). Data are medians [25th-75th percentile] for continuous variables, and absolute frequencies (column %) for count data. *p-values are from Kruskal-Wallis tests, χ^2-tests, and Fisher's exact tests, as appropriate. P-values ≤0.05 are highlighted in bold font. **RVO variables are only reported for the patients but not for controls. ***Anticoagulants include low-molecular weight heparins, direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, dabigatran), and vitamin K antagonists (phenprocoumon, acenocoumarol); Platelet inhibitors include low-dose aspirin, prasugrel, clopidogrel, and ticagrelor; Lipid-lowering agents include statins, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors. Abbreviations: BMI – Body Mass Index, RVO – Retinal vein occlusion, VTE – Venous thromboembolism.

5. Discussion

5.1 Demographics

Demographic variables in particular age, sex, smoking status and body mass index (BMI) were similar between retinal vein occlusion patients and controls. In relation to comorbidities, RVO patients were more likely to have had a stroke ($p=0.018$) and a venous thromboembolism ($p<0.001$). The number of patients on anticoagulants and platelet inhibitors was similar between RVO patients and controls. However, controls were more likely to take lipid-lowering agents ($p=0.031$).

5.2 Heme oxygenasis 1 gene (HMOX1)

Genotype frequencies of HMOX1 rs2071746 were comparable between RVO patients and controls ($p=0.44$). The distribution of HMOX1 rs2071746 genotypes in the study population was balanced with 30% of the invidividuals carrying the AA genotype, 51% heterozygous (AT) and 19% homozygous for the T allele. There was no significant association in uni- or multivariable logistic regression models after adjustment for demographic factors. This indicates that the polymorphism does not appear to confer a measurable risk for the development of RVO in this cohort.

HO-1 is known to play a central role in oxidative stress and is proposed to have anti-inflammatory properties by degrading pro-inflammatory heme (144). The rs2071746 polymorphism on the HMOX1 gene is a common polymorphism associated with cardiovascular disease. The A allele is linked to higher promotor activity compared to the T allele. In a recent meta-analysis, the AA genotype had reduced risk of coronary artery disease compared to those with the TT genotype (68). Despite these findings, caution should be given as the association with coronary artery disease could not be reproduced in a recent large German cohort (145) and two studies found no association between the rs2071746 polymorphism and HO-1 activity (146, 147). In our study population we could not find an association between the rs2071746 polymorphism and RVO.

It would have been interesting to investigate whether the rs2071746 polymorphism was associated with HO-1 acitivity in our study cohort. Therefore although the data suggest that the

HMOX1 rs2071746 variant does not substantially modify the risk for RVO, further investigation may be warranted.

Although this was no endpoint in this study, it is interesting to note, that we found a significant association of lower prevalence of diabetes mellitus and AA genotype in our study population ($p<0.001$). Given that a higher HO-1 activity is associated with a reduction in adipogenesis (148) and the A allele is associated with a higher promotor activity, this seems plausible. However, given the modest effect size and potential confounding, this finding should be interpreted catiously. A recent study investigating HMOX-1 polymorphisms in type 2 diabetes mellitus found an association with the GT(n) polymorphism, but not the rs2071746 polymorphism (146).

5.3 Matrix Metalloproteinase

The MMP2 rs243865 polymorphism in the promotor region of the MMP2 gene showed no association with RVO status ($p=0.69$). Its genotype frequencies was 61% individuals carried the CC genotype, 33% were heterozygous (CT) and 6% were homozygous for the T allele, which is consistent with Hardy-Weinberg equilibrium. However, we found an association of the C allele at the rs243865 and the presence of RVO (OR 16, $p=0.012$) in patients aged 55 years and younger. These findings indicate that the rs243865 polymorphism does not exert a major effect on the risk of developing RVO in the overall RVO group, but may be a risk factor in younger patients.

The C allele is associated with higher MMP-2 levels. MMP-2 is proposed to promote inflammatory processes (149). In RVO patients, both MMP-2 serum levels (150), aqueous levels (81) and MMP-2 activity were shown to be increased (151). Thus the association of the C allele with the presence of RVO in young patients seems plausible, although it was not significant in our overall cohort.

RVO affects primarily patients aged over 60 years. Young patients developing RVO are an interesting subgroup as they are more likely exhibit underlying inflammatory and/or hypercoagulable conditions and require a more thorough work-up (152, 153). These young RVO patients have been shown to have a significant increase in different inflammatory serum markers compared to older RVO patients (154). This might suggest that the pro-inflammatory

component plays an especially large role in young RVO patients, which would be in accordance with our results.

There is one study by Ortak (85) that already investigated this rs243865 SNP in RVO patients. Unlike this study, they found an association between the T allele at this SNP and RVO. In cardiovascular disease the T allele is suggested to be protective, similarly as in our results (155). No explanation is given for this discrepancy and this would require further investigation.

The TIMP2 rs4789936 genotypes were balanced across RVO patients and controls. The distribution of genotypes (GG 24%, GT 51%, TT 25%) was consistent with Hardy-Weinberg equilibrium. This polymorphism was already examined by Ortak (85). They could not find an association either. This would suggest that the TIMP2 rs4789936 polymorphism does not seem to play a major role in RVO.

5.4 Adiponectin

The present study demonstrated a significant difference in genotype distribution for the rs1501299 polymorphism between patients with RVO and control subjects. Specifically, the GG genotype was more grequent among RVO patients, while the TT genotype appeared less common, suggesting that presence of the T allele may confer a protective effect. The regression analysis further support this genetic association revealing a lower risk of RVO for carriers of at least one T allele. This effect persisted after multivariable adjustment, reinforcing the hypothesis that the adiponectin-related rs1501299 polymorphism may play a role in the pathogenesis of RVO.

Adiponectin exerts anti-inflammatory by multiple pathways. The T allele at rs1501299 is associated with higher plasma adiponectin levels (156) and is suggested to be protective for cardiovascular disease (157-159).

Opposite to our results suggesting a protective role of the T allele in RVO patients, a study by Demir et al (98) found that the T allele carriers at rs1501299 were significantly more likely to have a BRVO, but not CRVO. This discrepancy may be at least party explained by differences in the study population. Overall, our study cohort was older and showed a higher prevalence of arterial hypertension and stroke. More strikingly, there was a marked difference in genotype frequencies among the control groups. The control group of the study by Demir et al (98)

showed in 58% of controls the GG genotype, in 38% GT and in 4% TT compared to our control group, which showed in 47% the GG genotype, in 41% GT and in 12% TT.

In order to ensure that our control group was not affected by selection biased, we confirmed that the genotype distribution conformed to the Hardy-Weinberg equilibrium, indicating genetic consistency within the population. To further validate our findings, we compared our controls group's genotype frequencies with those reported in an independent Austrian cohort investing cardiovascular diasease (161). In that study, the distribution of the rs1501299 polymorphism was 53% GG, 39% GT and 8% TT, closely aligning with our control data. This similarity supports the representativeness of our control group and strengthens the reliability of the observed genetic associations.

Another study investigating a possible association between the rs1501299 polymorphism and RVO was performed by Christodoulou et al (99) They could not find an association, but in a subgroup analysis they found that the T allele was associated with RVO in patients aged over 75 years. These results should be, however, interpreted with great caution as it only included 33 RVO patients and 44 control subjects. The small sample size greatly limits the statistical power and generalizability. Further, the lack of adjustment for potential confounders may have influenced the observed association.

Subgroup analysis did not reveal an association between the rs1501299 polymorphism and RVO in younger patients (≤55 years) or in those with bilateral disease. This lack of significane in these subgroups may be attributable to smaller sample sizes and reduced statistical power.

In contrast, the rs2241766 polymorphism showed no significant differences between RVO patients and controls. The genotype frequencies (GG 2%, GT 19%, TT 79%) were distributed following the Hary Weinberg Equlibrium. The regression models showed no significant association with this polymorphism and RVO.

In our study cohort, all fifteen patients with bilateral RVO had the TT genotype of the adiponectin rs2241766 polymorphism, suggesting a significant association between the presence of the T allele and the occurrence of bilateral RVO. This finding may indicate a potential genetic predisposition among TT allele carriers to develop bilateral RVO. The TT allele carriers have been associated with cardiovascular disease in a meta-analysis (162), which might make the association found in our study reasonable. However, these results must be interpreted with caution, as the number of bilateral RVO cases in our cohort was small, limiting the statistical robustness and generalizability. The rarity of bilateral RVO make it difficult to

draw conclusions. Larger studies are warranted whether the adiponectin rs2241766 TT genotype indeed contributed to bilateral disease manifestation or merely reflects a coincidental finding within our population.

5.5 Paraoxonase-1

In this study, our findings indicate no significant association between the two investigated polymorphisms rs854560 and rs662 and occurrence of RVO risk in the studied cohort.
The genotype frequencies of the rs854560 polymorphism were evenly distributed (TT 41%, TA 45% and AA 13%) and followed the Hardy Weinberg equilibrium. The genotype frequencies were comparable between RVO patients and controls. This lack of association remained in the logistic regression across dominant, recessive and co-dominant models and after multivariable adjustments. This suggests that the rs854560 variant does not substantially contribute to the development of RVO.
Similarly, the rs662 polymorphism showed no significant difference in genotype distribution between RVO patients and controls. This genotype frequencies were evenely distributed and followed the Hardy Weinberg equilibrium. Logistic regression did not identify a significant effect on RVO susceptibility, either in a dominant or recessive model. This absence of association persisted after multivariable adjustment, further supporting the conclusion that the PON1 polymorphism rs662 is unlikely to be an independent risk factor for RVO.
In our data, the rs662 variant showed a significant correlation with myocardial infarction among GG genotype carriers, which was significantly prevalent in subjects with the GG genotype (9%), compared with AG (3%) and AA (8%). This finding aligns with existing literature linking PON1 variants to cardiovascular risk (163). The rs662 polymorphism was further associated with use of lipid-lowering agents. Use of lipid-lowering agents was significantly more prevalent among GG carriers (38%) compared to AG (20%) and AA (24%). This may reflect the higher burden of dyslipidemia among GG individuals consistent with literature on patients with unstable angina (164).
PON-1 prevents LDL peroxidation leading to atheroprotection. The A allele at the rs854560 polymorphism is associated with less PON1 activity. Ortak et al (165) found that the frequency of the AA genotype at rs854560 was significantly lower in patients with RVO than in the control subjects.

In contrast, our study could not replicate this association. Several factors may account for the discrepancies between our results and those of Ortak et al (165), including potential ethnic and environmental differences between the study populations. In terms of comparability, our study subjects were older and our controls had a higher prevalence of arterial hypertension, which might explain to some extent the difference. The allele distribution in our cohort were very similar to those reported by Ortak et al. In our study group the distribution was AA 13%, AG 45% and GG 41% and the study by Ortak had the following distribution AA 13%, AG 48% and GG 39%. Although our allele distribution was very similar, it is known from previously published data that the AA genotype occurs considerably more frequently in individuals of European descent than in those of Asian descent (166). This underlines the importance of considering ethnicity when discussing SNP.

Murata et al (167) examined the potential association between the PON1 rs662 polymorphism and CRVO. In their analysis, the AA genotype was observed more frequently among control subjects than in CRVO patients. This genotype has been linked to higher PON1 activity, which would in fact suggest a potential protective effect. The study included a very limited number of participants, only 42 CRVO patients and 45 controls, which substantially restricts the statistical power and generalizability of the results. This raises the possibility of a chance finding or population-specific bias, and may explain, why these results could not be reproduced in our study cohort.

5.6 Serum Amyloid A

In this study, we investigated the association between the SAA1 polymorphism rs12218 and the risk of RVO. While the univariable analysis revealed no significant association, multivariable logistic regression demonstrated a statistically significant protective effect of the T allele. Specifically, individuals carrying at least one T allele had a 40% lower odds of developing RVO after adjustment for potential confounders. The genotype distribution was comparable (39% TT, 42% TC and 19% CC) indicating that allele frequencies were in Hardy-Weinberg equilibrium.

The T allele has been linked to higher SAA1 activity (112) and lower risk of cardiovascular events such as myocardial infarction (111), stroke (114, 115) and coronary artery disease (116).

Thus the association we found seems plausible, but needs to be interpreted cautiously, as the protective effect became significant only after adjustment for covariates. This may indicate a weak association (i.e. subtle genetic effect), which becomes significant only after a statistical enhancement through model adjustment. When performing a multivariable adjustment, the confidence interval becomes narrower and thus results may become significant. This would suggest that there is in fact a weak association. The other reason for this may be a potential confounder. We did not find an association between the SAA1 rs12218 and other variables, however we only corrected for a few selected confounders.

Subgroup analysis did not reveal any significant associations, suggesting that the potential protective influence of the T allele represent a general trend across the RVO population.

Analysis of baseline characteristics by genotype further demonstrated no significant differences across variables reducing the likelihood that the observed genetic association was confounded by major systemic vascular risk factors.

It would have been interesting to measure SAA1 blood levels in our study cohort and investigate a possible influence of the rs12218 polymorphism. Experimental data suggest that SAA1 protein levels do not always correlate proportionally with mRNA expression, likely due to post-transcriptional regulatory mechanisms such as mRNA staibilisation (111). Investigating whether such mechanisms operate in chronic low-grade inflammation, as might be relevant in RVO, could provide valuable insight into the biological significance of this polymorphism.

5.7 Lipoprotein(a)

This study did not show a significant association between the LPA gene polymorphism rs3798220 and rs10455872 and RVO.

The LPA polymorphism rs3798220 showed a predominance of the TT genotype, observed in 90% of RVO patients and 93% of controls, whereas the heterozygous TC genotype was found in 10% of patients and 7% of controls. Only one participant exhibited the CC genotype. Given this distribution, a dominant model was used for statistical analysis. The results of the univariable logistic regression yielded insignificant results. However, after multivariable adjustment this association reached statistical significance. Although the adjusted finding might indicate a modest risk elevation, the overall low prevalence of the C allele and limited genotype variation suggest that this result should be interpreted cautiously.

For the rs10455872 polymorphism, the genotype distribution was similarly skewed toward the homozygous major allele, with 96% of RVO patients carrying the AA genotype and 4% the AG genotype and with 95% of controls carrying the AA genotype and 5% the AG genotype. No GG homozygotes were detected in our sample. Logistic regression using a dominant model revealed no significant association with RVO either in univariable or multivariable models. These results suggest that the LPA rs10455872 polymorphism does not play a major role in RVO.

Interestingly, when analyzing RVO subtypes, we observed that carriers of the C allele at rs3798220 less frequently presented with CRVO (17%) compared to TT homozygotes (36%). This may suggest that the rs3798220 polymorphism may have different effects on specific RVO phentoypes. However, given the small number of C-allele carries, this finding should be regarded as exploratory and requires validation in larger cohort.

For the rs10455872 polymorphism, a notable difference was observed in anticoagulant medication use. It was significantly more frequent in AG carriers (37%) compared with AA homozygotes (15%). The use of platelet inhibitors was significantly lower in AG carriers (7%) than in AA homozygotes (27%). These findings are unlikely to indicate a causal relationship, they may reflect differences in comorbidity management or chance variation due to the small number of AG carriers.

Lp(a) plays a significant role in cardiovascular disease and its levels have been found to be increased in RVO patients (9, 121-123). It is a genetically determined lipoprotein meaning its levels are primarily genetically determined and environmental factors play a minor role, and their levels remain relatively stable during an individual's lifetime (168). This would suggest that LPA polymorphisms are plausible candidates as risk factors for RVO. Although Lp(a) levels have been found to be increased in RVO patients, we did not find an association of these two polymorphisms in our study cohort. Although LPA polymorphism rs3798220 and rs10455872 explain around 36% of variation in Lp(a) levels (127), serum levels may be influenced more extensively by kringle repeats in the LPA gene, which we did not investigate. It would have been valuable to assess Lp(a) serum levels in our study cohort, as this could have provided additional insight into whether other genetic variants within the LPA gene might contribute to the risk of RVO.

The absence of a clear association between the studied LPA polymorphism and RVO does not exclude a possible role of Lp(a). The genotype frequencies of the rs3798220 and rs10455872

variants varies markedly across ethnicities, which could influence population-specific effects. For example, the C allele of rs3798220 occurs in approximately 4% of individuals of European ancestry (168), similar to our cohort, but up to 42% in Hispanic populations (169). Thus, our findings may not generalize to other ethnic groups.

5.8 ABO blood group

In this study, we did not observe any significant association between the ABO blood groups and RVO. We used two genetic markers (rs8176719 and rs8176746) to determine blood group status, we found that the distribution of blood groups among RVO patients (52% A, 11% B, 7% AB and 31% O) closely mirrored that of the control population (47% A, 14% B, 6% AB and 32% O). Logistic regression analysis confirmed that absence of an association, which remained unchanged after multivariable adjustment.

The ABO blood group has been widely investigated in relation to cardiovascular diseases. The O blood group associated with a lower risk for multiple cardiovascular diseases (137, 138) (139, 140) (141, 170) (142, 143) (171). This protective effect has been attributed to a reduced glycosyltransferase activity in individuals with blood group O, which in turn influences glycosylation of various plasma proteins and thus reduced levels of vWF and factor VIII. Both vWF and factor VIII play central roles in platelet adhesion and thrombus formation and reduced concentrations may confer to a lower prothrombotic tendency (172). Due to these effects, ABO blood group may be a candidate for a risk factor for RVO.

However, to date, only two studies have reported on ABO blood group and RVO. White et al (135) over 40 years ago investigated the potential role of ABO in ROV and found no significant differences in ABO blood groups between patients and controls. A more recent publication of Borella et al (136) with a larger sample size found that non-O blood groups had a moderately increased risk for developing RVO with an OR of 1.42 (95%CI 1.01–2.01). However, they only included patients referred to the Thrombotic and Hemorrhagic Diseases Unit, which might make their results prone to a selection bias towards individuals with a predisposition to coagulation disorders.

In this study, we used two SNPs, namely rs8176719 and rs8176746, to determine ABO blood group. The G allele at the rs8176719 polymorphism encodes for blood groups A or B. If there is a homozygous deletion of the G allele, it encodes blood group O. Although very unlikely,

theoretically, a person with a G allele at rs8176719 polymorphism, could still be blood group O brought about other polymorphisms. However, these are infrequent and unlikely to affect the overall results.

The absence of a detectable relationship between ABO blood group and RVO could reflect true biological independence or it may indicate that the effect is to small to be detected with our sample size.

5.9 Limitations

This study has several important limitations that should be acknowledged.

Although this study cohort was relatively large compared with previous investigations on RVO, the genetic polymorphisms examined may exert only subtle influences on disease risk. Detecting such small effect sizes may require substantially larger study cohorts to achieve sufficient statistical power. Thus, we cannot exclude the possibility that some true associations were missed resulting in false negative results due to small effect sizes.

Another limitation concerns potential selection bias. All of our RVO patients were recruited at our outpatient clinic at the Department of Ophthalmology. RVO patients are often only referred to our outpatient clinic if macular edema is present. Therefore, RVO patients, who did not develop significant macular edema, may be underrepresented in our cohort. This recruitment pattern could have limited the generalizability of our findings. Similarly, our control subjects were recruited from our outpatient clinic for cataract surgery. Although cataract is an age-related and nearly ubiquitous condition, its presence as an inclusion criteria may have introduced some bias. Patients visiting an ophthalmic clinic might differ from the general population in systemic health, which could further limit external validity.

Ethnic variability in allele frequencies represents another potential source of bias and limits the reproducibility of our findings across populations. As mentioned above, the LPA polymorphism is highly variable between ethnicities and allele frequencies differ from 4% to 42% in different ethnic groups (168), (169). Similar variability exists for several of the other polymorphisms examined in this study. As our cohort existed exclusively of individuals of predominantly European descent, our results may not be generazible to populations of different ethnic backgrounds.

A further limitation related to the lack of data on serum levels. Some of the investigated polymorphisms, in particular those within the LPA gene, were selected based on previous reports of elevated corresponding serum levels. However, we did not measure Lp(a) serum levels or other relevant serum markers, for that matter, in our study participants. Assessing these parameters could have provided valuable insights whether the examined polymorphisms translate into functional alterations in protein expression and maybe even protein activity. Such measurements would have enabled us to evaluate potential genotype-phenotype correlations within our cohort.

In this study, we explored twelve different polymorphisms, which introduces the issue of multiple statistical testing. Multiple testing is a problem often encountered in case control studies investigating numerous hypotheses at once. It increases the risk for type I errors, meaning that some observed associations may be statistically significant merely by chance. In other words, the more tests conducted, the higher is the probability of finding a significant result by chance. There are several methods to address the issue of multiple testing. The Bonferroni correction is a simple and more conservative method that divides the alpha level by the number of tests performed. So, the significance levels is divided by the number of tests performed i.e. if 12 tests are performed the adjusted alpha would be 0.0042. However, the Bonferroni correction may be overly stringent and thereby increases the likelihood of type 2 errors, thereby missing true associations. The Holm-Bonferroni method provides a stepwise adjustment that is somewhat less conservative and overcomes this problem partly by ordering the p-values from the multiple tests and adjusting them sequentially. Another less stringent method to control for type 1 error is the False Discovery Rate approach. The False Discovery Rate is the expected ratio of the number of false discoveries to the number of all positive discoveries (true and false). Permutation tests and bootstrapping can be both used to adress multiple testing by repeatedly sampling the data and recalculating the number. This allows a more flexible approach.

In this study we deliberately did not correct for multiple testing, because our primary aim was exploratory. Our goal was to identify potential associations that could serve as a basis for future hypothesis-driven studies rather than providing definitive confirmation of specific genetic effects. Therefore, we accepted a higher probability of false-positive findings in favor of sensitivity to detect possible genetic signals of interest. Nevertheless, the results should be interpreted with appropriate caution and validated in independent cohorts.

Another limitation of our study is the lack of adjustment for many demographic factors. We collected data on some key cardiovascular and lifestyle variables, however by far not all known risk factors for RVO. Unmeasured and residual confounding therefore remains a possibility.
In general, while our study provides some valuable insights into the potential genetic underpinnings of RVO, the aforementioned limitations should be considered when interpreting the results. Future studies with larger, multiethnic cohorts and comprehensive phenotypic and biochemical characterization are warranted to validate our findings.

5.10 Conclusion

In this exploratory analysis, we aimed to investigate a potential association between genetic polymorphism and retinal vein occlusion. We identified a protective effect associated with the T allele of the adiponectin polymorphism rs1501299, which was found to reduce the likelihood of RVO occurrence. Further, after adjusting for multiple variables, the T allele at the SAA1 polymorphism rs12218 was also observed to have a protective association. Additionally, in a subgroup analysis of patients aged 55 years or younger, we found a significant association between the C allele of the MMP2 polymorphism rs243865 and an increased risk for RVO.
We found no association between the rs2071746 polymorphism in the HMOX1 gene, the rs243865 polymorphism in the promotor region of the MMP2 gene, the two polymorphisms rs854560 (Q192R) and rs662 (Q192R) in the PON1 gene, the polymorphisms rs3798220 and rs10455872 in the LPA gene or the ABO blood groups and the presence of RVO.

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